OSELTAMIVIR PHOSPHATE, oseltamivir phosphate for oral suspension
Zydus Pharmaceuticals (USA) Inc.

INDICATIONS AND USAGE
Oseltamivir Phosphate is an influenza neuraminidase inhibitor (NAI) indicated for:

1.1 Treatment of Influenza
Oseltamivir Phosphate for Oral Suspension 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
Oseltamivir Phosphate for Oral Suspension is indicated for the prophylaxis of influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours.

1.3 Limitations of Use
Oseltamivir Phosphate for Oral Suspension is not a substitute for early influenza vaccination.

2 DOSAGE AND ADMINISTRATION
2.1 Dosage and Administration Overview
Full prescribing information is available at www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact Zydus at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

2.2 Recommended Dosage for Treatment of Influenza

- Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days (2.2).
- Patients weighing 30 kg or less: 30 mg once daily for 5 days (2.2).
- Patients weighing more than 30 kg: 30 mg once daily for 5 days (2.2).
- Children weighing 10 kg or more: 3 mg/kg once daily for 5 days (2.2).
- Children weighing less than 10 kg: 30 mg once daily for 5 days (2.2).
- Children under 1 year of age: 3 mg/kg once daily for 5 days (2.2).

2.3 Recommended Dosage for Prophylaxis of Influenza

- Adults and adolescents (13 years and older): 75 mg once daily for 10 days (2.3).
- Patients weighing 30 kg or less: 30 mg once daily for 10 days (2.3).
- Patients weighing more than 30 kg: 30 mg once daily for 10 days (2.3).
- Children weighing 10 kg or more: 3 mg/kg once daily for 10 days (2.3).
- Children weighing less than 10 kg: 30 mg once daily for 10 days (2.3).
- Children under 1 year of age: 3 mg/kg once daily for 10 days (2.3).

Community outbreak: Based on weight once daily for up to 6 weeks (2.3).

3 DOSAGE FORMS AND STRENGTHS
Oseltamivir Phosphate for Oral Suspension is available in packets containing 14.3 mg of oseltamivir phosphate per 5 mL of suspension.

4 CONTRAINDICATIONS
Serious skin/hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and exfoliative dermatitis: Do not use oseltamivir phosphate for prophylaxis and treatment if serious skin/hypersensitivity reactions occur or are suspected (5.2).

Neuropsychiatric events: Patients with influenza, including those receiving oseltamivir phosphate for oral suspension, may experience serious neuropsychiatric events such as acute onset of mania, manic episodes, psychosis, agitation, delirium, hallucinations, and delusions (5.1).

5 WARNINGS AND PRECAUTIONS
5.1 Serious Skin/Hypersensitivity Reactions
- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis
- Multiforme
- Discontinue oseltamivir phosphate for oral suspension and initiate appropriate treatment if allergic-like reactions occur or are suspected (5.2).

5.2 Neuropsychiatric Events
Neuropsychiatric events: Patients with influenza, including those receiving oseltamivir phosphate for oral suspension, may experience serious neuropsychiatric events such as acute onset of mania, manic episodes, psychosis, agitation, delirium, hallucinations, and delusions (5.1).

6 ADVERSE REACTIONS
6.1 General Trends
General trends: Symptoms of influenza include fever, myalgia, and headache (6.1).

6.2 Postmarketing
Adverse reactions which have been reported during postmarketing experience following the use of oseltamivir phosphate for oral suspension are listed in Table 1 (6.2).

6.3 Dose-Related Reactions
Dose-related reactions: A dose relationship for neuropsychiatric events has been seen (6.3).

6.4 Laboratory Abnormalities
Laboratory abnormalities: The most frequently reported laboratory abnormality is elevated hepatic enzymes (6.4).

7 DRUG INTERACTIONS
7.1 Other Antivirals
- Oseltamivir phosphate for oral suspension is not a substitute for early influenza vaccination.

7.2 Other Medicated Products
Oseltamivir phosphate for oral suspension is not a substitute for early influenza vaccination (7.2).

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Renal Impairment
8.6 Hepatic Impairment
8.7 Women of Childbearing Potential
8.8 Use in Patients with Chronic Conditions
8.9 Use in Patients with Renal and Hepatic Impairment

9 DRUG LABORATORY TESTS
9.1 Plasma and Serum levels
Plasma and serum levels: Monitor plasma and serum levels of oseltamivir phosphate in patients who have impaired renal function (9.1).

10 NONCLINICAL TOXICOLOGY
10.1 Carcinogenesis
10.2 Mutagenesis
10.3 Impairment of Fertility

11 DESCRIPTION
Oseltamivir phosphate for oral suspension is a white or almost white, polysiloxane, gelatin-based, oropharyngeal dosage form containing 14.3 mg of oseltamivir phosphate per 5 mL of suspension (11).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Oseltamivir phosphate for oral suspension is an influenza neuraminidase inhibitor (NAI) which is a synthetic compound with a benzimidazole moiety (12.1).

12.2 Pharmacokinetics
Pharmacokinetics: Oseltamivir phosphate is rapidly absorbed from the gastrointestinal tract and is rapidly converted to its active metabolite, oseltamivir carboxylate (12.2).

12.3 Pharmacodynamics
Pharmacodynamics: Oseltamivir phosphate for oral suspension inhibits the neuraminidase enzyme of influenza A and B viruses (12.3).

12.4 Special Populations
Special populations: In patients with impaired renal function, the plasma clearance and half-life of oseltamivir phosphate are increased (12.4).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis
13.2 Mutagenesis
13.3 Impairment of Fertility

14 CLINICAL STUDIES
14.1 Treatment of Influenza
Oseltamivir phosphate for oral suspension 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 (14.1).

14.2 Prophylaxis of Influenza
Oseltamivir phosphate for oral suspension is indicated for the prophylaxis of influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours (14.2).

15 ADVERSE REACTIONS
Adverse reactions: Adverse reactions which have been reported during postmarketing experience following the use of oseltamivir phosphate for oral suspension are listed in Table 1 (15).

16 HOW SUPPLIED/STORAGE AND HANDLING
How supplied: Oseltamivir phosphate for oral suspension is available in packets containing 14.3 mg of oseltamivir phosphate per 5 mL of suspension in bottles of 100 (16).

17 PATIENT COUNSELING INFORMATION
Patient counseling: Patients should be informed of the importance of early influenza vaccination (17).
2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

Administer oseltamivir phosphate for oral suspension 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)) using:

- Oseltamivir phosphate for oral suspension (as a powder). This is the preferred formulation (6 mg per mL) for patients who cannot swallow capsules. Prior to use, the supplied oseltamivir phosphate for oral suspension must be constituted with water by the pharmacist to produce the oral suspension (see Dosage and Administration (2.5)).

The oral suspension may be taken with or without food; however, tolerability may be influenced if oseltamivir phosphate for oral suspension is taken with food.

Adjust the oseltamivir phosphate for oral suspension dosage in patients with moderate or severe renal impairment (see Dosage and Administration (2.6)).

For patients who cannot swallow capsules, oseltamivir phosphate for oral suspension is the preferred formulation.

2.2 Recommended Dosage for Treatment of Influenza

Initiate treatment with oseltamivir phosphate for oral suspension within 48 hours of influenza symptom onset.

Adults and Adolescents (13 years of age and older)

The recommended oral dose of oseltamivir phosphate for oral suspension for treatment of influenza in adults and adolescents 13 years and older is 7.5 mg once daily (12.5 mL of oral suspension) twice daily for 5 days.

Pediatric Patients (2 weeks of age through 12 years of age)

Table 1 displays the recommended dosage of oseltamivir phosphate for oral suspension for treatment of influenza in pediatric patients 2 weeks of age through 12 years of age and provides information about prescribing the formulation for oral suspension.

2.3 Recommended Dosage for Prophylaxis of Influenza

Initiate post-exposure prophylaxis with oseltamivir phosphate for oral suspension within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with oseltamivir phosphate for oral suspension during a community outbreak.

Adults and Adolescents (12 years of age and older)

The recommended dosage of oseltamivir phosphate for oral suspension for prophylaxis of influenza in adults and adolescents 12 years and older is 7.5 mg once daily (12.5 mL of oral suspension) twice 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, oseltamivir phosphate for oral suspension may be continued for up to 12 weeks (see Use in Specific Populations (8.5)). The duration of prophylaxis for up to 6 weeks as long as oseltamivir phosphate for oral suspension is continued.

Pediatric Patients (2 years of age and older)

Table 2 displays the recommended oral dosage of oseltamivir phosphate for oral suspension for prophylaxis of influenza in pediatric patients 2 years of age through 12 years of age based on body weight and provides information about prescribing the formulation for oral suspension. Prophylaxis in pediatric patients is recommended for 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak (see Use in Specific Populations (8.4) and Clinical Studies (14.2)).

### Table 1: Oral Oseltamivir Phosphate Dosage for Oral Suspension Recommendations in Pediatric Patients for Treatment of Influenza

<table>
<thead>
<tr>
<th>Weight</th>
<th>Treatment Regimen for 5 Days</th>
<th>Prophylaxis Regimen for 10 Days</th>
<th>Volume of Oral Suspension (6 mg/mL) for Each Dose</th>
<th>Number of Bottles of Oral Suspension to Administer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients from 2 Weeks to less than 1 Year of Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any weight</td>
<td>45 mg (5 mL)</td>
<td>30 mg once daily</td>
<td>0.5 mL</td>
<td>1 bottle</td>
</tr>
<tr>
<td>Patients 1 to 12 Years of Age Based on Body Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 kg or less</td>
<td>30 mg (4 mL)</td>
<td>5 mg once daily</td>
<td>0.5 mL</td>
<td>1 bottle</td>
</tr>
<tr>
<td>5.1 kg to 10 kg</td>
<td>45 mg (6 mL)</td>
<td>7.5 mg once daily</td>
<td>0.75 mL</td>
<td>2 bottles</td>
</tr>
<tr>
<td>10.1 kg to 15 kg</td>
<td>60 mg (8 mL)</td>
<td>10 mg once daily</td>
<td>1 mL</td>
<td>2 bottles</td>
</tr>
<tr>
<td>15.1 kg to 20 kg</td>
<td>75 mg (10 mL)</td>
<td>15 mg once daily</td>
<td>1.5 mL</td>
<td>3 bottles</td>
</tr>
<tr>
<td>20.1 kg to 25 kg</td>
<td>90 mg (12 mL)</td>
<td>22.5 mg once daily</td>
<td>2.25 mL</td>
<td>3.5 bottles</td>
</tr>
<tr>
<td>25.1 kg to 30 kg</td>
<td>105 mg (14 mL)</td>
<td>30 mg once daily</td>
<td>3 mL</td>
<td>4 bottles</td>
</tr>
<tr>
<td>30.1 kg to 35 kg</td>
<td>120 mg (16 mL)</td>
<td>40 mg once daily</td>
<td>3.75 mL</td>
<td>5 bottles</td>
</tr>
</tbody>
</table>

* The recommended duration for post-exposure prophylaxis is 10 days and the recommended duration for community outbreak (mass-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients). Post-exposure prophylaxis may be greater than 10 days for post-exposure prophylaxis.

* An oral dosing dispensing device that measures the appropriate volume in mL should be used with the oral suspension.

* Use non-dosing dispensing device to measure the appropriate volume in mL with the oral suspension.

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 (less than or equal to 90 mL/minute). Dosage modifications are recommended in adults with estimated creatinine clearance less than or equal to 60 mL per minute and in patients with moderate or severe renal impairment.

### Table 2: Recommended Dosage Adjustments for Treatment and Prophylaxis of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis

<table>
<thead>
<tr>
<th>Renal Impairment (Creatinine Clearance)</th>
<th>Recommended Treatment Regimen</th>
<th>Recommended Prophylaxis Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (≥50 mL/min)</td>
<td>75 mg twice daily for 5 days</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Moderate (≥30-50 mL/min)</td>
<td>30 mg twice daily for 5 days</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>Severe (≤30 mL/min)</td>
<td>30 mg once daily for 5 days</td>
<td>30 mg every other day</td>
</tr>
<tr>
<td>ESRD Patients on Hemodialysis (≤10 mL/min)</td>
<td>30 mg immediately and then 30 mg after hemodialysis cycle (treatment duration not to exceed 5 days)</td>
<td>30 mg immediately and then 30 mg after alternate hemodialysis cycles</td>
</tr>
<tr>
<td>ESRD Patients on Continuous Ambulatory Peritoneal Dialysis (≤10 mL/min)</td>
<td>A single 30 mg dose administered immediately</td>
<td>30 mg immediately and then 30 mg once weekly</td>
</tr>
</tbody>
</table>
| ESRD Patients Not on Dialysis | Oseltamivir Phosphate for Oral Suspension is not recommended | Osaka.

* Oseltamivir phosphate for oral suspension can be used for 10 mg dosing.

* The recommended duration for post-exposure prophylaxis is at least 10 days and the recommended duration for community outbreak (mass-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients). Post-exposure prophylaxis may be greater than 10 days for post-exposure prophylaxis.

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.

2.5 Preparation and Storage of Constituted Oseltamivir Phosphate for Oral Suspension

Prior to dispensing in the patient, constitute oseltamivir phosphate for oral suspension (supplied as a powder):

1. Tap the closed bottle containing the oseltamivir phosphate powder several times to loosen the powder.
2. Measure 25 mL of water in a graduated cylinder.
3. Add the total amount of water for constitution to the bottle.
4. Close bottle with child-resistant cap tightly and shake the closed bottle well for 15 seconds.
5. Label the bottle with written instructions to Shake Well Before Use.

The constituted oral suspension contains 360 mg of oseltamivir base per 60 mL of volume (6 mg per mL) and is white, fruit-flavored. Use the constituted oral suspension within 17 days of preparation whenever stored under refrigeration, 2° to 8°C (36° to 46°F), or within 10 days if stored at controlled room temperature, 20° to 25°C (68° to 77°F). Write the expiration date of the constituted oral suspension on the bottle label.

Oral Suspension (see Microbiology (12.2)).

- Oseltamivir Phosphate for Oral Suspension is not recommended for patients with oral/nasal respiratory disease not undergoing dialysis (see Dosage and Administration (2.6) and Use in Specific Populations (8.6)).
5.6 Fructose Intolerance in Patients with Hereditary Fructose Intolerance

Fructose cannot be handled by patients with hereditary fructose intolerance. One dose of 75 mg oseltamivir phosphate for oral suspension delivers 2 grams of sorbitol. This is above the daily maximum limit of sorbitol for patients with hereditary fructose intolerance, and may cause diarrhea and flatulence.

4 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in labeling:

• Serious skin reactions (see Warnings and Precautions (5.1))

4.1 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. Also, adverse reaction rates observed in clinical trials may not reflect the rates observed in practice. Adverse reactions occurring in clinical trials of oseltamivir phosphate are discussed in the following order:

5.3 Risk of Bacterial Infections

There is no evidence for efficacy of oseltamivir phosphate for oral dosing 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. Oseltamivir phosphate for oral dosing has not been shown to prevent such complications. Prescribers should be alert to the potential for secondary bacterial infections and treat them as appropriate.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Treatment Trials</th>
<th>Prophylaxis Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oseltamivir Phosphate 75 mg twice daily (n = 1977)</td>
<td>Placebo (n = 1953)</td>
</tr>
<tr>
<td></td>
<td>Oseltamivir Phosphate 75 mg once daily (n = 2646)</td>
<td>Placebo (n = 1286)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Serious System Disorders</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>General Disorders</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in 2% of adults and adolescents and 1% or greater in oseltamivir phosphate-treated subjects compared to placebo-treated subjects are shown in Table 5. These events are listed by System Organ Class and ordered alphabetically within each class. Adverse reactions occurring in at least 1% of subjects in any treatment group are discussed in this section. 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 infectious and inflammatory events and subjects “at risk” (subjects with 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 of the subjects “at risk” was qualitatively similar to that in otherwise healthy adults/adolescents.

6.1 Clinical Trials Experience

Table 5 includes an incomplete list of adverse reactions that occurred in clinical trials of oseltamivir phosphate. Adverse reactions occurring in ≥1% of oseltamivir phosphate-treated adults and adolescents compared to placebo-treated 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 infectious and inflammatory events and subjects “at risk” (subjects with 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 of the subjects “at risk” was qualitatively similar to that in otherwise healthy adults/adolescents.

5.2 Neuropsychiatric Events

Neuropsychiatric events may occur in patients receiving oseltamivir phosphate. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious serious disease. Close monitoring of oseltamivir phosphate-treated patients for signs of abnormal behavior is recommended. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing oseltamivir phosphate for oral dosing for each patient.

4 CONTRAINDICATIONS

Oseltamivir Phosphate for Oral Suspension: 6 mg per mL (final concentration when constituted) as a white to light yellow powder blend for oral suspension. Contains sorbitol and citric acid. This product is not recommended for patients with known serious hypersensitivity to oseltamivir phosphate [see Warnings and Precautions (5.1)].
8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with oseltamivir phosphate for oral suspension in pregnant women to inform a drug-associated risk of adverse development outcomes. An available published epidemiological study suggests that oseltamivir phosphate for oral suspension, initiated at any time, is not associated with an increased risk of birth defects. However, these studies included a limited number of exposures and therefore the results may not reflect the risk in a larger population. When oseltamivir phosphate was administered to rats and rabbits during organogenesis, a maternally toxic dose was associated with teratogenic effects, including minor skeletal malformations. In rats, embryofetal effects consisting of a decreased number of live fetuses and increased fetal resorptions were observed at a maternally toxic dose, which precludes a definitive assessment of the risk (see Clinical Pharmacology [12.3]). In animal reproduction studies with oseltamivir, no adverse developmental effects were observed at clinically relevant exposures (see Data).

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In U.S. general population, the estimated background risk of major birth defects and miscarriage is 2.4% and 15.0%, respectively.

Clinical Considerations

Disorder-Normalized Mortality under Zika Virus Risk

Pregnant women are at higher risk of severe complications from influenza, which can lead to adverse pregnancy and/or neonatal outcomes including maternal death, stillbirth, birth defects, preterm delivery, low birth weight and small for gestational age.

Data

Published prospective and retrospective observational studies of more than 5,000 women exposed to oseltamivir phosphate during pregnancy including more than 2,600 women exposed in the first trimester suggest that the observed rate of congenital malformations was not increased above the rate in the general comparison population, regardless of when therapy was administered during the gestational period. However, individually, none of these studies had adequate sample sizes and some lacked information on dose which precludes a definitive assessment of the risk.

Animal Data

Oseltamivir was administered orally during organogenesis to pregnant rats (at 20, 260, or 1,550 mg/kg/day on gestation days 6 to 15) and rabbits (at 50, 250, or 1,550 mg/kg/day on gestation days 6 to 18). Fetal, embryofetal effects consisting of an increased incidence of minor skeletal malformations were observed at a maternally toxic dose (1,550 mg/kg/day) resulting in systemic drug exposures based on AUC for oseltamivir carboxylate 44 times human exposures at the maximum recommended human dose (MRHD) of oseltamivir phosphate (75 mg twice a day). In the rabbit study, maternal effects consisting of an increased incidence of minor skeletal abnormalities and variation were observed at a maternally toxic dose (1,550 mg/kg/day) resulting in systemic drug exposures based on AUC for oseltamivir carboxylate 190 times human exposures at the MRHD of oseltamivir phosphate.

In rats, embryofetal effects consisting of an increased incidence of minor skeletal abnormalities and variation were observed at maternally toxic doses (≥150 mg/kg/day) resulting in systemic drug exposures based on AUC for oseltamivir carboxylate 190 times human exposures at the maximum recommended human dose (MRHD) of oseltamivir phosphate (75 mg twice a day). In the rabbit study, maternal effects consisting of an increased incidence of minor skeletal abnormalities and variation were observed at a maternally toxic dose (1,550 mg/kg/day). No adverse maternal or offspring effects were observed at doses (200 mg/kg/day) resulting in systemic drug exposures based on AUC for oseltamivir carboxylate 44 times human exposures at the MRHD of oseltamivir phosphate.

8.2 Lactation

Risk Summary

Based on limited published data, oseltamivir and oseltamivir carboxylate have been shown to be present in human milk at low levels considered unlikely to lead to toxicity in the breastfed infant. It is not known whether oseltamivir affects human milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oseltamivir phosphate and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Data

Clinical pharmacokinetics have been assessed in breastfed infants whose mothers were treated with oseltamivir phosphate for 1 week. The milk:plasma ratio of oseltamivir was 0.72. Breastfed infants may experience an effect of oseltamivir exposure on milk production, but the impact of even high levels of oseltamivir exposure on human milk production is not known.

It is not known whether oseltamivir affects human milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oseltamivir phosphate and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

8.4 Pediatric Use

8.4.1 Treatment of Influenza

The safety and efficacy of oseltamivir phosphate for the treatment of influenza in pediatric patients 2 weeks to less than 1 year of age has been established (see Dosage and Administration [2.2], Clinical Pharmacology [12.3], and Clinical Studies [14.1]) and is based on:

- 123 to 17 years of age: Safety and efficacy in adolescent patients 13 to 17 years of age was supported by adequate and well-controlled trials in adults and adolescents and younger pediatric patients and safety data in adolescents treated with oseltamivir phosphate in a study of treatment and prophylaxis.
- 1 year to 12 years of age: Safety and efficacy in pediatric patients 1 year to 12 years of age was supported by results of one double-blind, placebo-controlled trial in 652 pediatric patients with influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily or placebo administered within 48 hours of symptom onset (see Clinical Studies [14.1]). Additional safety information was provided in a double-blind, placebo-controlled trial in pediatric patients 6 to 12 years of age with laboratory-confirmed influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily for 5 days (see Clinical Pharmacology [12.3]).
- 1 to 12 years of age: Safety and efficacy in pediatric patients 1 to 12 years of age was supported by results of a double-blind, placebo-controlled trial in 542 pediatric patients with influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily of placebo administered within 48 hours of symptom onset (see Clinical Studies [14.1]). Additional safety information was provided in a double-blind, placebo-controlled trial in pediatric patients 6 to 12 years of age with laboratory-confirmed influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily for 5 days (see Clinical Pharmacology [12.3]).
- 13 to 17 years of age: Efficacy and safety in adolescent patients 13 to 17 years of age was supported by results of one double-blind, placebo-controlled trial in 652 pediatric patients with influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily or placebo administered within 48 hours of symptom onset (see Clinical Studies [14.1]).

The safety and efficacy of oseltamivir phosphate for treatment of influenza in pediatric patients less than 2 weeks of age have not been established.

8.4.2 Prophylaxis of Influenza

The safety and efficacy of oseltamivir phosphate for prophylaxis of influenza in pediatric patients 1 year to 12 years of age has been established (see Dosage and Administration [2.2], Clinical Pharmacology [12.3], and Clinical Studies [14.1]) and is based on:

- 123 to 17 years of age: Prophylaxis in adolescent patients 13 to 17 years of age is supported by one randomized, placebo-controlled, post-exposure prophylaxis trial of oseltamivir phosphate 75 mg twice daily for 7 days in household contacts including 207 adolescents (see Clinical Studies [14.2]).
- 14 to 17 years of age: Oseltamivir phosphate for prophylaxis in pediatric patients 1 year to 12 years of age is supported by one randomized, placebo-controlled, post-exposure prophylaxis trial of oseltamivir phosphate 75 mg twice daily for 7 days in household contacts including 207 adolescents (see Clinical Studies [14.2]).
- 1 to 12 years of age: Oseltamivir phosphate for prophylaxis in pediatric patients 1 year to 12 years of age is supported by one randomized, placebo-controlled, post-exposure prophylaxis trial of oseltamivir phosphate 2 mg per kg per os twice daily for 10 days in household contacts including 207 adolescents (see Clinical Studies [14.2]).
- 13 to 17 years of age: Efficacy and safety in adolescent patients 13 to 17 years of age was supported by results of a double-blind, placebo-controlled trial in 652 pediatric patients with influenza who received oral oseltamivir phosphate 2 mg per kg per os twice daily for 5 days (see Clinical Studies [14.2]).

The safety and efficacy of oseltamivir phosphate for prophylaxis of influenza in pediatric patients less than 2 weeks of age have not been established.

8.5 Geriatric Use

No dose adjustment is needed for either oseltamivir or the concomitant drug when coadministering with oseltamivir phosphate for oral suspension.
were 65 years and older, while 364 (27%) were 75 years and older. In these double-blind, placebocontrolled trials in the treatment of influenza in patients at least 65 years old, 79 subjects (274 received placebo and 362 received oseltamivir phosphate) in various degrees of renal impairment and 5 degrees of hepatic impairment were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects [see Clinical Studies (14.4)].

Renal Impairment

Of the 4,651 subjects in clinical trials of oseltamivir phosphate for the prophylaxis of influenza, 1,046 (22%) were 65 years and older, while 739 (16%) were 75 years and older. In a combined, placebocontrolled trial in elderly residents of nursing homes who took oseltamivir phosphate for up to 42 days for the prophylaxis of influenza (oseltamivir phosphate in 276, placebo in 275), no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects [see Clinical Studies (14.2)].

8.6 Renal Impairment

Patients with renal impairment had higher blood levels of oseltamivir carboxylate compared to patients with normal renal function but the increased risk of oseltamivir phosphate-associated adverse events was not directly related to the increased oseltamivir carboxylate. No single patient had a serum creatinine concentration of greater than 10 and 50 μmol/L, and mild and moderate renal impairment (10 to 50 and 50 to 100 μmol/L) respectively, and severe renal impairment (serum creatinine >100 μmol/L) respectively were identified. Oseltamivir phosphate for oral suspension is recommended for patients with ESRD not undergoing dialysis [see Indications and Usage (3.3) and Clinical Pharmacology (12.2)].

8.7 Hepatic Impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. The safety and pharmacokinetic interactions in patients with severe hepatic impairment have not been evaluated [see Clinical Pharmacology (12.3)].

8.8 Use in Patients with Chronic Conditions

Efficacy of oseltamivir phosphate in the treatment of influenza in patients with chronic cardiac disease and/or respiratory disease was evaluated in one uncontrolled, placebo-controlled clinical trial. Efficacy in this trial population, as measured by time to alleviation of all symptoms, was not established, but no new safety signals were identified [see Clinical Studies (14.3)].

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 for the treatment or prophylaxis of influenza has not been established in immunocompromised patients [see Clinical Studies (14.3)]. Safety of oseltamivir phosphate has been demonstrated for up to 12 weeks for prophylaxis of influenza in immunocompromised patients [see Adverse Reactions (6.1)].

10 OVERDOSE

Reports of overdoses with oseltamivir phosphate have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, adverse reactions were reported. Adverse reactions reported following overdose were similar in nature to those observed with therapeutic doses of oseltamivir phosphate [see Adverse Reactions (6)].

11 DESCRIPTION

Oseltamivir Phosphate for Oral Suspension, an influenza neuraminidase inhibitor (NAI), is available as a powder for oral suspension, which when constituted with water as directed contains 6 mg per mL oseltamivir base. In addition to the active ingredient, the powder for oral suspension contains sorbitol, titanium dioxide, sodium gum, sodium benzoate, monosodium citrate, tartaric flavoring, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (8R,9S)-5-(2-amino-3-oxo-4-phenylpyrrol-1-yl)cyclohex-1-ene-1-carboxylic acid, O4H6; oseltamivir phosphate (0:1). The chemical formula is C18H19N3O4P·H2O (free base). The molecular weight is 512.4 for oseltamivir free base and 604.4 for oseltamivir phosphate salt. The structural formula is as follows:

8.10 Use in Patients with Renal Impairment

Adverse Reactions (6.1)

The volume of distribution (Vss) of oseltamivir carboxylate, following intravenous administration in 24 subjects (oseltamivir phosphate is not available as an IV formulation), range between 26.28 and 51.32. The binding of oseltamivir carboxylate to human plasma protein is 93%. The binding of oseltamivir to human plasma protein is 45%, which is insufficient to cause significant drug interactions.


drug interactions.

Absorption

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 no 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 enzymes 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 (<95%) by renal excretion.

Brown (1988, 198) states: "Inorganic phosphate (see Clinical Pharmacology (12.3)) causes a marked reduction in oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 7. Th
Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children.

Resistance

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus strains and there are insufficient pharmacokinetics and safety data to recommend a dose adjustment for pregnant women [see Use in Specific Populations (8.4)].

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.

Pediatric Subjects (1 year to less than 12 years of age) A pharmacokinetic analysis indicates that the mean exposure to the active metabolite in pediatric subjects aged 1 to 12 years was approximately 3-fold higher than in patients with normal renal function who received 75 mg oseltamivir daily. The pharmacokinetics of oseltamivir carboxylate in children (1 to 12 years of age) were similar to the pharmacokinetics of oseltamivir in the geriatric population (12 years and older). The pharmacokinetics of oseltamivir in healthy pediatric subjects aged ≥1 year have been evaluated in single-dose and multiple-dose studies. The pharmacokinetics of oseltamivir carboxylate in children aged 2 weeks to less than 1 year have been evaluated in single-dose studies. The pharmacokinetics of oseltamivir carboxylate in pediatric subjects aged less than 1 year have not been evaluated.
treatment study of immunocompromised subjects, treatment-associated genotype resistance was detected in 27% (53/198), 12% (4/33), and 1% (2/182) of influenza A/H1N1, A/H3N2, and B virus infections, respectively. Treatment-emergent resistance was observed at a higher frequency in hematopoietic stem cell transplant recipients (12% [2/19]).

The frequency of resistance selection in oseltamivir and the frequency of resistance in various subtypes vary seasonally and geographically.

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance-associated substitution H275Y was found to be more resistant than 15% of circulating 2008 H1N1 influenza virus isolates. The 2009 H1N1 influenza virus (‘swine flu’) was almost uniformly susceptible in oseltamivir. However, the frequency of circulating seasonal variants change from week to week. Prescribers should consider available information from the CDC on influenza virus drug susceptibility patterns and treatment effects before deciding whether to use oseltamivir phosphate for oral suspension.

Cross-resistance

Cross-resistance between oseltamivir and amantadine has been observed in neuraminidase biochemical assays. The H275Y (I numbering) or NS293 (II numbering) neuraminidase resistance-associated substitutions observed in the N1 neuraminidase subtype and the E107K or NS293 oseltamivir resistance-associated substitutions observed in the N2 neuraminidase subtype, are associated with reduced susceptibility to oseltamir but not amantadine. The Q273K or K288T neuraminidase resistance-associated substitutions observed in N1 neuraminidase, or the NS293 neuraminidase resistance-associated substitutions observed in influenza virus neuraminidase, confer reduced susceptibility to neuraminidase but not oseltamivir. The K295N neuraminidase resistance-associated substitution observed in N2, and the K236T, D193N, R122H, or G142S neuraminidase resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to both oseltamivir and amantadine. These examples do not represent an exhaustive list of cross-resistance-associated substitutions and prescribers should consider available information from the CDC on influenza virus drug susceptibility patterns and treatment effects before deciding whether to use oseltamivir phosphate for oral suspension.

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

Immune Response

No influenza virus/immune interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with oseltamivir phosphate did not impair seasonal human antibody response to infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenesis studies in mice and 16-month daily oral doses of the prodrug oseltamivir phosphate 150 mg/kg and 500 mg/kg, respectively, the prodrug and the active oseltamivir carboxylate induced no statistically significant increases in tumors over controls. The maximum daily exposure to the prodrug in these tests was approximately 130- and 320-fold, respectively, greater than those in humans at the highest recommended clinical dose based on AUC comparisons. The respective safety margins of the exposures to the active oseltamivir carboxylate were 15- and 20-fold.

Oseltamivir was found to be non-mutagenic in Ames tests and the human lymphocyte chromosomal assay with and without metabolic 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 Ames tests and the L5178Y mouse lymphoma assay with and without metabolic activation and negative in the SHE cell transformation test.

In fertility and embryonic development studies in mice, doses of oseltamir at 30, 250, and 2000 mg/kg were administered to females for 2 weeks before mating, during mating and until day 5 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 or early embryonic development at any dose level. The highest dose in this study was approximately 125 times the human systemic exposure (AUC) of oseltamivir carboxylate in subjects who undergo complete systemic exposure to oseltamivir carboxylate.

14 CLINICAL STUDIES

14.1 Treatment of Influenza

14.1.1 Adults

Two randomized, placebo-controlled, double-blind clinical trials of oseltamivir phosphate were conducted in adults between 18 and 65 years old, at 34 sites in the U.S., for the treatment of acute uncomplicated influenza. Eligible subjects had fever of at least 100°F, accompanied by at least one respiratory symptom (cough, nasal, or both) and at least one systemic symptom (myalgia, chills, headache, malaise, or fatigue), and influenza virus was known to be circulating in the community. Subjects were randomized to receive oral oseltamivir phosphate or placebo for 5 days. All enrolled subjects were allowed to take fever-reducing medication.

Of 1,225 subjects enrolled in these two trials, 549 (45%) subjects were influenza-infected (median age 38 years, 53% male; 90% Caucasian; 46% smokers). Of the 549 influenza-infected subjects, 95% were infected with influenza A, 3% with influenza B, and 2% with influenza of unknown type.

Study medication was started within 48 hours of onset of symptoms and administration twice daily for 5 days. Subjects were required to self-assess the influenza-associated symptoms (cough, sore throat, nasal congestion, fever, chills, headache, malaise, and myalgia) on a daily basis as “none,” “mild,” “moderate,” or “severe.” Time to improvement was calculated from the time of treatment initiation to the time all clinical symptoms were assessed as “none” or “mild.” In both trials, there was a 13-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate 75 mg twice a day for 5 days compared to subjects who received placebo. Subgroup analyses by gender showed no differences in treatment effect of oseltamivir phosphate in men and women.

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

14.1.2 Adolescents and Adults with Chronic Cardiac or Respiratory Disease

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

14.1.3 Geriatric Subjects

These 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 adults with the exception of fever being defined as higher than 97.5°F. Of 174 subjects enrolled in this trial, 452 (85%) were influenza-infected subjects, 67% were infected with influenza A, 33% with influenza B.

In post hoc analysis, there was a 1-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate 75 mg twice daily for 5 days compared to those who received placebo (p=NS). Use in Specific Populations (8.5). Some seasonal variability was noted in the efficacy outcomes.

14.1.4 Pediatric Subjects

14.1.4.1 1- to 12-year-olds

One double-blind, placebo-controlled treatment trial was conducted in pediatric subjects aged 1 to 12 years (median age 5.3 years) who had fever (at least 100°F) plus one respiratory symptom (cough, nasal congestion) and at least one systemic symptom (fever, chills, headache). All children had a confirmed diagnosis of influenza A or B via an influenza antigen test or viral culture. Two of the 30 subjects had mild, non-complicated influenza A virus infections whereas 6 were infected with influenza A and 3 with influenza B.

Efficacy index 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 independent criteria be met: (1) alleviation of cough; (2) alleviation of severe, (3) resolution of fever, and (4) parental opinion of a return to normal health and activity. Oseltamivir phosphate treatment of 2 mg per kg twice daily, started within 48 hours of onset of symptoms, reduced the time composite time to freedom from illness by 1.5 days compared to placebo. Subgroup analyses by gender showed no differences in treatment effect of oseltamivir phosphate in male and female pediatric subjects.

Pediatric Subjects (Less than 1 year of age)

Two open-label trials evaluated the safety and pharmacokinetics of oseltamivir and oseltamivir carboxylate in influenza-infected pediatric subjects 2 weeks in less than 1 year of age (including healthy full-term premature infants at least 36 weeks post conceptional age). Subjects received oseltamivir phosphate at dosages ranging from 2 to 3.5 mg per kg daily for 5 days depending on subject age. These clinical trials were not designed to evaluate clinical efficacy or adverse reactions.

Of the 138 subjects under the age of 1 year enrolled and dosed in the trials, the majority of the subjects were male (76%), white (97%), non-Hispanic (97%), full term (76%) and infected with influenza A (97%). Pharmacokinetic data indicated a dose of 7.5 mg per kg twice daily (peak plasma subject) was less than 1 year of age provided oseltamivir phosphate concentrations similar to or higher than those observed in older pediatric subjects and adults receiving the approved dose and provided the basis for approval (see Adverse Reactions (6.1) and Use in Specific Populations (8.4)).

14.2 Prophylaxis of Influenza
Oseltamivir phosphate for oral suspension is a prescription medicine used to:

What is PATIENT INFORMATION

Pennington, NJ 08534
Zydus Pharmaceuticals USA Inc.
St. Louis, MO 63044
Oseltamivir Phosphate for Oral Suspension


diarrhea
oral suspension (supplied as powder) delivers 2 grams of sorbitol. Inform patients with hereditary

LAIV within 2 weeks or 48 hours after oseltamivir phosphate administration, unless medically

immunization practices. Because of the potential for oseltamivir phosphate to inhibit replication of live

flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on

they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take

after exposure

Important Dosing Information

Precautions (5.2)

Advise patients and/or caregivers of the risk of neuropsychiatric events in oseltamivir phosphate-

Neuropsychiatric Events

suspension and see immediate medical attention if an allergic-like reaction occurs or is suspected

serious skin reactions. Instruct patients and/or caregiver to stop oseltamivir phosphate for oral

Advise patients and/or caregivers of the risk of severe allergic reactions (including anaphylaxis) or

Use)

17 PATIENT COUNSELING INFORMATION

For 12 weeks. The incidence of confirmed clinical influenza was 3% (7/238) in the placebo group

immunocompromised subjects (including 18 pediatric subjects 1 year to 12 years of age) who had

A double-blind, placebo-controlled trial was conducted for seasonal prophylaxis of influenza in 475

immunocompromised subjects (including 10 pediatric subjects 1 year to 12 years of age who had

medication since suspension for solid organ/tissue transplant recipients was 1,105 days for the

placebo group and 1,379 days for the oseltamivir phosphate group. Medication since transplantation for the

hematopoietic stem cell transplant recipients was 421 days for the placebo group and 357 days for the

oseltamivir phosphate group. Approximately 40% of subjects received influenza vaccine prior to

entering the study. The primary efficacy endpoint was the incidence of confirmed clinical influenza

among household contacts of patients who received oseltamivir phosphate within 48 hours after

24 hours, plus either a positive virus culture or a four-fold increase in virus antibody titters from

baseline or at illness

Among household contact 1 year to 12 years of age not already shedding virus at baseline, the

incidence of laboratory-confirmed clinical influenza was lower in the group who received oseltamivir

phosphate prophylaxis (3% (8/206) compared to 12% (24/200) in the placebo-treated subjects. The incidence of

laboratory-confirmed clinical influenza was 7% (18/268) in the oseltamivir phosphate-treated group.

The efficacy of oseltamivir phosphate in preventing naturally occurring influenza illness was

demonstrated in a randomized, open-label post-exposure prophylaxis trial conducted among

subjects.

(24/200) in the placebo-treated subjects compared to 1% (2/205) in the oseltamivir phosphate-treated

subjects.

Pediatric Subjects (1 year to 12 years of age)

The efficacy of oseltamivir phosphate in preventing naturally occurring influenza illness was

demonstrated in a randomized, open-label post-exposure prophylaxis trial conducted among

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subjects.

Pediatric Subjects (1 year to 12 years of age)

The efficacy of oseltamivir phosphate in preventing naturally occurring influenza illness was

demonstrated in a randomized, open-label post-exposure prophylaxis trial conducted among

subjects.
Step 6. Rinse oral dosing dispenser under running tap water and allow to air dry after each use.

Step 5. Close the bottle with the child-resistant bottle cap after each use.

Step 4. Give the full contents of oral dosing dispenser directly into the mouth.

Step 3. Measure the oral suspension with an appropriate oral dosing dispenser to be sure you get the correct dose. Contact your pharmacist if you do not have an appropriate oral dosing dispenser.

Step 2. Open the bottle by pushing downward on the child-resistant bottle cap and twisting it in the direction of the arrow.

Step 1. Shake the oseltamivir phosphate for oral suspension well before each use.

**Instructions For Use**

**What are the ingredients in oseltamivir phosphate for oral suspension?**

Active ingredient: oseltamivir phosphate

Inactive ingredients: sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, sodium saccharin and water.

**What is oseltamivir phosphate for oral suspension used for?**

Oseltamivir phosphate for oral suspension is used to help prevent and treat the flu.

**How should I take oseltamivir phosphate for oral suspension?**

- Take oseltamivir phosphate for oral suspension exactly as your healthcare provider tells you to.
- Take oseltamivir phosphate for oral suspension with or without food. There is less chance of stomach upset if you take oseltamivir phosphate for oral suspension with food.

**What should I tell my healthcare provider before taking oseltamivir phosphate for oral suspension?**

- Tell your healthcare provider if you are allergic to oseltamivir phosphate or any of the ingredients in oseltamivir phosphate for oral suspension.
- Tell your healthcare provider if you:
  - have kidney problems.
  - have a history of frequent (fruit sugar) intolerance. Oseltamivir phosphate for oral suspension contains sorbitol and may cause stomach upset and ferment in people who are fructose intolerant.
  - have any other medical conditions.
  - are pregnant or plan to become pregnant. Available information indicates that oseltamivir phosphate for oral suspension 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 and over-the-counter medicines, vitamins, and herbal supplements.**

**What are the possible side effects of oseltamivir phosphate for oral suspension?**

Oseltamivir phosphate for oral suspension may cause serious side effects, including:

- Serious skin and allergic reactions. Oseltamivir phosphate for oral suspension can cause serious skin and allergic reactions. Stop taking oseltamivir phosphate for oral suspension and get medical help right away if you get any of the following symptoms:
  - skin rash or blisters
  - itching
  - swelling of your face, eyes, lips, tongue, or throat
  - 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 for oral suspension, 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 effect of oseltamivir phosphate for oral suspension is used for treatment of the flu is nausea, vomiting, and headache.

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

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

These are not all of the possible side effects of oseltamivir phosphate for oral suspension.

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 for oral suspension?**

- Store oseltamivir phosphate for oral suspension in the refrigerator for up to 17 days at room temperature.
- Keep oseltamivir phosphate for oral suspension in a child-resistant package.

**Keep oseltamivir phosphate for oral suspension and all medicines out of the reach of children.**

**General information about the safe and effective use of oseltamivir phosphate for oral suspensions.**

**Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use oseltamivir phosphate for oral suspension for a condition for which it was not prescribed. Do not give oseltamivir phosphate for oral suspension 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 for oral suspension that is written for health professionals. For more information, contact Zydis Pharmaceuticals at 1-877-991-6779.

**What are the ingredients in oseltamivir phosphate for oral suspension?**

**Active ingredient: oseltamivir phosphate**

**Inactive ingredients: oseltamivir phosphate for Oral Suspension: sorbitol, monosodium citrate, xanthan gum, titanium dioxide, monoglyceride sodium fumarate, sodium saccharin and water.**

Manufactured by:

Nesher Pharmaceuticals USA LLC
St. Louis, MO 63144

Distributed by:

Zydis Pharmaceuticals USA Inc.
Pennington, NJ 08534

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised 08/2019

**Instructions For Use**

Oseltamivir phosphate for oral suspension (ne-os-TAM-i-ve)

**How do I give a dose of oseltamivir phosphate for oral suspension?**

**Step 1.** Shake the oseltamivir phosphate for oral suspension well before each use.

**Step 2.** Open the bottle by pushing downward on the child-resistant bottle cap and twisting it in the direction of the arrow.

**Step 3.** Measure the oral suspension with an appropriate oral dosing dispenser to be sure you get the correct dose. Contact your pharmacist if you do not have an appropriate oral dosing dispenser.

**Step 4.** Give the full contents of oral dosing dispenser directly into the mouth.

**Step 5.** Close the bottle with the child-resistant bottle cap after each use.

**Step 6.** Rinse oral dosing dispenser under running tap water and allow to air dry after each use.

This Instructions For Use has been approved by the U.S. Food and Drug Administration. Revised 08/2019
## OSELTAMIVIR PHOSPHATE

### Oseltamivir Phosphate for Oral Suspension

**Zydus Pharmaceuticals (USA) Inc.**

**NDC 70710-1165-6**

Oseltamivir Phosphate for Oral Suspension

6 mg/mL *

60 mL (usable volume after constitution)

Zydus Pharmaceuticals

Rx Only

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### Product Information

<table>
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<tr>
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<tr>
<td>Item Code (Source)</td>
<td>NDC: 70710-1165</td>
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### Active Ingredient/Active Moiety

<table>
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<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tr>
<td>OSELTAMIVIR PHOSPHATE</td>
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<tr>
<td>OSELTAMIVIR ACID</td>
<td>(UNII: K6106LV5Q8)</td>
<td>6 mg/mL</td>
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### Inactive Ingredients

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<th>Ingredient Name</th>
<th>Strength</th>
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</thead>
<tbody>
<tr>
<td>MONOSODIUM CITRATE</td>
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<tr>
<td>SACCHARIN SODIUM</td>
<td></td>
</tr>
<tr>
<td>SODIUM BENZOATE</td>
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</tr>
<tr>
<td>SORBITOL</td>
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</tr>
<tr>
<td>TITANIUM DIOXIDE</td>
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</tr>
<tr>
<td>WATER</td>
<td></td>
</tr>
<tr>
<td>XANTHAN GUM</td>
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</table>

### Product Characteristics

| Color | WHITE |
| Shape | TUTTI FRUTTI |
| Flavor | TUTTI FRUTTI |

### Packaging

<table>
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<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
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<th>Marketing End Date</th>
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<td>1 in 1 CARTON</td>
<td>09/14/2017</td>
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### Marketing Information

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<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
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<tr>
<td>ANDA</td>
<td>ANDA209113</td>
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**Labeler** - Zydus Pharmaceuticals (USA) Inc. (156861945)

**Registrant** - Nesher Pharmaceuticals (USA) LLC (969028351)

**Establishment**

**Name** | **Address** | **Business Operations**
---|---|---
Nesher Pharmaceuticals (USA) LLC | 5801 S. Ben White Blvd., Austin, TX 78744 | ANALYSIS, MANUFACTURE