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

INDICATIONS AND USAGE
1.1 Treatment of Influenza
Oseltamivir Phosphate for Oral Suspension is indicated for the treatment of acute, uncomplicated infections due to influenza A and B 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 prophylaxis of influenza in patients 1 year and older.

1.3 Limitations of Use
Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also affect drug effectiveness.

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2.2 Recommended Dosage for Treatment of Influenza
2.3 Recommended Dosage for Prophylaxis of Influenza
2.4 Dosage in Patients with Renal Impairment
2.5 Preparation and Storage of Constituted Oseltamivir Phosphate for Oral Suspension

3 DOSAGE FORMS AND STRENGTHS
Oseltamivir Phosphate for Oral Suspension is available in 75 mg (tablet taste mask) and 150 mg (tablet taste mask) strengths.

4 CONTRAINDICATIONS
Oseltamivir Phosphate for Oral Suspension is contraindicated in patients with known serious hypersensitivity to oseltamivir or any of the components of oseltamivir phosphate for oral suspension.

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* Sections or subsections contained the full prescribing information are not listed.
benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment options when deciding whether to use Oseltamivir Phosphate for Oral Suspension [see Microbiology (12.6)].

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

### 2.4 Recommended Dosage for Prophylaxis of Influenza

Initiate post-exposure prophylaxis with oseltamivir phosphate for oral suspension within 48 hours of influenza symptom onset.

**Adults and Adolescents (13 years of age and older)**

Table 1 displays the recommended dosage of oseltamivir phosphate for oral suspension for treatment of influenza in adults and adolescents 13 years of age and older. The amount supplied (e.g., number of bottles) for seasonal prophylaxis may be greater than for post-exposure prophylaxis.

#### Table 1 Recommended Dosage Modifications for Treatment and Prophylaxis of Influenza in Pediatric Patients for Treatment and Prophylaxis of Influenza

<table>
<thead>
<tr>
<th>Weight</th>
<th>Recommended Dosage for Oral Suspension (30 mg or 60 mg)</th>
<th>Recommended Dosage for Oral Suspension (75 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 kg or less</td>
<td>15 mg once daily</td>
<td>22.5 mg once daily</td>
</tr>
<tr>
<td>5.1 kg to 12.5 kg</td>
<td>30 mg once daily</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>12.6 kg to 23 kg</td>
<td>45 mg once daily</td>
<td>45 mg once daily</td>
</tr>
<tr>
<td>23.1 kg to 40 kg</td>
<td>60 mg once daily</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>40.1 kg or more</td>
<td>75 mg once daily</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

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) for seasonal prophylaxis may be greater than for post-exposure prophylaxis.

For patients less than 13 years of age, follow the dosing recommendations in the preceding sections for the treatment of influenza and for post-exposure prophylaxis in adults and adolescents 13 years of age and older. Post-exposure prophylaxis in pediatric patients 1 year to 12 years of age can be interrupted if influenza is not diagnosed within 48 hours of exposure.

### 2.5 Preparation and Storage of Concentrated Oseltamivir Phosphate for Oral Suspension

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

1. Top the closed bottle containing the oseltamivir phosphate powder several times to loosen the powder.
2. Measure 35 mL of water in a graduated cylinder.
3. Add the total amount of water to concentrate the bottle.
4. Close bottle with child-resistant cap tightly and shake the concentrated bottle well for 15 seconds.
5. Label the bottle with instructions to Shake Well Before Use.

The concentrated oral suspension contains 30 mg of oseltamivir phosphate per 60 mL of solution (5 mg per mL) and is white, tutti-frutti-flavored. Use the concentrated oral suspension within 17 days of preparation when stored under refrigeration, 2° to 8°C (36° to 46°F), or within 10 days if stored at controlled room temperature, 21°C to 25°C (70°F to 77°F). Write the expiration date of the concentrated oral suspension on the bottle label.

Ensure patients have an oral dosing dispenser that measures the appropriate volume in milliliters. Consult patient on how to utilize the oral dosing dispenser and correctly measure the oral suspension as prescribed (see Tables 1 and 2).

### 3 DOSAGE FORMS AND STRENGTHS

Oseltamivir Phosphate for Oral Suspension 6 mg per mL (final concentration when combined)

White or light yellow powder blend for constitution.
4 CONTRAINDICATIONS

Oseltamivir phosphate (for oral suspension) is contraindicated in patients with known serious hyperosmolarity or in 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/Hyperosmolarity 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 oseltamivir phosphate. Any oseltamivir phosphate oral suspension for oral suspension and intravenous treatment at any allergic-like reaction occurs or is suspected. The use of oseltamivir phosphate for oral suspension is contraindicated in patients with known serious hyperosmolarity to oseltamivir phosphate [see Warnings and Precautions (5.1)].

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 death, in patients with influenza who were receiving oseltamivir phosphate [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 unaccompanied by oseltamivir phosphate usage data. These events were reported primarily among pediatric patients and older adults or with unusual rapid resolution. The correlation of occurrence of these events with oseltamivir phosphate has not been established. Influenza is associated with a variety of neuropsychiatric and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior. In these cases, the duration of treatment and in cases of complications the rate of complications during drug treatment or complications during drug withdrawal, oseltamivir phosphate for oral suspension has not been shown to prevent such complications. Prescribers should be alert for the potential for secondary infectious and non-infectious causes.

5.3 Risk of Bacterial Infections

There is no evidence for efficacy of oseltamivir phosphate for oral suspension in any illness caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms and may mimic influenza. Serious bacterial infections may occur during or following the illness. This summary includes otherwise healthy adults/adolescents. In general, the safety profile in the subjects “at risk” was qualitatively similar to that in otherwise healthy adults/adolescents.

5.4 Fructose Intolerance in Patients with Hereditary Fructose Intolerance

Oseltamivir phosphate for oral suspension delivers 2 grams of sorbitol. This is above the daily maximum limit of 1 gram of sorbitol for patients with hereditary fructose intolerance, and may cause dyspepsia and diarrhea.

6 ADVERSE REACTIONS

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

- Serious skin/hyperosmolarity reactions [see Warnings and Precautions (5.1)]
- Neuropsychiatric events [see Warnings and Precautions (5.2)]
- Hypertension [see Warnings and Precautions (5.3)]
- Arrhythmia [see Warnings and Precautions (5.4)]
- Fructose intolerance [see Warnings and Precautions (5.5)]
- Hepatitis, liver function tests abnormal [see Warnings and Precautions (5.6)]
- Rash, dermatitis, urticaria, toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme [see Warnings and Precautions (5.1)]

6.1 Clinical Trial 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 Adults and Adolescent Subjects (12 years and older)

The overall safety profile of oseltamivir phosphate was based on data from 2,664 adult and adolescent subjects who received the recommended dosage of 75 mg orally twice daily for 5 days for treatment of influenza and 1,983 adult and adolescent subjects who received the recommended dosage of 75 mg orally once daily for up to 6 weeks for prophylaxis of influenza 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 events occurred at a weight-based dosing of 2 mg per kg twice daily for 5 days or weight-based dosing of 2 mg per kg once daily for up to 6 weeks. 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*  

<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 = 3,040)</td>
<td>Oseltamivir Phosphate 75 mg once daily (n = 1,983)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 1,077)</td>
<td>Placebo (n = 1,286)</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Flushing</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Pain</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Adverse reactions that occurred in 1% or more of oseltamivir phosphate-treated adults and adolescents and 1% or more of oseltamivir phosphate-treated subjects are compared to placebo-treated subjects in either the treatment or prophylaxis trials.

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (13 years to 12 years of age)

A total of 1,481 pediatric subjects (including otherwise healthy pediatric subjects aged 3 years to 12 years and adolescent subjects aged 13 years to 16 years) participated in clinical trials of oseltamivir phosphate for oral suspension for the treatment of influenza. A total of 303 pediatric subjects received treatment with oseltamivir phosphate for oral suspension at a 2 mg per kg twice daily for 5 days or weight-based dosing. Vomiting was the only adverse reaction reported at a frequency of at least 2% in children receiving oseltamivir phosphate (15%) compared to placebo (6%).

Among the 141 pediatric subjects aged 3 years to 12 years who received oseltamivir phosphate at doses of 30 to 40 mg once daily for 10 days for post-exposure prophylaxis study included infant controls (n = 95) and in a separate 6-week seasonal influenza prophylaxis safety study (n = 49), vomiting was the most frequently reported reaction (15% on oseltamivir phosphate versus 5% in the placebo group).

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (2 weeks to less than 3 years of age)

Assessment of adverse reactions in pediatric subjects aged 2 weeks to less than 3 years of age was based on two-open label studies that included safety data on 1,275 oseltamivir phosphate-treated subjects 2 weeks or less than 1 year of age (including premature infants at 4 weeks post-conceptional age) exposed to oseltamivir phosphate at doses ranging from 3 to 12 mg per kg for the treatment or oral compassionate daily for 5 days. The safety profile of oseltamivir phosphate was similar across the age range studied, with vomiting (3%), diarrhea (1%) and diaphoresis (1%) being the most frequently reported adverse reactions, and was generally comparable to that observed in clinical pediatric and adult subjects.

Adverse Reactions from the Prophylaxis Trial in Immunocompromised Subjects

In 12-week seasonal prophylaxis study in 47 immunocompromised subjects, including 19 pediatric subjects 1 year to 12 years of age, the safety profile in the 228 subjects receiving oseltamivir phosphate 75 mg once daily was consistent with that previously observed in otherwise healthy pediatric prophylaxis clinical trials [see Clinical Studies (14.2)].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of oseltamivir 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 oseltamivir phosphate exposure.

- General disorders and administration site condition: swelling of the face or tongue, allergy, anaphylactic/anaphylactoid reactions, hypokalemia
- Skin and subcutaneous tissue disorders: rash, urticaria, angioedema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme [see Warnings and Precautions (5.1)]
- Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis
- Cardiac: Arrhythmia
- Endocrine and metabolic disorders: Hypothyroidism, liver function tests abnormal
- Nervous system disorders: Seizure
- Mental disorder: Agitation of diabetes
- Psychiatric disorders: Abnormal behavior, delirium, including symptoms such as hallucinations,
7 DRUG INTERACTIONS

7.1 Influenza Vaccines

Live Aminated Influenza Vaccine

The concurrent use of oseltamivir phosphate with live aminated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for oseltamivir phosphate to inhibit replication of live virus strains, it possible that the efficacy of LAIV may be reduced when oseltamivir phosphate is administered within 2 weeks before or 48 hours after oseltamivir phosphate for oral suspension administration, unless medically indicated.

Inactivated Influenza Vaccine

Inactivated influenza vaccine can be administered at any time relative to use of oseltamivir phosphate.

7.2 Drugs Without Clinically Significant Drug Interaction with Oseltamivir Phosphate for Oral Suspension

No drug interactions are noted for either oseltamivir or the concomitant drug when coadministering oseltamivir with amoxicillin, acetaminophen, aspirin, cimetidine, atazanavir, or ritonavir (see Clinical Pharmacology (12.3)).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with oseltamivir phosphate for oral suspension in pregnant women. Published prospective and retrospective observational studies of approximately 1,500 women exposed to oseltamivir phosphate during pregnancy during include approximately 400 women exposed in the first trimester. The women suggest that the observed rate of congenital malformations was no more than the rate in the general comparison population, regardless of whether therapy was administered during the gestational period. However, some of these studies had inadequate sample sizes and some lacked information on dose which preclude a definitive assessment of the risk.

Animal Data

Studies for effects on embryo-fetal development were conducted in rats (50, 250 and 1500 mg/kg/day) and rabbits (90, 190, 290 and 580 mg/kg/day) by oral routes. Relative exposures at these doses were respectively, 2.1, 10 and 10,000 times human exposure (steady state) for 4, 6, and 50 times human exposure in the rat, 0.09 to 0.3 and 0.09 to 0.3 times human exposure in the rabbit. Pharmacokinetic studies indicated that there was fetal exposure in both species. Based on maternal toxicities, no dose-related efficacy or safety differences were observed in rats and rabbits (50, 150 and 500 mg/kg/day) by the oral route. Relative exposures at these doses were respectively, 2.3, 10 and 100 times human exposure (steady state) for 4, 6, and 50 times human exposure in the rat, 0.09 to 0.3 and 0.09 to 0.3 times human exposure in the rabbit. The overall incidence of skeletal abnormalities was low and slight maternal toxicities were observed in the rabbit. As the maternal toxic dose, statistically significant increases in the incidence rates of a variety of minor skeletal abnormalities and variants were observed in rats exposed to oseltamivir phosphate. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

8.3 Nursing Mothers

Risk Summary

Based on limited published data, oseltamivir phosphate carboxylate are present in human milk at low levels considered unlikely to lead to toxicity in the breastfed infant. Exercise caution when oseltamir phosphate for oral suspension is administered to a nursing woman.

8.4 Pediatric Use

Treatment of Influenza

The safety and efficacy of oseltamivir phosphate for the treatment of influenza in pediatric patients 2 weeks old to 17 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:

- 13 to 17 years of age: Safety and efficacy in afflicted children 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 adolescent treated with oseltamivir phosphate in a study of treatment and prophylaxis.

- 1 year to 12 years of age: Safety and efficacy pediatric patients 1 year to 12 years of age was supported by results of two double-blind, placebo-controlled trial in 452 pediatric patients with influenza where oseltamivir phosphate 2 mg per kg twice daily or placebo was 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 2 weeks in less than 1 year of age: Safety and efficacy in pediatric patients 2 weeks in less than 1 year of age was supported by a single- and well-controlled trials conducted in and since pediatric patients and two open-label trials of oseltamivir phosphate (2 to 3.5 mg per kg twice daily for 5 days) in 13 pediatric subjects 2 weeks in less than 1 year of age. reduce two risks, the oseltamivir phosphate concentration in these subjects were similar to or higher than the oseltamivir plasma concentrations observed in older pediatric subjects and adults (see Clinical Pharmacology (12.3), and 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.

Prophylaxis of Influenza

The safety and efficacy of oseltamivir phosphate for prophylaxis of influenza in pediatric patients 1 year to 17 years of age has been established (see Dosage and Administration (2.2), Clinical Pharmacology (12.3), and Clinical Studies (14.2)) and is based on:

- 13 to 17 years of age: Prophylaxis in afflicted children patients 13 to 17 years of age is supported by one randomized, placebo-controlled, post-exposure household prophylaxis trial of oseltamivir phosphate 75 mg once orally once daily for 7 days in household contacts including 207 adolescents (see Clinical Studies (14.2)).

- 13 to 17 years of age: Prophylaxis in pediatric patients 1 year to 12 years of age is supported by one randomized, open-label, post-exposure household prophylaxis trial including pediatric subject 1 year to 12 years of age who received the 30 mg oseltamivir phosphate for oral suspension (oseltamir phosphate) once daily for 10 days (see Clinical Studies (14.2)). Additional safety information was provided in a well controlled prophylaxis (randomized clincial allergy trial) in 40 patients 1 year to 12 years of age.

The safety and efficacy of oseltamivir phosphate for prophylaxis of influenza have not been established for pediatric patients less than 1 year of age.

8.5 Geriatric Use

Treatment of Influenza

Treatment of Influenza

Children of 4.5 to 12 years of age in clinical trials of oseltamivir phosphate for the treatment of influenza, 549 (29%) were 65 years and older, while 325 (17%) were 75 years and older. In these double-blind, placebo-controlled trials in the treatment of influenza patients at least 65 years old, 140 of 741 subjects (19%) were 65 years and older, while 719 (16%) were 75 years and older. In a randomized, placebo-controlled trial in elderly residents of nursing homes who took oseltamivir phosphate for up to 4 days, the proportions of subjects who received oseltamivir phosphate (25% placebo 27%) were 61 years and older, while 325 (17%) were 75 years and older. In the study, in which baseline characteristics were well balanced between the elderly and younger subjects, and other recent clinical experience has not identified differences in responses between the elderly and younger subjects (see Clinical Studies (14.2)).

8.6 Reimbursement

Patients with renal impairment had higher levels of oseltamivir carboxylate compared to patients with normal renal function which may increase the risk of oseltamivir phosphate associated adverse
5.7 Hepatic Impairment

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

5.8 Use in Patients with Renal Conditions

Efficacy of oseltamivir phosphate in the treatment of influenza in patients with chronic renal disease and/or respiratory disease was evaluated in one randomized, placebo-controlled clinical trial. Efficacy in the population, as measured by time to alleviation of all symptoms, was not established, but no new safety signals were identified (see Clinical Studies 14.2). No clinical trials 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.

6.3 Immunosuppressed Patients

Efficacy of oseltamivir phosphate for the treatment of prophylaxis of influenza has not been established in immunosuppressed patients (see Clinical Studies 14.2). Safety of oseltamivir phosphate for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients (see Adverse Reactions 6.1).

10 OVERDOSAGE

Recovery of overdose with oseltamivir phosphate has been observed 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 6.1).

11 DESCRIPTION

Oseltamivir Phosphate for Oral Suspension, an influenza neuraminidase inhibitor (NAI), is available as a powder for oral suspension, which when reconstituted with water at a dose of 5 mg per mL oseltamivir base.

In addition to the active ingredient, the powder for oral suspension contains xanthan gum, sodium benzoate, monosodium citrate, tutti-frutti flavoring, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3S,4S,5S)-5-acetylamino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C₂₃H₂₈NO₃.P.O₄ (five bases). The molecular weight is 532.4 for oseltamivir base and 640.4 for oseltamivir phosphate salt. The structural formula is as follows:

![Chemical Structure of Oseltamivir Phosphate]

22 CLINICAL PHARMACOLOGY

12.3 Mechanism of Action

Oseltamivir is an antiviral drug with activity against influenza virus (see Microbiology 12.4).

12.3.2 Pharmacokinetics

Absorption and Metabolism

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and extensively converted predominantly by hepatic enzymes to oseltamivir carboxylate. At least 70% 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 4).

Absorption

The volume of distribution (Vd) of oseltamivir carboxylate following intravenous administration to 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 proteins is low (3%). The binding of oseltamivir to human plasma proteins is 45%, 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 1.3 to 5 hours in 12 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 9 hours in 11 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 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.

Renal clearance (Ccr) exceeds glomerular filtration rate (GFR) indicating that tubular secretion (via organic anion transport) occurs in addition to glomerular filtration. Less than 20% of orally administered dose is eliminated in feces.

Specific Populations

Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily (about 6.7 times the maximum recommended oseltamivir phosphate dosage) to 16 patients with varying 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 prophylactic regimens are provided in Table 7. The pharmacokinetics in patients with reduced renal function or ESRD are not undergoing dialysis (see Indications and Usage 1.3) and Use in Specific Populations (1.4).
Influenza B virus neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. These associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated patterns and treatment effects when deciding whether to use oseltamivir phosphate for oral suspension. Prescribers should consider available information from the CDC on influenza virus drug susceptibility virus isolates. The 2009 H1N1 influenza virus ("swine flu") was almost uniformly susceptible to been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance- Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been recovered by serial passage of virus in cell culture in the presence of increasing.
examples do not represent an exhaustive list of cross-resistance associated substitutions and prescribers should consider available information from CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate for viral suspension. No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase (class oseltamivir, zanamivir) and M2 ion channel (class rimantadine, amantadine). 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 evaluation has not been established.

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

23 NONCLINICAL TOXICITY
23.1 Carcinogenicity, Mutagenesis, Impairment of Fertility
23.1.1 Carcinogenicity
Two-year carcinogenicity studies in mice and rats given oral and doses of the prodrug oseltamivir phosphate 400 mg/kg and 500 mg/kg, respectively, revealed no tumor incidences in the mice or the rats, respectively. A statistically significant increase in tumors was not observed in the two-year study in the rats. In the one-year study in mice, the highest dose tested was 180 mg/kg, without any evidence of tumor induction. A dose of 500 mg/kg was the highest dose administered to rats, and no evidence of tumor development was observed.

23.1.2 Mutagenesis
The prodrug oseltamivir phosphate (75 mg twice daily for 5 days) was not mutagenic in the following tests: in vitro bacterial tests (Ames test, E. coli WP2 uvrA tester strains), forward and reverse genetic tests in S. typhimurium tester strains, and mammalian cell tests (Chinese hamster ovary, V79-4, Chinese hamster lung, V79, and Chinese hamster ovary cells). The prodrug was also nonmutagenic in a mouse lymphoma test. The highest dose tested was 1000 mg/kg, and no evidence of tumor development was observed.

23.1.3 Impairment of Fertility
In a fertility and early embryonic development study in rats, the prodrug oseltamivir phosphate was administered through oral exposure to male and female rats before mating, during mating, and after mating. No evidence of fertility impairment, embryonic or fetal malformations, or teratogenic effects was observed at any dose level. A dose of 35 mg/kg was the highest dose tested; this dose is approximately 500 times the human exposure when given at the approved dose.

24 CLINICAL STUDIES
24.1 Treatment of Influenza
Adults and Adolescents (13 years of age and older)

A double-blind, placebo-controlled, multicenter trial was conducted in adults and adolescents (13 years of age and older) with laboratory-confirmed influenza A or B. The efficacy endpoint for all of these trials was the incidence of laboratory-confirmed clinical influenza defined as meeting all of the following criteria (all signs and symptoms must have been recorded within 24 hours):

- At least one constitutional symptom (myalgia, chills/sweats, malaise, fatigue, or headache)
- At least one respiratory symptom (cough, sore throat, nasal congestion, rhinorrhea, or hoarseness)
- Influenza virus was known to be circulating in the community
- Subjects were randomized to receive oral oseltamivir phosphate or placebo for 10 days.

Of the 3369 subjects enrolled, 2409 (72%) subjects were influenza-infected (median age 36 years; 53% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected subjects, 828 (98%) were infected with influenza A and 21% (21%) were infected with influenza B. Study medication was started within 48 hours of onset of symptoms and administration daily for 5 days. Subjects were required to self-assess their influenza-associated symptoms by rating the severity of each symptom on a four-point scale (none/mild, mild, moderate, severe). If symptoms persisted, a new subscore was calculated from the time of treatment initiation to time of last daily subscore recording.

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 the treatment effect of oseltamivir phosphate in men and women.

In the group of subjects who received oseltamivir phosphate, the incidence of laboratory-confirmed influenza was 4% (12/272) in the placebo-treated subjects compared to less than 1% (1/276) in the oseltamivir phosphate-treated subjects.

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

3.1.3 Impairment of Fertility
In a fertility and early embryonic development study in rats, the prodrug oseltamivir phosphate was administered through oral exposure to male and female rats before mating, during mating, and after mating. No evidence of fertility impairment, embryonic or fetal malformations, or teratogenic effects was observed at any dose level. A dose of 35 mg/kg was the highest dose tested; this dose is approximately 500 times the human exposure when given at the approved dose.

Children (13 years of age and older)

A double-blind, placebo-controlled, multicenter trial was conducted in children aged 13 years and older with laboratory-confirmed influenza A or B. The efficacy endpoint for all of these trials was the incidence of laboratory-confirmed clinical influenza defined as meeting all of the following criteria (all signs and symptoms must have been recorded within 24 hours):

- At least one constitutional symptom (myalgia, chills/sweats, malaise, fatigue, or headache)
- At least one respiratory symptom (cough, sore throat, nasal congestion, rhinorrhea, or hoarseness)
- Influenza virus was known to be circulating in the community
- Subjects were randomized to receive oral oseltamivir phosphate or placebo for 10 days.

Of the 3369 subjects enrolled, 2409 (72%) subjects were influenza-infected (median age 36 years; 53% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected subjects, 828 (98%) were infected with influenza A and 21% (21%) were infected with influenza B. Study medication was started within 48 hours of onset of symptoms and administration daily for 5 days. Subjects were required to self-assess their influenza-associated symptoms by rating the severity of each symptom on a four-point scale (none/mild, mild, moderate, severe). If symptoms persisted, a new subscore was calculated from the time of treatment initiation to time of last daily subscore recording.

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 the treatment effect of oseltamivir phosphate in men and women.

In the group of subjects who received oseltamivir phosphate, the incidence of laboratory-confirmed influenza was 4% (12/272) in the placebo-treated subjects compared to less than 1% (1/276) in the oseltamivir phosphate-treated subjects.

24.2 Treatment of Influenza
Adults and Adolescents (13 years of age and older)

A double-blind, placebo-controlled, multicenter trial was conducted in adults and adolescents (13 years of age and older) with laboratory-confirmed influenza A or B. The efficacy endpoint for all of these trials was the incidence of laboratory-confirmed clinical influenza defined as meeting all of the following criteria (all signs and symptoms must have been recorded within 24 hours):

- At least one constitutional symptom (myalgia, chills/sweats, malaise, fatigue, or headache)
- At least one respiratory symptom (cough, sore throat, nasal congestion, rhinorrhea, or hoarseness)
- Influenza virus was known to be circulating in the community
- Subjects were randomized to receive oral oseltamivir phosphate or placebo for 10 days.

Of the 3369 subjects enrolled, 2409 (72%) subjects were influenza-infected (median age 36 years; 53% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected subjects, 828 (98%) were infected with influenza A and 21% (21%) were infected with influenza B. Study medication was started within 48 hours of onset of symptoms and administration daily for 5 days. Subjects were required to self-assess their influenza-associated symptoms by rating the severity of each symptom on a four-point scale (none/mild, mild, moderate, severe). If symptoms persisted, a new subscore was calculated from the time of treatment initiation to time of last daily subscore recording.

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 the treatment effect of oseltamivir phosphate in men and women.

In the group of subjects who received oseltamivir phosphate, the incidence of laboratory-confirmed influenza was 4% (12/272) in the placebo-treated subjects compared to less than 1% (1/276) in the oseltamivir phosphate-treated subjects.
What should I tell my healthcare provider before taking oseltamivir phosphate for oral suspension. Do not take oseltamivir phosphate for oral suspension if you are allergic to oseltamivir phosphate or any of the ingredients in oseltamivir phosphate for oral suspension. 

Talk to your healthcare provider about when you should receive an annual flu vaccination.

Oseltamivir phosphate for oral suspension (os-el-TAM-ih-veer phosphate) is not recommended for people with end-stage renal disease (ESRD) who are not receiving dialysis.

Oseltamivir phosphate for oral suspension does not prevent bacterial infections that may happen with the flu. Oseltamivir phosphate for oral suspension does not treat or prevent illness that is caused by infections that are not caused by the flu.

It is not known if oseltamivir phosphate for oral suspension is:

- a treatment for chronic, open-label post-exposure prophylaxis trials in household contacts that included pediatric subjects aged 1 to 12 years, both as index cases and as family contacts. All index cases in this trial received oseltamivir phosphate for oral suspension 30 to 60 mg intranasally once daily for 10 days. The efficacy measure was the incidence of laboratory-confirmed clinical influenza for the household. Laboratory-confirmed clinical influenza was defined as meeting all of the following criteria:
  - oral temperature at least 100°F (37.8°C).
  - cough and/or corpus recorded within 48 hours, and
  - either adenoid or oral secretions on a scale of 0 to 3 greater increase in antibody titers from baseline or at illness visits.

Among household contacts 1 year to 12 years of age who were already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was lower in the group who received oseltamivir phosphate prophylaxis (3% [17/519]) compared to the group who did not receive oseltamivir phosphate prophylaxis (17% [81/469]).

Influencing factors

A double-blind, placebo-controlled trial was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects (including 10 pediatric subjects 1 to 12 years of age) who had received solid organ (liver, kidney, heart and lung) or hematopoietic stem cell transplants (HSCT).

It is not known if oseltamivir phosphate for oral suspension is:

- a treatment for chronic, open-label post-exposure prophylaxis trials in household contacts that included pediatric subjects aged 1 to 12 years, both as index cases and as family contacts. All index cases in this trial received oseltamivir phosphate for oral suspension 30 to 60 mg intranasally once daily for 10 days. The efficacy measure was the incidence of laboratory-confirmed clinical influenza for the household. Laboratory-confirmed clinical influenza was defined as meeting all of the following criteria:
  - oral temperature at least 100°F (37.8°C).
  - cough and/or corpus recorded within 48 hours, and
  - either adenoid or oral secretions on a scale of 0 to 3 greater increase in antibody titers from baseline or at illness visits.

Among household contacts 1 year to 12 years of age who were already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was lower in the group who received oseltamivir phosphate prophylaxis (3% [17/519]) compared to the group who did not receive oseltamivir phosphate prophylaxis (17% [81/469]).
Instructions For Use

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

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

How do I give oseltamivir phosphate for oral suspension?

1. Take oseltamivir phosphate for oral suspension exactly as your healthcare provider tells you to.
2. Take oseltamivir phosphate for oral suspension with food or without food. There is less chance of stomach upset if you take oseltamivir phosphate for oral suspension with food.
3. If you miss a dose of oseltamivir phosphate for oral suspension, 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 for oral suspension at your scheduled time. Do not take 2 doses at the same time.
4. If your healthcare provider or pharmacist has instructed you to take oseltamivir phosphate for oral suspension, 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 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 hives
  - your skin blisters and peels
  - blisters or sores in your mouth
  - itching
  - swelling of your face, eyes, lips, tongue, or throat
  - trouble breathing
  - chest pain or tightness

- Change in behavior. People, especially children, who have had the flu can develop serious 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, slurred movements, seizures, or start hearing voices or seeing things that are not really there (hallucinations).

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

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

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

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

Tell 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 or it is 2 hours or less before your next dose, do not take the missed dose. Take your next dose of oseltamivir phosphate for oral suspension at your scheduled time. Do not take 2 doses at the same time.

How should I give oseltamivir phosphate for oral suspension?

Before you take oseltamivir phosphate for oral suspension, tell your healthcare provider if you:

- have kidney problems.
- have a history of fructose (fruit sugar) intolerance. Oseltamivir phosphate for oral suspension contains sorbitol and may cause stomach upset and diarrhea in people who are fructose intolerant.
- have any other medical condition.
- 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 breast feed. Oseltamivir phosphate contains small amounts.

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

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

How can 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 food or without food. There is less chance of stomach upset if you take oseltamivir phosphate for oral suspension with food.

- If you miss a dose of oseltamivir phosphate for oral suspension, 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 for oral suspension at your scheduled time. Do not take 2 doses at the same time.

- If your healthcare provider or pharmacist has instructed you to take oseltamivir phosphate for oral suspension, read the detailed Instructions for Use at the end of this leaflet. Ask your pharmacist if you have any questions.

What are the ingredients in oseltamivir phosphate for oral suspension?

Oseltamivir phosphate for oral suspension contains:

- Active ingredient: oseltamivir phosphate
- Inactive ingredients: Oseltamivir Phosphate for Oral Suspension: sorbitol, monosodium citrate, sodium gum, titanium dioxide, and fruit flavors.

Manufactured by:
Novartis Pharmaceuticals USA LLC
St. Louis, MO 63164
Distributed by:
Zydus Pharmaceuticals USA LLC
Pennington, NJ 08534
This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised:03/2017

Instructions For Use

Oseltamivir phosphate for oral suspension (as-e-TAM-ib-ovi)

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

Step 1. Shake the oseltamivir phosphate for oral suspension bottle 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 oseltamivir phosphate dose using a proper 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 the 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 have been approved by the U.S. Food and Drug Administration.

PD12621-1
Rev. 06/2017

PACKAGE LABEL PRINCIPAL DISPLAY PANEL
NDC 70710-1165-6
Oseltamivir Phosphate for Oral Suspension
6 mg/mL
50 mL (usable volume after constitution)
Zydus Pharmaceuticals
Rx Only
Oseltamivir Phosphate
for Oral Suspension

6 mg/mL*

60 mL (usable volume after constitution)

Rx Only

Oseltamivir Phosphate
Oseltamivir phosphate for suspension

Product Information
Product Type: HUMAN PRESCRIPTION DRUG
Item Code (Source): NDC:70710-1165

Route of Administration: ORAL

Active Ingredient/Active Moiety
Ingredient Name: OSELTAMIVIR PHOSPHATE (UNII: 4A3O49NGEZ)
Ingredient Name: OSELTAMIVIR CARBOXYLATE (UNII: K6106LV5Q8)
Strength: 6 mg in 1 mL

Inactive Ingredients
Ingredient Name: MONOSODIUM CITRATE (UNII: 68538UP9SE)
Ingredient Name: SACCHARIN SODIUM (UNII: SB8ZUX40TY)
Ingredient Name: SODIUM BENZOATE (UNII: OJ245FE5EU)
Ingredient Name: SORBITOL (UNII: 506T60A25R)
Ingredient Name: TITANIUM DIOXIDE (UNII: 15FIX9V2JP)
Ingredient Name: WATER (UNII: 059QF0KO0R)
Ingredient Name: XANTHAN GUM (UNII: TTV12P4NEE)

Product Characteristics
Color: WHITE
Shape: Score
Size: Tutti Frutti
Imprint Code: Contains

Packaging
Item Code: NDC:70710-1165-6
Package Description: 1 in 1 CARTON
Marketing Start Date: 09/14/2017
Marketing End Date: 1

Marketing Information
Marketing Category: ANDA
Application Number or Monograph Citation: ANDA209113
Marketing Start Date: 09/14/2017
Marketing End Date: 

Labeler - Zydus Pharmaceuticals (USA) Inc. (156861945)
Registrant - Nesher Pharmaceuticals (USA) LLC (969028351)

Establishment
Name: Nesher Pharmaceuticals (USA) LLC
Address: BOTTLE, TYPE II, Not a Combination Product

Revised: 9/2017