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

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

1.2 Prophylaxis of Influenza
Oseltamivir Phosphate for Oral Suspension is indicated for the prophylaxis of influenza in patients 1 year and older.

1.3 Limitations of Use
Influenza viruses change over time. Other factors (for example, changes in viral virulence) might also diminish clinical effectiveness. Medical factors might influence the patient's needs for prophylaxis. The effectiveness of prophylaxis might diminish if treatment of influenza is initiated.

These highlights do not include all the information needed to use OSELTAMIVIR PHOSPHATE FOR ORAL SUSPENSION safely and effectively. For full prescribing information see OSELTAMIVIR PHOSPHATE FOR ORAL SUSPENSION.
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 of age and older (see Dosage and Administration (2.3)).

- Oseltamivir phosphate oral suspension (supplied as a powder). This is the preferred formulation for oral administration.
- Orally disintegrating tablets (supplied as a powder). This is the preferred formulation for oral administration.
- Oseltamivir phosphate for oral suspension (supplied as a powder) in a suspension that requires dilution with water to ensure the proper concentration for administration.

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

Adjust the oseltamivir phosphate oral suspension dosage in patients with moderate or severe renal impairment (see Dosage and Administration (2.4)).

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 of age and older is 75 mg once daily (12.5 mL of oral suspension [6 mL of the oral suspension contains 360 mg of oseltamivir base] [6 mg per mL]) 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 oral suspension within 48 hours following close contact with an infected individual. Initiate continuous prophylaxis with oseltamivir phosphate oral suspension during a community outbreak.

Adults and Adolescents (12 years of age and older)
The recommended dosage of oseltamivir phosphate oral suspension for prophylaxis of influenza in adults and adolescents 12 years of age and older is 75 mg once daily (12.5 mL of oral suspension) 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 oral suspension may be continued for up to 12 weeks (see Use in Specific Populations (8.5)). The duration of prophylaxis for as long as oseltamivir phosphate for oral suspension is continued.

Pediatric Patients (1 year to 12 years of age)
Table 1 displays the recommended oral dosage of oseltamivir phosphate oral suspension for prophylaxis of influenza in pediatric patients 1 year to 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)).

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

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Treatment Regimen</th>
<th>Prophylaxis Regimen (10 days)</th>
<th>Volume of Oral Suspension (6 mL/mL per Dose)</th>
<th>Number of Bottles of Oral Suspension in Dispense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any weight</td>
<td>30 mg once daily</td>
<td>30 mg once daily</td>
<td>5 mL</td>
<td>2 bottles</td>
</tr>
<tr>
<td>5.0 to 12</td>
<td>Not applicable</td>
<td>30 mg once daily</td>
<td>10 mL</td>
<td>3 bottles</td>
</tr>
<tr>
<td>13.0 to 21</td>
<td>5.0 mg once daily</td>
<td>5.0 mg once daily</td>
<td>5 mL</td>
<td>1 bottle</td>
</tr>
<tr>
<td>22.0 to 40</td>
<td>7.5 mg once daily</td>
<td>7.5 mg once daily</td>
<td>7.5 mL</td>
<td>2 bottles</td>
</tr>
<tr>
<td>41.0 or more</td>
<td>10.0 mg once daily</td>
<td>10.0 mg once daily</td>
<td>10 mL</td>
<td>2 bottles</td>
</tr>
</tbody>
</table>

* The recommended dosage for continuous ambulatory peritoneal dialysis (CAPD) patients.

2.4 Dosage in Patients with Renal Impairment

Table 2 displays the dosage recommendations for the treatment and prophylaxis of influenza in patients with various stages of renal disease undergoing dialysis (see Use in Specific Populations (8.6)) and Clinical Pharmacology (12.3).

Table 2: Recommended Dosage Modifications 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 (60-59 mL/min)</td>
<td>75 mg once daily for 5 days</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Moderate (30-59 mL/min)</td>
<td>30 mg once daily</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>Severe (≤10 mL/min)</td>
<td>30 mg once daily</td>
<td>30 mg every other day</td>
</tr>
<tr>
<td>ESRD Patients on Hemodialysis (≤9 mL/min)</td>
<td>30 mg immediately and then 30 mg every other day after every hemodialysis cycle (treatment duration not to exceed 5 days)</td>
<td>30 mg immediately and then 30 mg every other day after alternate hemodialysis cycles</td>
</tr>
<tr>
<td>ESRD Patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) (≤9 mL/min)</td>
<td>A single 30 mg dose administered immediately</td>
<td>30 mg immediately and then 30 mg once weekly</td>
</tr>
<tr>
<td>ESRD Patients on Dialysis (≥10 mL/min)</td>
<td>Oseltamivir Phosphate for Oral Suspension is not recommended</td>
<td>Oseltamivir Phosphate for Oral Suspension is not recommended</td>
</tr>
</tbody>
</table>

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

2.5 Preparation and Storage of Constituted Oseltamivir Phosphate for Oral Suspension

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

1. Unpack the vial of oseltamivir phosphate powder. Insert the supplied syringe into the vial and withdraw 0.6 mL of the contents. If stored at 2° to 8°C (36° to 46°F), the powder is suitable for use for 6 months; if stored at room temperature, the powder is suitable for use for 3 months.
2. Add 0.6 mL of water to a graduated cylinder.
3. Add the total amount of water to the vial of oseltamivir phosphate powder. Mix the contents of the vial with a tightly fitting spatula or similar device.
4. Use the 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 room temperature.

Oseltamivir Phosphate for Oral Suspension is not recommended for patients with end-stage renal disease.
5. 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:
- Serious idiosyncratic hypersensitivity reactions [see Warnings and Precautions (5.1)]
- Neuropsychiatric events [see Warnings and Precautions (5.1)]

4.4 Clinical Trials Experience

Due to the nature of clinical trials conducted under varying conditions, adverse reactions observed in 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 Adolescents 12 years of age and older

The overall safety profile of oseltamivir phosphate is based on data from 2,646 adult and adolescent subjects who received the recommended dosage of 7.5 mg orally twice daily for 5 days for treatment of uncomplicated influenza or for up to 6 weeks for prophylaxis of influenza in clinical trials. A total of 859 pediatric subjects received treatment with oseltamivir phosphate for oral suspension either at a 2 mg per kg twice daily for 5 days or weight-band dosing. Vomiting was the only adverse reaction reported at a frequency of ≥1% in subjects receiving oseltamivir phosphate for oral suspension either at a 2 mg per kg twice daily for 5 days or weight-band dosing.

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects 12 years of age and older

A total of 1,841 pediatric subjects (including otherwise healthy pediatric subjects aged 1 year to 12 years of age and asthmatic pediatric subjects aged 6 to 12 years) participated in clinical trials of oseltamivir phosphate given for the treatment of influenza. A total of 639 pediatric subjects received treatment with oseltamivir phosphate for oral suspension at a dose of 30 mg of oseltamivir base daily for 10 days in a phase 2a randomized prophylactic study in household contacts (n = 95), and in a separate 6-week seasonal influenza prophylaxis safety study (n = 40). Vomiting was the only adverse reaction reported at a frequency of ≥1% in subjects receiving oseltamivir phosphate (16%) compared to placebo (8%). Among the 140 pediatric subjects aged 1 year to 12 years who received oseltamivir phosphate at doses of 20 to 40 mg orally once daily for 10 days in a postmarketing surveillance study in household contacts (n = 95), and in a separate 6-week seasonal influenza prophylaxis safety study (n = 40), vomiting was the most frequent adverse reaction (8%) on oseltamivir phosphate versus 2% in the placebo group.

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects 12 years of age and older

Assessment of adverse reactions in pediatric subjects 2 weeks to less than 1 year of age

Adverse Reactions from Treatment and Prophylaxis Trials in Immunocompromised Subjects

This 12-week seasonal prophylaxis study in 475 immunocompromised subjects, including 18 pediatric subjects 1 year to 12 years of age, the safety profile in the 236 subjects receiving oseltamivir phosphate 75 mg once daily was consistent with the previously observed adverse events in oseltamivir phosphate clinical trials [see Clinical Studies (14.2)].

4.6 Premarketing Experience

The following adverse reactions have been identified during pre-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 drug exposure.

General disorders and administration site conditions: swelling of the face or tongue, allergy, anaphylactoid reactions, hypokalaemia
7 DRUG INTERACTIONS

7.1 Influenza Vaccines

Live Attenuated Influenza Vaccine

The concurrent use of oseltamivir phosphate with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for oseltamivir phosphate to inhibit replication of live vaccine virus and possible reduction of LAIV efficacy, avoid administration of LAIV 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 dose adjustments are needed for either oseltamivir or the concurrent drug when co-administering oseltamivir with amoxicillin, acyclovir, azithromycin, azithromycin and clarithromycin, atenolol, budesonide, cimetidine, co-trimoxazole, colchicine, cromolyn sodium, danazol, diltiazem, disulfiram, doxycycline, famotidine, furosemide, ganciclovir, indinavir, isoniazid, ketoconazole, lasix, levo- terpinol, lopinavir, miconazole, milrinone, mifepristone, midazolam, minoxidil, moxifloxacin, nelfinavir, nefazodone, nitric oxide, nifedipine, ondansetron, paclitaxel, prednisolone, propafenone, quinidine, ranitidine, ritonavir, saquinavir, sildenafile, imatinib, and valproate. Inadequate published data are available for other drugs without clinically significant drug interactions with oseltamivir phosphate for oral suspension. See Dosage and Administration (2.2) for a list of drugs with adequate and well-controlled trials in pediatric patients for oseltamivir phosphate for oral suspension.

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 animal and epidemiological data suggest that oseltamivir phosphate for oral suspension, when given to pregnant animals, is not associated with an increased risk of birth defects. However, these studies individually are limited by small sample sizes, use of different comparison groups, and some lack of information due to which a definitive assessment of the risk. In animal studies, there was a dose-dependent increase in incidence rates of a variety of minor skeletal abnormalities and variations in offspring of rats and rabbits exposed at maternally toxic doses of 60 and 20 mg per kg, respectively. Oseltamivir phosphate for oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see Clinical Pharmacology (12.3) and Risk Summary).

Clinical Considerations

Disease Associated Malignant and/or Embryofetal Risk

Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal 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 approximately 1,500 women exposed to oseltamivir phosphate during pregnancy including approximately 400 women exposed in the first trimester suggest that the observed rate of congenital malformations was not increased above the rate in the general population, regardless of whether therapy was administered during the gestational period. However, individually, none of these studies had adequate sample sizes and some lacked information in those who preclude a definitive assessment of the risk.

Animal Data

Studies for embryo-fetal development were conducted in rats (20, 250, and 500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these doses were, respectively, 2, 15, and 510 times human exposure (based on AUC) and 3, 8, and 50 times human exposure (based on AUC). In the rat study, minimal maternal toxicity was reported in the 1000 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. In the relatively late stages of pregnancy, statistically significant increases in the incidence rates of a variety of minor skeletal abnormalities and variations were observed in the exposed offspring. However, the individual incidence rates of each skeletal abnormality or variation remained within the background rates of occurrence in the species studied.

8.3 Nursing Mothers

Risk Summary

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

8.4 Pediatric Use

Management of Influenza

The safety and efficacy of oseltamivir phosphate for treatment of influenza in pediatric patients 2 weeks of age to 17 years of age has been established in adequate and well-controlled trials in adults and adolescents and younger pediatric patients. Preventive use of oseltamivir phosphate in pediatric patients 2 weeks of age to 17 years of age is supported by a 6-week seasonal prophylaxis trial of pediatric patients 6 to 12 years of age with low birth weight and small for gestational age.

8.5 Geriatric Use

Management of Influenza

Of the 4,765 adults in clinical trials of oseltamivir phosphate for the treatment of influenza, 548 (28%) were 65 years of age or older, while 325 (7%) were 75 years and older. In three double-blind, placebo-controlled trials of the treatment of influenza in adults at least 65 years old, 325 received 75 mg subjects (374 received placebo and 382 received oseltamivir phosphate); 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 response between the elderly and younger subjects. See Clinical Studies (14.3).
Oseltamivir phosphate is an antiviral drug with activity against influenza virus (see Microbiology (12.2)).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oseltamivir is an acyclic, N-2-substituted 2,3-dehydroxy derivative of 2,3-dihydroxy-5-amino-1-cyclohexene-1-carboxylic acid with acetylaminopyrrole as the active moiety. Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula of oseltamivir phosphate is as follows:

![Chemical structure of oseltamivir phosphate]

Oseltamivir phosphate is a prodrug that is converted to oseltamivir carboxylate, which is the active moiety. Oseltamivir carboxylate is an inhibitor of the viral neuraminidase (NA) enzyme, which is essential for the release of viral particles from infected cells. Oseltamivir carboxylate inhibits the NA enzyme by competitive inhibition, which prevents the enzyme from cleaving sialic acids from host cell receptors, thus blocking the release of new virus particles.

12.2 Pharmacokinetics

Absorption and Bioavailability

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate and less than 5% of the administered dose is excreted unchanged in the urine. Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (about 6.7 times the maximum recommended oseltamivir phosphate dosage) for 5 days to subjects with various degrees of renal impairment showed that serum creatinine clearance of 10 ml/min may increase the risk of oseltamivir phosphate-associated adverse reactions.

Administration of 100 mg of oseltamivir phosphate twice daily (about 1.3 times the maximum recommended oseltamivir phosphate dosage) for 5 days to subjects with various degrees of renal impairment showed that serum creatinine clearance of 10 ml/min may increase the risk of oseltamivir phosphate-associated adverse reactions.

Absorption in patients with impaired renal function is not affected.

Elimination

Oseltamivir is eliminated primarily by renal excretion. The plasma concentration of oseltamivir carboxylate is inversely proportional to declining renal function.

Population-derived pharmacokinetic parameters were determined for patients with varying degrees of renal function including ESRD patients on hemodialysis. Median simulated exposures of oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 7. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis (see Indications and Usage (1.2) and Clinical Pharmacology (12.3)).

8.7 Hepatic Impairment

No dose 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 (12.2)).

10 OVERDOSAGE

Reports of overdoses with oseltamivir phosphate have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdoses, adverse reactions were reported. Adverse reactions reported following overdoses 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.

Oseltamivir Phosphate for Oral Suspension contains the following inactive ingredients: xanthan gum, sodium benzoate, monosodium citrate, tutti-frutti flavoring, and saccharin sodium.

Table 6 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules Twice Daily (n=28)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oseltamivir</th>
<th>Oseltamivir Carboxylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng·h/mL)</td>
<td>65 (26)</td>
<td>348 (18)</td>
</tr>
<tr>
<td>( AUC_{0-12h} ) (ng·h/mL)</td>
<td>112 (57)</td>
<td>2715 (20)</td>
</tr>
</tbody>
</table>

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (about 6.7 times the maximum recommended oseltamivir phosphate dosage) (see Dosage and Administration (2)).

Contraindication with food had no significant effect on the peak plasma concentration (251 ng/mL, under fasted conditions and 241 ng/mL, under fed conditions) and the area under the plasma concentration-time curves (820 ng·h/mL, under fasted conditions and 819 ng·h/mL, under fed conditions) of oseltamivir carboxylate.

Distribution

The volume of distribution (\( V_d \)) of oseltamivir carboxylate, following intravenous administration in 24 subjects (oseltamivir phosphate is not available as an IV formulation), ranged between 23 and 26 liters. The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir carboxylate to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Elimination

Absorbed oseltamivir is primarily (99%) eliminated by conversion to the active metabolite, oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in healthy subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated unchanged in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in these subjects after oral administration.

Metabolism

Oseltamivir carboxylate is extensively converted in 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 (99%) by renal excretion. Renal clearance (11.8 L/hr) exceeds glomerular filtration rate (7.5 L/hr), indicating that tubular secretion is a major route of elimination. Less than 20% of an oral radiolabeled dose is eliminated in feces.

Specific Population

8.6 Renal Impairment

Patients with renal impairment had higher blood levels of oseltamivir carboxylate compared to patients with normal renal function which may increase the risk of oseltamivir phosphate-associated adverse reactions. Therefore, dose adjustment is recommended for patients with a serum creatinine clearance between 10 and 50 ml/min and for patients with end-stage renal disease (ESRD) undergoing routine hemodialysis or continuous peritoneal dialysis treatment (see Dosage and Administration (2.4)). Oseltamivir phosphate for oral suspension is not recommended for patients with ESRD not undergoing dialysis (see Indications and Usage (1.2) and Clinical Pharmacology (12.3)).

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

<table>
<thead>
<tr>
<th>Normal Creatinine</th>
<th>Mild/Creatinine</th>
<th>Moderate/Creatinine</th>
<th>Severe/Creatinine</th>
<th>ESRD/Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng·h/mL)</td>
<td>65 (26)</td>
<td>348 (18)</td>
<td>112 (57)</td>
<td>2715 (20)</td>
</tr>
<tr>
<td>( AUC_{0-12h} ) (ng·h/mL)</td>
<td>112 (57)</td>
<td>2715 (20)</td>
<td>687 (30)</td>
<td>1445 (10)</td>
</tr>
</tbody>
</table>

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 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 Pharmacology (12.4)).

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 prophylaxis of influenza has not been established in immunocompromised patients (see Clinical Pharmacology (12.2)). Safety of oseltamivir phosphate for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients (see Adverse Reactions (6)).
In clinical trials, oseltamivir carboxylate exposure was not altered in subjects with mild or moderate hepatic impairment (see Use in Specific Populations (8.7)).

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the oseltamivir phosphate dosage regimen resulted in lower exposure to the active metabolite in pregnant women (55%) compared to nonpregnant women (65%). However, this pooled exposure is expected to have activity against susceptible influenza virus strains and there are insufficient pharmacokinetics and safety data to recommend a dose adjustment for pregnant women (see Use in Specific Populations (8.7)).

Pediatric Subjects (1 year to 12 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single-dose pharmacokinetic study in pediatric subjects aged 5 to 16 years (n=18) and in a small number of pediatric subjects aged 1 to 12 years. Younger pediatric subjects cleared both the oseltamivir and the active metabolite faster than adult subjects resulting in lower exposure for a given mg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric subjects over 12 years of age are similar to those in adult subjects (see Use in Specific Populations (8.6)).

Pediatric Subjects (2 to 11 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in cell culture studies using tricistronic cultures of pediatric subjects aged 1 to 11 years. Younger pediatric subjects had similar pharmacokinetics as adults. However, the oseltamivir and oseltamivir carboxylate exposure following a 2.5-mg dose in subjects under 1 year of age is expected to be within the observed exposure in adults and adolescents receiving 75 mg twice daily and 120 mg daily (see Use in Specific Populations (8.6)).

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25% to 30% higher in geriatric subjects (age range 65 to 80 years) compared to younger adults, given comparable doses of oseltamivir. Half-lives observed in the geriatric subjects were similar to those seen in young adults. Based on clinical data and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis (see Use in Specific Populations (8.1)).

Drug Interaction Studies

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

In vivo studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a substrate for P-gp.

Coadministration of probenecid results in an approximate 2-fold increase in exposure to oseltamivir carboxylate due to a decrease in active tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when coadministering with probenecid. No clinically relevant pharmacokinetic interactions have been observed when coadministering oseltamivir with amoxicillin, clarithromycin, erythromycin, amoxicillin (magnesium and aluminum hydroxide salts and calcium carbonate), raltegravir, simvastatin, or warfarin.

12.4 Microbiology

Mechanism of Action

Oseltamivir phosphate is an orally administered oseltamivir carboxylate, requiring oral hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is a substrate of influenza virus neuraminidase, which is essential for virus release from infected cells. The median IC50 values of oseltamivir to influenza A/H1N1, influenza A/H3N2, and influenza B clinical isolates were 2.5 nM (range 0.93-4.16 nM, N=74), 0.96 nM (range 0.50-1.80 nM, N=40), and 0.13 nM (range 0.03-0.49 nM, N=19), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate.

Antiviral Activity

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

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

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Mechanism of Action

Antiviral Activity

Drug Interaction Studies

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Pediatric Subjects (2 to 11 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in cell culture studies using tricistronic cultures of pediatric subjects aged 1 to 11 years. Younger pediatric subjects had similar pharmacokinetics as adults. However, the oseltamivir and oseltamivir carboxylate exposure following a 2.5-mg dose in subjects under 1 year of age is expected to be within the observed exposure in adults and adolescents receiving 75 mg twice daily and 120 mg daily (see Use in Specific Populations (8.6)).

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25% to 30% higher in geriatric subjects (age range 65 to 80 years) compared to younger adults, given comparable doses of oseltamivir. Half-lives observed in the geriatric subjects were similar to those seen in young adults. Based on clinical data and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis (see Use in Specific Populations (8.1)).

Drug Interaction Studies

Pediatric Subjects (1 year to 12 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single-dose pharmacokinetic study in pediatric subjects aged 5 to 16 years (n=18) and in a small number of pediatric subjects aged 1 to 12 years. Younger pediatric subjects cleared both the oseltamivir and the active metabolite faster than adult subjects resulting in lower exposure for a given mg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric subjects over 12 years of age are similar to those in adult subjects (see Use in Specific Populations (8.6)).

Pediatric Subjects (2 to 11 years of age)

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in cell culture studies using tricistronic cultures of pediatric subjects aged 1 to 11 years. Younger pediatric subjects had similar pharmacokinetics as adults. However, the oseltamivir and oseltamivir carboxylate exposure following a 2.5-mg dose in subjects under 1 year of age is expected to be within the observed exposure in adults and adolescents receiving 75 mg twice daily and 120 mg daily (see Use in Specific Populations (8.6)).
Cross-resistance

Cross-resistance between oseltamivir and amantadine has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitution observed in the N1 neuraminidase subtype, and the H177Y of N2 oseltamivir resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to oseltamivir but not amantadine. The Q273K and H274Y amantadine resistance-associated substitutions observed in N1 neuraminidase, or the R246K amantadine resistance-associated substitution observed in influenza B virus neuraminidase, confer reduced susceptibility to amantadine but not oseltamivir. The R226K oseltamivir resistance-associated substitution observed in N2, and the D222N, D219E, V121I, or G245S oseltamivir 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 procedures should consider available information for drug susceptibility patterns and treatment effects when deciding to use oseltamivir phosphate for oral suspension.

Immunogenicity

No influenza vaccine or 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.

13 NONCLINICAL TOXICOLOGY

13.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats given daily oral doses of the proviral oseltamivir phosphate, 400 mg/kg and 500 mg/kg, respectively, the proviral and active form oseltamivir carboxylate induced no statistically significant increase in tumors in mice or rats. The maximum daily exposures to the proviral phosphate were approximately 130- and 320-fold, respectively, greater than those in humans at the recommended clinical dose based on AUC comparisons. The respective exposure margin of the active oseltamivir carboxylate was 55- and 20-fold. Oseltamivir was found to be non-genotoxic in Ames tests and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian hamster embryo (SHE) cell transformation assay. Oseltamivir carboxylate was non-genotoxic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In fertility and embryonic development studies, doses of oseltamivir phosphate 20, 260, and 1500 mg/kg were administered to females for 2 weeks before mating, during mating and up to day 5 of pregnancy. Males were dosed for 2 weeks before mating, during mating, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose studied was approximately 100 times the human systemic exposure (AUC) at the usual dose of oseltamivir that occurs after administration of the maximum recommended dose.

14 CLINICAL STUDIES

14.1 Treatment of Influenza

Adults

Two randomized, placebo-controlled, double-blind clinical trials of oseltamivir phosphate were conducted inclusive of 16 and more than 65 years old, one in U.S. and one outside the U.S., for the treatment of acute uncomplicated influenza. Eligible subjects had fever of at least 100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms, or sore throat) and one non-respiratory symptom (myalgia, chills/sweats, malaise, fatigue or headache), and influenza virus was known to be circulating in the community. Subjects were randomized to receive oral oseltamivir phosphate or placebo for 5 days. All enrolled subjects were allowed to take fever-reducing medications. Of 2,253 subjects enrolled in these two trials, 90% (80%) of subjects were influenza-infected (median age 38 years; 52% male; 58% Caucasian 33% Asian). Of the 90% influenza-infected subjects, 95% were infected with influenza A, 3% with influenza B, and 1% with influenza of unknown type.

Study medication was started within 48 hours of onset of symptoms and administered daily for 5 days. Subjects were required to self-assess the influenza-associated symptoms (nasal congestion, sore throat, cough, sneeze, achy, fatigue, headache, or chills/sweats) as none, mild, moderate, or severe. Time to improvement was calculated from time of initiation of treatment to the time when all symptoms were assessed as none or mild. In these 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 the treatment effect of oseltamivir phosphate in men and women.

The treatment of influenza in an increased efficacy was demonstrated in subjects who received higher doses of oseltamivir phosphate.

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 adolescent subjects 13 years of age or older with chronic cardiac (excluding chronic idiopathic hypertension) or respiratory disease. Subjects were randomized to receive oral oseltamivir phosphate or placebo for 5 days. There were no significant differences in the treatment effect of oseltamivir phosphate there was a more rapid cessation of febrile illness. No difference in incidence of influenza complications was observed between the treatment and placebo groups in this population.

Geriatric Subjects

Three double-blind placebo-controlled treatment trials were conducted in elderly subjects who were at least 65 years of age in three consecutive seasons. The enrollment criteria were similar to that of adult trials with the exception for fever being defined as higher than 99.0°F. 741 subjects enrolled, 476 (65%) subjects were influenza-infected; of these, 95% were infected with influenza type A and 5% with influenza type B.

In the pooled analysis, there was a 1-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate 75 mg twice daily for 5 days compared to those who received placebo (p<0.05) (Use in Specific Populations (8.5)). Some seasonal variability was noted in the clinical efficacy outcomes.

Pediatric Subjects (1 year to 12 years of age)

One double-blind placebo-controlled treatment trial was conducted in pediatric subjects aged 1 year to 12 years (median age 3.5 years), who had fever of at least 100°F plus one respiratory symptom (cough or cold) when influenza virus was known to be circulating in the community. Of 468 subjects enrolled in this trial, 452 (89%) were influenza-infected subjects, 67% were infected with influenza A, 30% with influenza B, and 3% with influenza of unknown type.

Efficacy trials trial was determined by the time to alleviation or resolution of influenza symptoms and symptom severity measured by a composite endpoint that required the following four individual conditions be met: (1) alleviation of fever, (2) alleviation of cough, (3) alleviation of nasal/respiratory symptoms, and (4) improvement of overall physical and emotional health. Oseltamivir phosphate treatment of 2 g per kg body weight, dosed orally in the form of a syrup, reduced the median time to improvement in 68 hours of onset of symptoms, reduced the total composite time to freedom from illness by 5.2 days compared to placebo. Subgroup analyses by gender showed no differences in the treatment effect of oseltamivir phosphate in male and female pediatric subjects.

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

Two open-label trials evaluated the safety and pharmacokinetics of oseltamivir carboxylate in influenza-infected pediatric subjects 2 weeks to less than 1 year of age (excluding pneumonia infants at least 30 weeks postconceptual age). Subjects received oseltamivir phosphate at doses ranging from 0.35 to 0.55 g per kg body weight for 5 days depending on subject age. These clinical trials were not designed to evaluate clinical efficacy or virologic response.

Of the 186 subjects under the age of 1 year enrolled and dosed in the trials, the majority of the subjects were male (75%), white (79%), non-Hispanic (74%), full term (76%) and infected with influenza A (80%). Pharmacokinetic data indicated a dose of 3 mg per kg twice daily is pediatric subject dose. Subjects received oseltamivir phosphate for periods of time shorter 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 (8.6)).

14.2 Prophylaxis of Influenza

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

The efficacy of oseltamivir prophylaxis in preventing naturally occurring influenza has been demonstrated in seasonal prophylaxis clinical trials and one post-exposure prophylaxis trial in household contacts. The efficacy endpoint for all of these trials was incidence of laboratory-confirmed clinical influenza defined as either of the following criteria (all signs and symptoms must have been recorded within 24 hours):

- oral temperature greater than or equal to 99.0°F (37.2°C),
- at least one respiratory symptom (cough, nasal congestion),
- at least one constitutional symptom (aches and pains, fatigue, headache, chills/sweats), and
- either positive virus isolation or a four-fold increase in virus antibody titer from baseline.

In a proof of concept of two seasonal prophylaxis trials in healthy non-immunized adults (aged 18 to 65 years), oseltamivir phosphate 75 mg once daily reduced 0-
Oseltamivir phosphate for oral suspension does not prevent bacterial infections that may happen with the flu.

Oseltamivir phosphate for oral suspension is a prescription medicine used to:

- prevent the flu in people who start treatment after exposure to flu viruses within 48 hours of the first appearance of flu symptoms in the index case and continue for 7 days after the last exposure.

Important Dosing Information

- Instruct patients to begin treatment with oseltamivir phosphate for oral suspension as soon as possible from the first appearance of flu symptoms, within 48 hours of onset of symptoms. Similarly, instruct patients to start taking oseltamivir phosphate for oral suspension for prevention as soon as possible after exposure to flu viruses.

Precautions (5.2)

- Advise patients and/or caregivers of the risk of neuropsychiatric events in oseltamivir phosphate-treated patients with influenza and instruct patients to contact their physician if they experience signs of abnormal behavior while receiving oseltamivir phosphate for oral suspension.

- Do not freeze. Alternatively, store constituted suspension for up to 10 days at 25°C (77°F); excursions to 30°C (86°F) are permissible.

- Do not use if crystals or sediments are visible in the suspension.

- Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Seizures (5.4)

- Seizures in patients with and without a history of seizures, including status epilepticus, have been reported in patients treated with oseltamivir phosphate for oral suspension.

Drug Interactions (7.1)

- Do not give both oseltamivir phosphate and probenecid to the same patient.

HOW SUPPLIED/STORAGE AND HANDLING

Oseltamivir Phosphate for Oral Suspension (Supplied as Powder)

- Supplied as a white to light yellow powder blend in a glass bottle. After constitution, the powder blend produces a white to light yellow, suitably-flavored oral suspension. Each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir phosphate (immunocompromised).

17 PATIENT COUNSELING INFORMATION

Advisory to the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Skin/Hypersensitivity Reactions

- Advise patients and caregivers to report any skin reaction including hives, swelling (including of the lips, tongue, eyelids, or larynx), or urticaria to their health care provider immediately.

Neuropsychiatric Events

- Advise patients and caregivers of the risk of neuropsychiatric events in oseltamivir phosphate-treated patients with influenza and instruct patients to contact their physician if they experience signs of abnormal behavior while receiving oseltamivir phosphate for oral suspension.

Important Dosing Information

- Instruct patients to begin treatment with oseltamivir phosphate for oral suspension as soon as possible from the first appearance of flu symptoms, within 48 hours of onset of symptoms.

Influenza Vaccine

- Instruct patients that oseltamivir phosphate for oral suspension is not a substitute for receiving an annual influenza vaccine.

Patient Information

Oseltamivir phosphate for oral suspension (as of TAM-Br-vx)

What is Oseltamivir Phosphate for Oral Suspension?

Oseltamivir phosphate for oral suspension is prescription medicine used to:

- treat the flu (influenza) in people 1 year of age and older who have flu symptoms for an average of 2 to 4 days.

- prevent the flu in people who are 1 year of age and older.

- It is not known if oseltamivir phosphate for oral suspension is:
  - effective in people who start treatment after 2 days of developing flu symptoms.
  - effective for the treatment of the flu in people with chronic (long-term) health problems or breathing problems.

- In the seasonal (community outbreak) prophylaxis trial in elderly residents of skilled nursing homes, the incidence of laboratory-confirmed clinical influenza was 5% (25/519) for the placebo group compared with 1% (5/237) in the oseltamivir phosphate group.

- In the post-exposure prophylaxis trial, among household contacts who were given placebo, laboratory-confirmed clinical influenza was 4% (12/272) in the placebo-treated subjects compared to less than 1% (2/236) in the oseltamivir phosphate-treated subjects.

In the post-exposure prophylaxis trial, in children 13 years of age or older, laboratory-confirmed clinical influenza was 7% (15/205) in the placebo-treated subjects compared to 1% (2/205) in the oseltamivir phosphate-treated subjects.

- In children aged 13 years of age or older, laboratory-confirmed clinical influenza was 7% (15/205) 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 determined in randomized, open-label post-exposure prophylaxis trial in household contacts that included pediatric subjects aged 1 year 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, enterally once daily for 10 days. The efficacy parameter was the incidence of laboratory-confirmed clinical influenza in the household. Laboratory-confirmed clinical influenza was defined as meeting all of the following criteria:

- oral temperature at least 100°F (37.7°C).
- cough and/or corpus collected within 48 hours, and
- at least two other clinical symptoms consistent with influenza (e.g., headache, myalgia, and/or malaise).

- Among household contacts 1 year to 12 years of age not already shedding virus at baseline, the incidence of laboratory-confirmed clinical illness was lowest in the group who received oseltamivir phosphate prophylaxis (3% [5/170]) compared to the group who did not receive oseltamivir phosphate prophylaxis (17% [30/179]).

A double-blind, placebo-controlled trial was conducted for seasonal prophylaxis of influenza in 675 immunocompromised subjects (including 58 pediatric subjects aged 1 to 12 years of age) who had received solid organ (kidney, liver, heart, and kidney/heart) or hematopoietic stem cell transplants (HSCT).

- Median time since transplant to onset of symptoms was 312 days for the placebo group and 337 days for the oseltamivir phosphate group. Median time since transplant for hematopoietic stem cell transplant recipients was 424 days for the placebo group and 667 days for the oseltamivir phosphate group. Approximately 40% of subjects received influenza vaccine prior to enrolling in the study. The primary efficacy endpoint was the incidence of confirmed clinical influenza, defined as oral temperature higher than 99.9°F (37.7°C) plus cough and/or corpus, all recorded within 24 hours, plus either a positive virus culture or a four-fold increase in virus antibody titer from baseline. Subjects received treatment with oseltamivir phosphate 75 mg or placebo once daily for 12 weeks. The incidence of confirmed clinical influenza was 6% (21/323) in the placebo group compared with 2% (5/277) in the oseltamivir phosphate group; this difference was not statistically significant.

- A secondary analysis was performed among the same clinical groups and RT-PCR for laboratory confirmation of influenza infection. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR confirmed clinical influenza infection was 3% (7/233) in the placebo group and <1% (1/232) in the oseltamivir phosphate group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Oseltamivir Phosphate for Oral Suspension (Supplied as Powder)

- Supplied as a white to light yellow powder blend in a glass bottle. After constitution, the powder blend produces a white to light yellow, suitably-flavored oral suspension. Each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir phosphate (immunocompromised).

Storage

Store dry powder at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store constituted oral suspension under refrigeration for up to 17 days at 2° to 8°C (36° to 46°F). Do not freeze.

Alternatively, store constituted suspension for up to 10 days at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Skin/Hypersensitivity Reactions

- Advise patients and caregivers of the risk of severe allergic reactions (including anaphylaxis) or serious skin reactions. Instruct patients and caregivers to stop oseltamivir phosphate for oral suspension and seek immediate medical attention if an allergic-like reaction occurs or is suspected [see Warnings and Precautions (5.1)].

Neuropsychiatric Events

- Advise patients and caregivers of the risk of neuropsychiatric events in oseltamivir phosphate-treated patients with influenza and instruct patients to contact their physician if they experience signs of abnormal behavior while receiving oseltamivir phosphate for oral suspension.

Important Dosing Information

- Instruct patients to begin treatment with oseltamivir phosphate for oral suspension as soon as possible from the first appearance of flu symptoms, within 48 hours of onset of symptoms. Similar to treatment for influenza in immunocompromised patients, patients in this trial received oseltamivir phosphate 75 mg or placebo once daily by mouth for 10 days. The efficacy parameter was the incidence of laboratory-confirmed clinical influenza as defined by the same criteria used in the post-exposure prophylaxis trial.

Influenza Vaccine

- Instruct patients that oseltamivir phosphate for oral suspension is not a substitute for receiving an annual flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines established by the American Academy of Pediatrics.

- In the seasonal (community outbreak) prophylaxis trial in elderly residents of skilled nursing homes, the incidence of laboratory-confirmed clinical influenza was 5% (25/519) for the placebo group and 1,379 days for the oseltamivir phosphate group. Median time since transplant for the placebo group and 1,379 days for the oseltamivir phosphate group. Median time since transplant for the placebo group and 1,379 days for the oseltamivir phosphate group. Median time since transplant for the placebo group and 1,379 days for the oseltamivir phosphate group.

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

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

Who should not take Oseltamivir phosphate for oral suspension?

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

What should I tell my healthcare provider before taking 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 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 carpes into breast milk in small amounts.

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

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

How should I take oseltamivir phosphate for oral suspension?

- Shake the oseltamivir phosphate for oral suspension well before each use.
- Open the bottle by pushing downward on the child-resistant bottle cap and twisting it in the direction of the arrow.
- 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.

How should I store 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 itches 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 the flu can develop nervous system problems and abnormal behavior that can be life threatening. During treatment with oseltamivir phosphate for oral suspension, watch for changes in behavior such as restlessness, agitation, inability to sleep, disorientation, or confusion, hallucinations, delusions, and paranoia. If you notice any of these changes, stop taking oseltamivir phosphate for oral suspension and call your healthcare provider or pharmacist right away.

The most common side effects of oseltamivir phosphate for oral suspension are:

- Headache
- Stomach upset
- Diarrhea
- Vomiting

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.

- Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of oseltamivir phosphate for oral suspension.
- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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. They may have different medicine needs.

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.

Active ingredient: oseltamivir phosphate

 inactive ingredients:
 sorbitol, monosodium citrate, sunflower gum, trisodium citrate, sodium lactate citric acid, and water.

Manufactured by:
Novartis Pharmaceuticals USA LLC
St. Louis, MO 63164

Distributed by:
Zydus Pharmaceuticals USA LLC
Pennington, NJ 08534

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

Instructions For Use

How to Use oseltamivir phosphate for oral suspension

Step 1. Rinse oral dosing dispenser under running tap water and allow to air dry 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.
Step 3. Measure the oral suspension with an appropriate oral dosing dispenser to be sure you get the direction of the arrow.
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 have been approved by the U.S. Food and Drug Administration. Revised 06/2016

PACKAGE LABEL PRINCIPAL DISPLAY PANEL

MDC 70710-1165-6 Oseltamivir Phosphate for Oral Suspension 6 mg/mL * Rx Only
Oseltamivir Phosphate
for Oral Suspension

6 mg/mL*
60 mL (usable volume afterconstitution)

Rx Only

**Oseltamivir Phosphate**
oral oseltamivir phosphate for suspension

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

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