



**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use OSELTAMIVIR PHOSPHATE CAPSULES safely and effectively. See full prescribing information for OSELTAMIVIR PHOSPHATE CAPSULES.

OSELTAMIVIR phosphate capsules USP, for oral use  
Initial U.S. Approval: 1999

**INDICATIONS AND USAGE**

- Osetamivir phosphate is an influenza neuraminidase (NAI) inhibitor indicated for:
  - Treatment of acute, uncomplicated influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours. (1.1)
  - Prophylaxis of influenza A and B in patients 1 year and older. (1.2)

**Limitations of Use:**

- Not a substitute for annual influenza vaccination. (1.3)
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1.3)
- Not recommended for patients with end-stage renal disease not undergoing dialysis. (1.3)

**DOSE AND ADMINISTRATION**

- Treatment of influenza (2.2)**
  - Adults and adolescents (13 years and older): 75 mg twice daily for 5 days
  - Pediatric patients 1 to 12 years of age: Based on weight twice daily for 5 days
  - Pediatric patients 2 weeks to less than 1 year of age: 3 mg/kg twice daily for 5 days
  - Renally impaired adult patients (creatinine clearance >30-60 mL/min): Reduce to 30 mg twice daily for 5 days (2.4)
- Renally impaired adult patients (creatinine clearance >10-30 mL/min): Reduce to 30 mg once daily for 5 days (2.4)
- ESRD patients on hemodialysis: Reduce to 30 mg immediately and then 30 mg after every hemodialysis cycle. Treatment duration not to exceed 5 days (2.4)
- ESRD patients on CAPD: Reduce to a single 30 mg dose immediately (2.4)

**Prophylaxis of influenza (2.3)**

- Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days
  - Community outbreak: 75 mg once daily for up to 6 weeks
- Pediatric patients 1 to 12 years of age: Based on weight once daily for 10 days
  - Community outbreak: Based on weight once daily for up to 6 weeks
- Renally impaired adult patients (creatinine clearance >30-60 mL/min): Reduce to 30 mg once daily (2.4)

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**  
1.1 **Treatment of Influenza**  
Osetamivir phosphate capsules, USP is indicated for the treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours.

1.2 **Prophylaxis of Influenza**  
Osetamivir phosphate is indicated for the prophylaxis of influenza A and B in patients 1 year and older.

1.3 **Limitations of Use**  
Osetamivir phosphate capsules is not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.  
Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use osetamivir phosphate capsules (See Microbiology (12.4)).  
Osetamivir phosphate capsules is not recommended for patients with end-stage renal disease not undergoing dialysis (See Dosage and Administration (2.4) and Use in Specific Populations (8.6)).

**2 DOSAGE AND ADMINISTRATION**  
2.1 **Dosage and Administration Overview**  
Administer osetamivir phosphate capsules for the treatment of influenza in patients 2 weeks of age or older (See Dosage and Administration (2.2)) or for prophylaxis of influenza in patients 1 year and older (See Dosage and Administration (2.3)).

The capsules may be taken with or without food; however, tolerability may be enhanced if osetamivir phosphate capsules is taken with food.  
Adjust the osetamivir phosphate capsules dosage in patients with moderate or severe renal impairment (See Dosage and Administration (2.4)).

For patients who cannot swallow capsules, osetamivir phosphate for oral suspension is the preferred formulation. When osetamivir phosphate for oral suspension is not available from the wholesaler or the manufacturer, osetamivir phosphate capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). During emergency situations and when neither the oral suspension or the age-appropriate strengths of osetamivir phosphate capsules to mix with sweetened liquids are available, then a pharmacist may compound an emergency supply of oral suspension from osetamivir phosphate 75 mg capsules (See Dosage and Administration (2.6)).

2.2 **Recommended Dosage for Treatment of Influenza**  
Initiate treatment with osetamivir phosphate capsules within 48 hours of influenza symptom onset.  
**Adults and Adolescents (13 years of age and older)**  
The recommended oral dosage of osetamivir phosphate capsules for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily (one 75 mg capsule twice daily) for 5 days.

**Pediatric Patients (2 weeks of age through 12 years of age)**  
Table 1 displays the recommended oral dosage of osetamivir phosphate for treatment of influenza in pediatric patients 2 weeks of age and older and provides information about prescribing the capsule or the formulation for oral suspension.

2.3 **Recommended Dosage for Prophylaxis of Influenza**  
Initiate post-exposure prophylaxis with osetamivir phosphate capsules within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with osetamivir phosphate capsules during a community outbreak.

**Adults and Adolescents (13 years of age and older)**  
The recommended dosage of osetamivir phosphate capsules for prophylaxis of influenza in adults and adolescents 13 years and older is 75 mg orally once daily (one 75 mg capsule once daily) for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, osetamivir phosphate capsules may be continued for up to 12 weeks (See Use in Specific Populations (8.9)). The duration of protection lasts for as long as osetamivir phosphate capsules dosing is continued.

**Pediatric Patients (1 year to 12 years of age)**  
Table 1 displays the recommended oral dosage of osetamivir phosphate capsules for prophylaxis of influenza in pediatric patients 1 year to 12 years of age based on body weight and provides information about prescribing the capsule or the formulation for oral suspension. Prophylaxis in pediatric patients 2 weeks to less than 1 year of age is based on weight and is provided in Table 2 and up to 6 weeks during a community outbreak (See Use in Specific Populations (8.4) and Clinical Studies (14.2)).

**Table 1 Osetamivir Phosphate Dosage Recommendations in Pediatric Patients for Treatment and Prophylaxis of Influenza**

Weight	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days*	Volume of Oral Suspension (6 mg/mL) for each Dose	Number of Bottles of Oral Suspension to Dispense	Number of Capsules to Dispense (Strength)†
<b>Patients from 2 Weeks to less than 1 Year of Age</b>					
Any weight	3 mg/kg twice daily	Not applicable	0.5 mL/kg‡	1 bottle	Not applicable
<b>Patients 1 to 12 Years of Age Based on Body Weight</b>					
15 kg or less	30 mg twice daily	30 mg once daily	5 mL	1 bottle	10 capsules (30 mg)
15.1 kg to 23 kg	45 mg twice daily	45 mg once daily	7.5 mL	2 bottles	10 capsules (45 mg)
23.1 kg to 40 kg	60 mg twice daily	60 mg once daily	10 mL	2 bottles	20 capsules (30 mg)
40.1 kg or more	75 mg twice daily	75 mg once daily	12.5 mL	3 bottles	10 capsules (75 mg)

\* The recommended duration for post-exposure prophylaxis is 10 days and the recommended duration for community outbreak (seasonal/pre-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients). The amount supplied (e.g., number of bottles or capsules) for seasonal prophylaxis may be greater than for post-exposure prophylaxis.  
‡ Osetamivir phosphate for oral suspension is the preferred formulation for patients who cannot swallow capsules.  
§ For patients less than 1 year of age, provide an appropriate dosing device that can accurately measure and administer small volumes.

2.4 **Dosage in Patients with Renal Impairment**  
Table 2 displays the dosage recommendations for the treatment and prophylaxis of influenza in adults with various stages of renal impairment (estimated creatinine clearance of less than or equal to 90 mL per minute). Dosage modifications are recommended in adults with an estimated creatinine clearance less than or equal to 60 mL per minute (See Use in Specific Population (8.6) and Clinical Pharmacology (12.3)).

**Table 2 Recommended Dosage Modifications for Treatment and Prophylaxis of Influenza in Adults with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis**

Renal Impairment (Creatinine Clearance)	Recommended Treatment Regimen*	Recommended Prophylaxis Regimen†
Mild (>60-90 mL/minute)	75 mg twice daily for 5 days	75 mg once daily
Moderate (>30-60 mL/minute)	30 mg twice daily for 5 days	30 mg once daily
Severe (>10-30 mL/minute)	30 mg once daily for 5 days	30 mg every other day
ESRD Patients on Hemodialysis (<10 mL/minute)	30 mg immediately and then 30 mg after every hemodialysis cycle (treatment duration not to exceed 5 days)	30 mg immediately and then 30 mg after alternate hemodialysis cycles
ESRD Patients on Continuous Ambulatory Peritoneal Dialysis‡ (<10 mL/minute)	A single 30 mg dose administered immediately	30 mg immediately and then 30 mg once weekly
ESRD Patients not on Dialysis	oseltamivir phosphate capsules is not recommended	oseltamivir phosphate capsules is not recommended

\* Capsules or oral suspension can be used for 30 mg dosing.  
† The recommended duration for post-exposure prophylaxis is at least 10 days and the recommended duration for community outbreak (seasonal/pre-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients).  
‡ Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.  
2.6 **Emergency Preparation of Oral Suspension from 75 mg Osetamivir Phosphate Capsules**  
The following directions are provided for use only during emergency situations and when FDA-approved, commercially manufactured osetamivir phosphate for oral suspension is not available from wholesalers or the manufacturer.

- Renally impaired adult patients (creatinine clearance >10-30 mL/min): Reduce to 30 mg once every other day (2.4)
- Adults on hemodialysis: Reduce to 30 mg immediately and then 30 mg after alternate hemodialysis cycles for the recommended duration of prophylaxis (2.4)
- ESRD patients on CAPD: Reduce to 30 mg immediately and then 30 mg once weekly for the recommended duration of prophylaxis (2.4)

**DOSE FORMS AND STRENGTHS**

Capsules: 30 mg, 45 mg, 75 mg (3)

**CONTRAINDICATIONS**

Patients with known serious hypersensitivity to osetamivir or any of the components of osetamivir phosphate capsules (4)

**WARNINGS AND PRECAUTIONS**

- Serious skin/hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme. Discontinue osetamivir phosphate capsules and initiate appropriate treatment if allergic-like reactions occur or are suspected. (5.1)
- Neuropsychiatric events: Patients with influenza, including those receiving osetamivir phosphate capsules, particularly pediatric patients, may be at an increased risk of confusion or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

**ADVERSE REACTIONS**

Most common adverse reactions (>1% and more common than with placebo):  
• Treatment studies - Nausea, vomiting, headache. (6.1)  
• Prophylaxis studies - Nausea, vomiting, headache, pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alvogon, distributor for Natco Pharma Limited at 1-866-770-3024 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

**DRUG INTERACTIONS**

Live attenuated influenza vaccine (LAIV), intranasal:  
Avoid administration of LAIV within 2 weeks before or 48 hours after osetamivir phosphate capsules use, unless medically indicated. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

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\*Sections or subsections omitted from the full prescribing information are not listed.

The following emergency preparation instructions will provide one patient with enough osetamivir phosphate for a 5-day course of treatment of influenza or a 10-day course of prophylaxis of influenza:

**Step #1:** Determine the dosage of osetamivir phosphate for the patient (See Dosage and Administration (2.2, 2.3, and 2.4)) then determine the total volume of oral suspension needed to be prepared (See Table 3).

**Table 3 Emergency Preparation: Volume of Prepared Oral Suspension (6 mg per mL) Based Upon Osetamivir Phosphate Capsules Dose**

Osetamivir Phosphate Dose*	Total Volume to Prepare per Patient
15 mg or less	37.5 mL
30 mg	75 mL
45 mg	100 mL
60 mg	125 mL
75 mg	150 mL

\* If the osetamivir phosphate dose is between the doses listed, use the greater listed dose to determine the total volume of prepared oral suspension.

**Step #2:** Preparation must be performed with only one of the following vehicles (other vehicles have not been studied): Cherry Syrup (Humco®), Ora-Sweet®SF (sugar-free) (Padlock Laboratories), or simple syrup. Determine the number of capsules and the amount of water and vehicle needed to prepare the total volume (See Table 3) of prepared oral suspension (6 mg per mL) for a complete treatment or prophylaxis course (See Table 4).

**Table 4 Emergency Preparation: Number of Osetamivir Phosphate 75 mg Capsules and Amount of Water and Vehicle Needed to Prepare the Total Volume of a Prepared Oral Suspension (6 mg per mL)**

Total Volume of Prepared Oral Suspension	37.5 mL	75 mL	100 mL	125 mL	150 mL
Number of Osetamivir Phosphate 75 mg Capsules (Total Strength)†	3 (225 mg)	6 (450 mg)	8 (600 mg)	10 (750 mg)	12 (900 mg)
Amount of Water	2.5 mL	5 mL	7 mL	8 mL	10 mL
Volume of Vehicle					
Cherry Syrup (Humco®) OR Ora-Sweet®SF (Padlock Laboratories) OR simple syrup	34.5 mL	69 mL	91 mL	115 mL	137 mL

\*Includes overage to ensure all doses can be delivered

**Step #3:** Follow the instructions below for preparing the 75 mg osetamivir phosphate capsules to produce the oral suspension (6 mg per mL).

- Place the specified amount of water into a polyethylene terephthalate (PET) or glass bottle (see Table 4). Constitution in either bottle types is not recommended because there is no stability data with other bottle types.
- Carefully separate the capsule body and cap and pour the contents of the required number of osetamivir phosphate 75 mg capsules into the PET or glass bottle.
- Gently swirl the suspension to ensure adequate wetting of the osetamivir phosphate powder for at least 2 minutes.
- Slowly add the specified amount of vehicle to the bottle.
- Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. The active drug, osetamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of osetamivir phosphate capsules which are insoluble in these vehicles.
- Put an ancillary label on the bottle indicating "Shake Well Before Use."
- Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
- Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations. Place an appropriate expiration date on the label according to storage conditions below.

- Include the recommended dosage on the pharmacy label as per Tables 1 and 2 (See Dosage and Administration (2.2, 2.3, and 2.4)).
- Store the prepared oral suspension in glass or PET bottles either:
  - In a refrigerator (2° to 8°C (36° to 46°F)): Stable for 5 weeks when stored in a refrigerator.
  - At room temperature (25°C (77°F)): Stable for 5 days when stored at room temperature.

**3 DOSAGE FORMS AND STRENGTHS**

- Osetamivir phosphate capsules:
- 30-mg capsules (39.40 mg of Osetamivir phosphate is equivalent to 30 mg of Osetamivir (free base)); White to off-white powder filled in Size "4" capsule with yellow color cap imprinted with "30 mg" with blue color ink and yellow color body imprinted with "NAT" with blue color ink.
  - 45-mg capsules (59.10 mg of Osetamivir phosphate is equivalent to 45 mg of Osetamivir (free base)); White to off-white powder filled in Size "4" capsule with grey color cap imprinted with "45 mg" with blue color ink and grey color body imprinted with "NAT" with blue color ink.
  - 75-mg capsules (98.50 mg of Osetamivir phosphate is equivalent to 75 mg of Osetamivir (free base)); White to off-white powder filled in size "2" capsules with yellow color cap imprinted with "75 mg" with blue color ink and grey color body imprinted with "NAT" with blue color ink.

**4 CONTRAINDICATIONS**

Osetamivir phosphate capsules is contraindicated in patients with known serious hypersensitivity to osetamivir or any component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme (See Warnings and Precautions (5.1)).

**5 WARNINGS AND PRECAUTIONS**

5.1 **Serious Skin/Hypersensitivity Reactions**  
Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience with osetamivir phosphate capsules. Stop osetamivir phosphate capsules and institute appropriate treatment if an allergic-like reaction occurs or is suspected. The use of osetamivir phosphate capsules is contraindicated in patients with known serious hypersensitivity to osetamivir phosphate capsules (See Contraindications (4) and Adverse Reactions (6.2)).

5.2 **Neuropsychiatric Events**  
There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving osetamivir phosphate capsules (See Adverse Reactions (6.2)). Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on osetamivir phosphate capsules usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of osetamivir phosphate capsules to these events has not been established. Influenza can be associated with a variety of neurologic and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. Closely monitor osetamivir phosphate capsules-treated patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing osetamivir phosphate capsules for each patient.

5.3 **Risk of Bacterial Infections**  
There is no evidence for efficacy of osetamivir phosphate capsules in any illness caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Osetamivir phosphate capsules have not been shown to prevent such complications. Prescribers should be alert to the potential for secondary bacterial infections and treat them as appropriate.

**6 ADVERSE REACTIONS**

In clinical studies, adverse reactions are discussed below and elsewhere in the labeling:  
• Serious skin and hypersensitivity reactions (See Warnings and Precautions (5.1))  
• Neuropsychiatric events (See Warnings and Precautions (5.2))

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adverse Reactions from Treatment and Prophylaxis Trials in Adult and Adolescent Subjects (13 years of age and older)**  
The overall safety profile of osetamivir phosphate is based on data from 2,646 adult and adolescent subjects that received the recommended dosage of 75 mg orally twice daily for 5 days for treatment of influenza and 1,943 adult and adolescent subjects that received the recommended dosage of 75 mg orally once daily for up to 6 weeks for prophylaxis of influenza in clinical trials.

The most common adverse reactions in the pooled treatment and pooled prophylaxis trials in adults and adolescents are displayed in Table 5. The majority of these adverse reactions were reported on a single occasion, occurred on either the first or second treatment day and resolved spontaneously within 1-2 days. This summary includes otherwise healthy adults/adolescents and subjects "at risk" (subjects at higher risk of developing complications associated with influenza, e.g., elderly patients and patients with chronic cardiac or respiratory disease). In general, the safety profile in the subjects "at risk" was qualitatively similar to that in otherwise healthy adults/adolescents.

**Table 5 Adverse Reactions Occurring in ≥1% of Adults and Adolescents (13 years of age and older) in Treatment and Prophylaxis Trials\***

System Organ Class Adverse Reaction	Treatment Trials		Prophylaxis Trials	
	Osetamivir phosphate 75 mg twice daily (n = 2646)	Placebo (n = 1977)	Osetamivir phosphate 75 mg once daily (n = 2646)	Placebo (n = 1586)
<b>Gastrointestinal Disorders</b>				
Nausea	10%	6%	8%	4%
Vomiting	8%	3%	2%	1%
<b>Nervous System Disorders</b>				
Headache	2%	1%	17%	16%
<b>General Disorders</b>				
Pain	<1%	<1%	4%	3%

\* Adverse reactions that occurred in ≥1% of osetamivir phosphate-treated adults and adolescents and 21% greater in osetamivir phosphate-treated subjects compared to placebo-treated subjects in either the treatment or prophylaxis trials.

**Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (1 year to 12 years of age)**

A total of 1,481 pediatric subjects (including otherwise healthy pediatric subjects aged 1 year to 12 years and asthmatic pediatric subjects aged 6 to 12 years) participated in clinical trials of osetamivir phosphate for the treatment of influenza. A total of 869 pediatric subjects received treatment with osetamivir phosphate for oral suspension either at a 2 mg per kg twice daily for 5 days or weight-band dosing. Vomiting was the only adverse reaction reported at a frequency of ≥1% in subjects receiving osetamivir phosphate (16%) compared to placebo (8%).

Amongst the 148 pediatric subjects aged 1 year to 12 years who received osetamivir phosphate at doses of 30 to 60 mg once daily for 10 days in a post-exposure prophylaxis study in household contacts (n = 99), and in a separate 6-week seasonal influenza prophylaxis safety study (n = 49), vomiting was the most frequent adverse reaction (8% on osetamivir phosphate versus 2% in the no prophylaxis group).

**Adverse Reactions from Treatment Trials in Pediatric Subjects (2 weeks to less than 1 year of age)**  
Assessment of adverse reactions in pediatric subjects 2 weeks to less than 1 year of age was based on two open-label studies that included safety data on 135 influenza-infected subjects 2 weeks to less than 1 year of age (including premature infants at least 36 weeks post-conceptual age) exposed to osetamivir phosphate at doses ranging from 2 to 3.5 mg per kg of the formulation for oral suspension twice daily orally for 5 days. The safety profile of osetamivir phosphate was similar across the age range studied, with vomiting (9%), diarrhea (7%) and diaper rash (7%) being the most frequently reported adverse reactions, and was generally comparable to that observed in older pediatric and adult subjects.

**Adverse Reactions from the Prophylaxis Trial in Immunocompromised Subjects**  
In a 12-week seasonal prophylaxis study in 475 immunocompromised subjects, including 18 pediatric subjects 1 year to 12 years of age, the safety profile in the 238 subjects receiving osetamivir phosphate 75 mg once daily was consistent with that previously observed in otherwise healthy osetamivir phosphate prophylaxis clinical trials (See Clinical Studies (14.2)).

**6.2 Postmarketing Experience**

The adverse reactions have been identified during post-approval use of osetamivir phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to osetamivir phosphate exposure.

**General disorders and administration site conditions:** Swelling of the face or tongue, allergy, anaphylactic/anaphylactoid reactions, hypothermia  
**Skin and subcutaneous tissue disorders:** Rash, dermatitis, urticaria, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme (See Warnings and Precautions (5.1))

**Gastrointestinal Disorders:** Gastrointestinal bleeding, hemorrhagic colitis

**Cardiac Disorders:** Arrhythmia

**Hepatobiliary Disorders:** Hepatitis, abnormal liver function tests

**Nervous System Disorders:** Seizure

**Metabolism and Nutrition Disorders:** Aggravation of diabetes

**Psychiatric Disorders:** Abnormal behavior, delirium, including symptoms such as hallucinations, agitation, anxiety, altered level of consciousness, confusion, nightmares, delusions (See Warnings and Precautions (5.2))

**7 DRUG INTERACTIONS**

- trouble breathing
- chest pain or tightness
- **Change in behavior.** People, especially children, who have the flu, can develop nervous system problems and abnormal behavior that can lead to death. During treatment with oseltamivir phosphate capsules, tell your healthcare provider right away if you or your child have confusion, speech problems, shaky movements, seizures, or start hearing voices or seeing things that are not really there (hallucinations).

The most common side effects of oseltamivir phosphate capsules when used for treatment of the flu include nausea, vomiting, and headache.

The most common side effect of oseltamivir phosphate capsules when used for prevention of the flu include nausea, vomiting, headache, and pain.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of oseltamivir phosphate capsules.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store oseltamivir phosphate capsules?

- Store oseltamivir phosphate capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away any unused oseltamivir phosphate capsules that are out of date or no longer needed.

### Keep oseltamivir phosphate capsules and all medicines out of the reach of children.

### General information about the safe and effective use of oseltamivir phosphate capsules.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use oseltamivir phosphate capsules for a condition for which it was not prescribed. Do not give oseltamivir phosphate capsules to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about oseltamivir phosphate capsules that is written for health professionals. For more information, **contact Alvogon, distributor for Natco Pharma Limited at 1-866-770-3024.**

### What are the ingredients in oseltamivir phosphate capsules?

**Active ingredient:** oseltamivir phosphate

**Inactive ingredients:**

**Oseltamivir phosphate capsules:** Croscarmellose sodium, povidone K-30, pregelatinized starch, sodium stearyl fumarate and talc.

**The 30 mg shell (yellow / yellow) contains:** Gelatin, iron oxide red, iron oxide yellow, purified water and titanium dioxide.

**The 45 mg shell (grey / grey) contains:** Gelatin, iron oxide black, purified water and titanium dioxide.

**The 75 mg shell (yellow / grey) contains:** Gelatin, iron oxide black (in body), iron oxide red, iron oxide yellow (in cap), purified water and titanium dioxide.

Manufactured by:  
**NATCO PHARMA LIMITED**  
Kothur- 509 228,  
India.

Distributed by:  
**Alvogon, Inc.**  
Pine Brook, NJ 07058 USA

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised 06/2016

## INSTRUCTIONS FOR USE

### Oseltamivir phosphate capsules USP, for oral use (os-el-TAM-ih-veer)

**How do I mix the contents of oseltamivir phosphate capsules with sweetened liquids, if directed by my healthcare provider or pharmacist?**

**You will need:**

- the prescribed dose of oseltamivir phosphate capsules
- a small bowl
- sweetened liquid, such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water)

Step 1. Open the contents of the prescribed dose of oseltamivir phosphate capsules into a small bowl.

Step 2. Add a small amount of the sweetened liquid to the capsule contents.

Step 3. Stir the mixture and give the entire dose of oseltamivir phosphate.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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No clinical trial data are available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

#### 8.9 Immunocompromised Patients

Efficacy of oseltamivir phosphate capsules for the treatment or prophylaxis of influenza has not been established in immunocompromised patients [See *Clinical Studies (14.2)*]. Safety of oseltamivir phosphate capsules for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients [See *Adverse Reactions (6.1)*].

#### 10 OVERDOSAGE

Reports of overdoses with oseltamivir phosphate capsules have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse reactions were reported. Adverse reactions reported following overdose were similar in nature to those observed with therapeutic doses of oseltamivir phosphate capsules [See *Adverse Reactions (6.1)*].

#### 11 DESCRIPTION

Oseltamivir phosphate, USP, an influenza neuraminidase inhibitor (NAI), is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use.

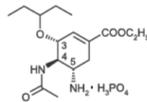
In addition to the active ingredient, each capsule contains croscarmellose sodium, povidone K-30, pregelatinized starch, sodium stearyl fumarate and talc.

The 30 mg shell (yellow / yellow) contains: Gelatin, iron oxide red, iron oxide yellow, purified water and titanium dioxide.

The 45 mg shell (grey / grey) contains: Gelatin, iron oxide black, purified water and titanium dioxide. The 75 mg shell (yellow / grey) contains: Gelatin, iron oxide black (in body), iron oxide red, iron oxide yellow (in cap), purified water and titanium dioxide.

Each capsule is printed with blue ink, which includes butyl alcohol, dehydrated alcohol, FD&C blue No. 2 aluminum lake, isopropyl alcohol, propylene glycol, shellac and strong ammonium solution.

Oseltamivir phosphate, USP is a white to off white powder with the chemical name (3R,4R,5S)-4-acetylamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is  $C_{20}H_{31}N_2O_6$  (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



#### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

Oseltamivir is an antiviral drug with activity against influenza virus [See *Microbiology (12.4)*].

##### 12.3 Pharmacokinetics

###### Absorption and Bioavailability

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate capsules and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate and less than 5% of the oral dose reaches the systemic circulation as oseltamivir (see Table 6).

**Table 6 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules Twice Daily (n=20)**

Parameter	Oseltamivir	Oseltamivir Carboxylate
C <sub>max</sub> (ng/mL)	65 (26)	348 (18)
AUC <sub>0-24h</sub> (ng h/mL)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (about 6.7 times the maximum recommended oseltamivir phosphate capsules dosage) [See *Dosage and Administration (2)*]. Co-administration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6218 ng h/mL under fasted conditions and 6069 ng h/mL under fed conditions) of oseltamivir carboxylate.

###### Distribution

The volume of distribution (V<sub>d</sub>) of oseltamivir carboxylate, following intravenous administration in 24 subjects (oseltamivir phosphate is not available as an IV formulation), ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

###### Elimination

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to the active metabolite, oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated unchanged in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration.

###### Metabolism

Oseltamivir is extensively converted to the active metabolite, oseltamivir carboxylate, by esterases located predominantly in the liver. Oseltamivir carboxylate is not further metabolized. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

###### Excretion

Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h), indicating that tubular secretion (via organic anion transporter) occurs in addition to glomerular filtration. Less than 20% of an oral radiolabeled dose is eliminated in feces.

###### Specific Populations

###### Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily (about 1.3 times the maximum recommended dosage) for 5 days to subjects with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function.

Population-derived pharmacokinetic parameters were determined for patients with varying degrees of renal function including ESRD patients on hemodialysis. Median simulated exposures of oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 7. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis [See *Indications and Usage (1.3)*, and *Use in Specific Populations (8.5)*].

**Table 7 Simulated Median Treatment Exposure Metrics of Oseltamivir Carboxylate in Patients with Normal Renal Function, with Renal Impairment and ESRD Patients on Hemodialysis**

Renal Function/Impairment	Normal Creatinine Clearance	Mild Creatinine Clearance	Moderate Creatinine Clearance	Severe Creatinine Clearance	ESRD Creatinine Clearance
	90-140 mL/min (n=57)	60-90 mL/min (n=45)	30-60 mL/min (n=13)	10-30 mL/min (n=11)	<10 mL/min on Hemodialysis (n=24)

#### Recommended Treatment Regimens

PK exposure parameter	75 mg twice daily	75 mg twice daily	30 mg twice daily	30 mg once daily	30 mg every 12 hours
C <sub>max</sub> (ng/mL)	145	253	180	219	221
C <sub>min</sub> (ng/mL)	298	464	306	477	1170
AUC <sub>0-24h</sub> (ng h/mL)*	11224	18476	12008	16818	23200

#### Recommended Prophylaxis Regimens

PK exposure parameter	75 mg once daily	75 mg once daily	30 mg once daily	30 mg every other day	30 mg alternate HD cycle
C <sub>max</sub> (ng/mL)	39	62	57	70	42
C <sub>min</sub> (ng/mL)	213	311	209	377	903
AUC <sub>0-24h</sub> (ng h/mL)*	5294	8336	6262	8317	11200

\*AUC normalized to 48 hours.

In continuous ambulatory peritoneal dialysis (CAPD) patients, the peak concentration of oseltamivir carboxylate following a single 30 mg dose of oseltamivir or once weekly oseltamivir was approximately 3-fold higher than in patients with normal renal function who received 75 mg twice daily. The plasma concentration of oseltamivir carboxylate on Day 5 (147 ng/mL) following a single 30 mg dose in CAPD patients is similar to the predicted C<sub>max</sub> (160 ng/mL) in patients with normal renal function following 75 mg twice daily. Administration of 30 mg once weekly to CAPD patients resulted in plasma concentrations of oseltamivir carboxylate at the 168 hour sample of 63 ng/mL, which were comparable to the C<sub>min</sub> in patients with normal renal function receiving the approved regimen of 75 mg once daily (30 ng/mL).

###### Hepatic Impairment

In clinical studies, oseltamivir carboxylate exposure was not altered in subjects with mild or moderate hepatic impairment [See *Use in Specific Populations (8.7)*].

###### Pregnant Women

A pooled population pharmacokinetic analysis indicates that the oseltamivir phosphate capsules dosage regimen resulted in lower exposure to the active metabolite in pregnant women (n=58) compared to non-pregnant women (n=30). However, this predicted exposure is expected to have activity against susceptible influenza virus strains and are therefore pharmacokinetics and safety data to recommend a dose adjustment for pregnant women [See *Use in Specific Populations (8.1)*].

###### Pediatric Subjects (1 year to 12 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single-dose pharmacokinetic study in pediatric subjects aged 5 to 16 years (n=18) and in a small number of pediatric subjects aged 3 to 12 years (n=5) enrolled in a clinical trial. Younger pediatric subjects cleared both the prodrug and the active metabolite faster than adult subjects resulting in a lower exposure for a given mg/kg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric subjects over 12 years of age are similar to those in adult subjects [See *Use in Specific Populations (8.4)*].

###### Pediatric Subjects (2 weeks to less than 1 year of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in two open-label studies of pediatric subjects less than one year of age (n=122) infected with influenza. Apparent clearance of the active metabolite decreases with decreasing age in subjects less than 1 year of age; however the oseltamivir and oseltamivir carboxylate exposure following a 3 mg/kg dose in subjects under 1 year of age is expected to be within the observed exposure in adults and adolescents receiving 75 mg twice daily and 150 mg twice daily [See *Use in Specific Populations (8.4)*].

###### Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25 to 35% higher in geriatric subjects (age range 65 to 78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric subjects were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis [See *Use in Specific Populations (8.5)*].

###### Drug Interaction Studies

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronoyl transferases.

Co-administration of probenecid results in an approximate two-fold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when co-administering with probenecid. No clinically relevant pharmacokinetic interactions have been observed when co-administering oseltamivir with amoxicillin, acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), rimantadine, amantadine, or warfarin.

#### 12.4 Microbiology

##### Mechanism of Action

Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase affecting release of viral particles. The median C<sub>50</sub> values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and influenza B clinical isolates were 2.5 nM (range 0.93-4.16 nM, N=74), 0.96 nM (range 0.13-7.95 nM, N=774), and 60 nM (20-285 nM, N=256), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate.

##### Antiviral Activity

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly variable depending on the assay method used and the influenza virus. The 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub>) were in the range of 0.0008 micromolar to greater than 35 micromolar and 0.004 micromolar to greater than 100 micromolar, respectively (1 micromolar=0.284 microgram per mL). The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.

##### Resistance

Cell culture studies: Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate. Reduced susceptibility of influenza virus to inhibition by oseltamivir carboxylate may be conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins.

Clinical studies: Reduced susceptibility isolates have been obtained during treatment with oseltamivir and from sampling during community surveillance studies. Changes in the viral

neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are summarized in Table 8. The clinical impact of this reduced susceptibility is unknown.

Hemagglutinin (HA) substitutions selected in cell culture and associated with reduced susceptibility to oseltamivir carboxylate (influenza virus subtype-specific numbering) A11T, K172R, and R453M in H3N2, and H90Q in influenza B virus (Yamagata lineage). In some cases, HA substitutions were selected in conjunction with known NA resistance substitutions and may contribute to reduced susceptibility to oseltamivir; however, the impact of HA substitutions on antiviral activity of oseltamivir in humans is unknown and likely to be strain-dependent.

**Table 8 Neuraminidase Amino Acid Substitutions Associated with Reduced Susceptibility to Oseltamivir**

Amino Acid Substitution*
<b>Influenza A (N1 numbering in brackets)</b>
I117V (I117V), I119V (I119V), R152K (R152K), Y155H (Y155H), F173V (F174V), D198G/N (D198G/N), I222K/R/T/V (I222K/R/T/V), S246N (S247N), G248R+H266V (G248R+H267V), H274Y (H275Y), N294S (N295S), Q312R+H427T (Q313R+H427T), N325K (N325K), R371K (R368K)
<b>Influenza A (N2 numbering in brackets)</b>
E41G, E119V/V, D151V, I222L/V, Q226H, SAGS245-248 deletion, S247F, R292K, N294S
<b>Influenza B (B numbering in brackets)</b>
E119A (E117A), P141S (P139S), G142R (G140R), R152K (R150K), D198E/N/V (D197E/N/V), I222L/T/V (I221L/T/V), A246D/S/T (A245D/S/T), H274Y (H273Y), N294S (N294S), R371K (R374K), G402S (G407S)

\* All numbering is N2, except where indicated

Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. The incidence of oseltamivir treatment-associated resistance in pediatric treatment studies has been detected at rates of 27 to 37% and 3 to 18% (3/11 to 7/19 and 1/34 to 9/50 post-treatment isolates, respectively) for influenza A/H1N1 virus and influenza A/H3N2 virus, respectively. The frequency of resistance selection to oseltamivir and the prevalence of such resistant virus vary seasonally and geographically.

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who had not received oseltamivir treatment. The oseltamivir resistance-associated substitution H275Y was found in more than 99% of US-circulating 2008 H1N1 influenza virus isolates. The 2009 H1N1 influenza virus ("swine flu") was almost uniformly susceptible to oseltamivir but not oseltamivir. The H275Y substitution can change from season to season. Prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate capsules.

##### Cross-resistance

Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitution observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated substitutions observed in influenza B virus neuraminidase, are associated with reduced susceptibility to oseltamivir but not zanamivir. The R292R resistance-associated substitution observed in N2, and the I222T, D198E/N, or G402S oseltamivir resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. These examples do not represent an exhaustive list of cross-resistance-associated substitutions and prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate capsules.

No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase inhibitor class (oseltamivir, zanamivir) and the M2 ion channel inhibitor class (amantadine, rimantadine). However, a virus may carry a neuraminidase inhibitor-associated substitution in neuraminidase and an M2 ion channel inhibitor associated substitution in M2 and may therefore be resistant to both classes of inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

##### Immune Response

No influenza vaccine/oseltamivir interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with oseltamivir phosphate capsules did not impair normal humoral antibody response to infection.

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats given daily oral doses of the prodrug oseltamivir phosphate up to 400 mg/kg and 500 mg/kg, respectively, the prodrug and the active form oseltamivir carboxylate induced no statistically significant increases in tumors over controls. The mean maximum daily exposures to the prodrug in mice and rats were approximately 130- and 226-fold, respectively, greater than those in humans at the recommended clinical dose based on AUC comparisons. The respective safety margins of the exposures to the active oseltamivir carboxylate were 15- and 50-fold.

Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating and from mating until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during mating, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose in this study was approximately 100 times the human systemic exposure (AUC<sub>0-24h</sub>) of oseltamivir carboxylate that occurs after administration of the maximum recommended human dose.

#### 14 CLINICAL STUDIES

##### 14.1 Treatment of Influenza

###### Adults

Two randomized, placebo-controlled, double-blind clinical trials of oseltamivir phosphate capsules were conducted in adults between 18 and 65 years old, one in the U.S. and one outside the U.S., for the treatment of acute uncomplicated influenza. Eligible subjects had fever of at least 100°F, accompanied respiratory symptom (cough, sore throat, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue, or headache), and influenza virus was known to be circulating in the community. Subjects were randomized to receive oral oseltamivir phosphate capsules or placebo for 5 days. All enrolled subjects were allowed to take fever-reducing medications.

Of 1,355 subjects enrolled in these two trials, 849 (63%) subjects were influenza-infected (median age 34 years; 52% male, 80% Caucasian, 31% smokers). Of the 849 influenza-infected subjects, 85% were infected with influenza A, 5% with influenza B, and 2% with influenza of unknown type.

Study medication was started within 40 hours of onset of symptoms and administered twice daily for 5 days. Subjects were required to self-assess the influenza-associated symptoms (nasal congestion, sore throat, cough, aches, fatigue, headaches, and chills/sweats) twice daily as "none," "mild," "moderate," or "severe." Time to improvement was calculated from the time of treatment initiation to the time when all symptoms were assessed as "none" or "mild." In both trials, there was a 1.3-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate capsules 75 mg twice a day for 5 days compared to subjects who received placebo. Subgroup analyses by gender showed no differences in the treatment effect of oseltamivir phosphate capsules in men and women.

In the treatment of influenza, no increased efficacy was demonstrated in subjects who received higher doses of oseltamivir phosphate capsules.

###### Adolescents and Adults with Chronic Cardiac or Respiratory Disease

A double-blind, placebo-controlled, multicenter trial was unable to demonstrate efficacy of oseltamivir phosphate capsules (75 mg twice daily for 5 days) in the treatment of influenza in adult and adolescent subjects (13 years of age) with chronic cardiac (excluding chronic idiopathic hypertension) or respiratory diseases, as measured by time to alleviation of all symptoms. However, in patients treated with oseltamivir phosphate capsules there was a more rapid cessation of febrile illness. No difference in the incidence of influenza complications was observed between the treatment and placebo groups in this population.

###### Geriatric Subjects

Three double-blind placebo-controlled treatment trials were conducted in subjects who were at least 65 years of age in three consecutive seasons. The enrollment criteria were similar to that of adult trials with the exception of fever being defined as higher than 97.5°F. Of 741 subjects enrolled, 476 (65%) subjects were influenza-infected; of these, 96% were infected with influenza type A and 5% with influenza type B.

In the pooled analysis, there was a 1-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate capsules 75 mg twice daily for 5 days compared to those who received placebo (n=48) [See *Use in Specific Populations (8.5)*]. Some seasonal variability was noted in the clinical efficacy outcomes.

###### Pediatric Subjects (1 year to 12 years of age)

One double-blind placebo-controlled treatment trial was conducted in pediatric subjects aged 1 year to 12 years (median age 5 years) who had fever (at least 100°F) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. Of 698 subjects enrolled in this trial, 452 (65%) were influenza-infected (50% male, 68% Caucasian). Of the 452 influenza-infected subjects, 67% were infected with influenza A and 33% with influenza B.

The efficacy in this trial was determined by the time to alleviation or resolution of influenza signs and symptoms, measured by a composite endpoint that required the following four individual conditions be met: i) alleviation of cough, ii) alleviation of coryza, iii) resolution of fever, and iv) parental opinion of a return to normal health and activity. Oseltamivir phosphate treatment of 2 mg per kg twice daily, started within

## PATIENT INFORMATION

### Oseltamivir phosphate capsules USP, for oral use (os-el-TAM-ih-veer)

#### What is oseltamivir phosphate capsules?

Oseltamivir phosphate capsules is a prescription medicine used to:

- treat the flu (influenza) in people 2 weeks of age and older who have had flu symptoms for no more than two days.
- prevent the flu in people who are 1 year of age and older.

It is not known if oseltamivir phosphate capsules is:

- effective in people who start treatment after 2 days of developing flu symptoms.
- effective for the treatment of the flu in people with long-time (chronic) heart problems or breathing problems.
- effective for the treatment or prevention of flu in people who have weakened immune systems (immunocompromised).
- safe and effective for the treatment of the flu in children less than 2 weeks of age.
- safe and effective in the prevention of the flu in children less than 1 year of age.

Oseltamivir phosphate capsules does not treat or prevent illness that is caused by infections other than the influenza virus.

Oseltamivir phosphate capsules does not prevent bacterial infections that may happen with the flu.

Oseltamivir phosphate capsules is not recommended for people with end-stage renal disease (ESRD) who are not receiving dialysis.

**Oseltamivir phosphate capsules does not take the place of receiving a flu vaccination. Talk to your healthcare provider about when you should receive an annual flu vaccination.**

#### Who should not take oseltamivir phosphate capsules?

Do not take oseltamivir phosphate capsules if you are allergic to oseltamivir phosphate or any of the ingredients in oseltamivir phosphate capsules. **See the end of this leaflet for a complete list of ingredients in oseltamivir phosphate capsules.**

#### What should I tell my healthcare provider before taking oseltamivir phosphate capsules?

**Before you take oseltamivir phosphate capsules, tell your healthcare provider if you:**

- have problems swallowing oseltamivir phosphate capsules.
- have kidney problems
- have any other medical conditions

- are pregnant or plan to become pregnant. Available information indicate that oseltamivir phosphate capsules does not increase the risk of birth defects.
- are breastfeeding or plan to breastfeed. Oseltamivir phosphate can pass into breast milk in small amounts.

**Tell your healthcare provider about all the medicines you take,** including prescription or over-the-counter medicines, vitamins, and herbal supplements.

**Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.**

#### How should I take oseltamivir phosphate capsules?

- Take oseltamivir phosphate capsules exactly as your healthcare provider tells you to.
- Take oseltamivir phosphate capsules with food or without food. There is less chance of stomach upset if you take oseltamivir phosphate capsules with food.
- If you miss a dose of oseltamivir phosphate capsules, take it as soon as you remember. If it is 2 hours or less before your next dose, do not take the missed dose. Take your next dose of oseltamivir phosphate capsules at your scheduled time. Do not take 2 doses at the same time.
- If oseltamivir phosphate for oral suspension is not available or you cannot swallow oseltamivir phosphate capsules, your healthcare provider or pharmacist may instruct you to open oseltamivir phosphate capsules and mix the capsules contents with sweetened liquids such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water).
- **If your healthcare provider or pharmacist has instructed you to take oseltamivir phosphate for oral suspension or open your oseltamivir phosphate capsules, read the detailed Instructions for Use at the end of this leaflet. Ask your pharmacist if you have any questions.**

#### What are the possible side effects of oseltamivir phosphate capsules?

Oseltamivir phosphate capsules may cause serious side effects, including:

- **Serious skin and allergic reactions.** Oseltamivir phosphate capsules can cause serious skin and allergic reactions. Stop taking oseltamivir phosphate capsules and get medical help right away if you get any of the following symptoms:
  - skin rash or hives
  - swelling of your face, eyes, lips, tongue, or throat
  - your skin blisters and peels
  - trouble breathing
  - blisters or sores in your mouth
  - chest pain or tightness
  - itching

- **Change in behavior.** People, especially children, who have the flu, can develop nervous system problems and abnormal behavior that can lead to death. During treatment with oseltamivir phosphate capsules, tell your healthcare provider right away if you or your child have confusion, speech problems, shaky movements, seizures, or start hearing voices or seeing things that are not really there (hallucinations).

The most common side effects of oseltamivir phosphate capsules when used for treatment of the flu include nausea, vomiting, and headache.

The most common side effect of oseltamivir phosphate capsules when used for prevention of the flu include nausea, vomiting, headache, and pain.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of oseltamivir phosphate capsules.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store oseltamivir phosphate capsules?**

- Store oseltamivir phosphate capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away any unused oseltamivir phosphate capsules that are out of date or no longer needed.

#### **Keep oseltamivir phosphate capsules and all medicines out of the reach of children.**

#### **General information about the safe and effective use of oseltamivir phosphate capsules.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use oseltamivir phosphate capsules for a condition for which it was not prescribed. Do not give oseltamivir phosphate capsules to other people, even if they have the same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about oseltamivir phosphate capsules that is written for health professionals. For more information, **contact Alvogen, distributor for Natco Pharma Limited at 1-866-770-3024.**

#### **What are the ingredients in oseltamivir phosphate capsules?**

**Active ingredient:** oseltamivir phosphate

#### **Inactive ingredients:**

**Oseltamivir phosphate capsules:** Croscarmellose sodium, povidone K-30, pregelatinized starch, sodium stearyl fumarate and talc.

**The 30 mg shell (yellow / yellow) contains:** Gelatin, iron oxide red, iron oxide yellow, purified water and titanium dioxide.

**The 45 mg shell (grey / grey) contains:** Gelatin, iron oxide

black, purified water and titanium dioxide.

**The 75 mg shell (yellow / grey) contains:** Gelatin, iron oxide black (in body), iron oxide red, iron oxide yellow (in cap), purified water and titanium dioxide.

Manufactured by:  
**NATCO PHARMA LIMITED**  
Kothur- 509 228,  
India.

Distributed by:  
**Alvogen, Inc.**  
Pine Brook, NJ 07058 USA

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised 06/2016

### **INSTRUCTIONS FOR USE**

#### **Oseltamivir phosphate capsules USP, for oral use (os-el-TAM-ih-veer)**

#### **How do I mix the contents of oseltamivir phosphate capsules with sweetened liquids, if directed by my healthcare provider or pharmacist?**

#### **You will need:**

- the prescribed dose of oseltamivir phosphate capsules
- a small bowl
- sweetened liquid, such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water)

Step 1. Open the contents of the prescribed dose of oseltamivir phosphate capsules into a small bowl.

Step 2. Add a small amount of the sweetened liquid to the capsule contents.

Step 3. Stir the mixture and give the entire dose of oseltamivir phosphate.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised 06/2016