**Limitations of Use**

Oseltamivir Phosphate Capsules, USP are indicated for the prophylaxis of influenza A and B in patients 1 year and older.

**Prophylaxis of Influenza**

Oseltamivir Phosphate Capsules, USP are indicated for the treatment of acute, uncomplicated illness due to influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours.

**Treatment of Influenza**

Oseltamivir Phosphate Capsules, USP are indicated for the prophylaxis of influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours.

**Precautions**

This product has been shown to be effective within 48 hours of symptom onset.

**Adverse Reactions**

The most common adverse reactions (>1% and more common than with placebo) are:

- **Nausea**
- **Vomiting**
- **Headache**
- **Pain**

**Contraindications**

Patients with known severe hypersensitivity to oseltamivir or any of the components of oseltamivir phosphate capsules should not receive this product.

**Warnings and Precautions**

Serious side effects and serious adverse events, including death, have occurred in children and adolescents treated with oseltamivir phosphate capsules for the prophylaxis or treatment of influenza. Some of these events have been observed in patients with influenza, including those receiving oseltamivir phosphate capsules, particularly pediatric patients, and may be at an increased risk of serious fluorinated steroidal leukocytosis and other serious side effects, such as seizures, necrotizing fasciitis, or acute renal failure. Therefore, the use of oseltamivir phosphate capsules should be considered carefully in patients with severe underlying comorbidities, including those with severe acute respiratory illness.

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2. DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

Administer oseltamivir phosphate capsules for the treatment of influenza in patients 2 weeks of age or older [see Dosage and Administration (2.2) or for prophylaxis of influenza in patients 1 year and older [see Dosage and Administration (2.3)].

The capsules may be administered without food; however, tolerability may be enhanced if oseltamivir phosphate capsules are taken with food.

Adjust the oseltamivir phosphate capsules dosage in patients with moderate or severe renal impairment [see Dosage and Administration (2.6)].

For patients who cannot swallow capsules, oseltamivir phosphate for oral suspension is the preferred formulation. When oseltamivir phosphate for oral suspension is not available from a wholesaler or the manufacturer, oseltamivir phosphate capsules may be opened and mixed with several liquids such as regular or sugar-free chocolate syrup, cool-aid, or lemon lime-flavored soda to enhance tolerability. The mixture should be given immediately after preparation, as oseltamivir phosphate may precipitate when mixed with certain liquids. Oseltamivir phosphate for oral suspension may be prepared as an emergency supply of oral suspension from oseltamivir phosphate 75 mg capsules [see Dosage and Administration (2.6)].

2.2 Recommended Dosage for Treatment of Influenza

Initiate treatment with oseltamivir phosphate capsules within 48 hours of influenza symptom onset.

Adults and Adolescents (13 years of age and older) [see Use in Specific Population (8.6 and 8.7), Microbiology (12.4)]: The recommended oral dose of oseltamivir phosphate capsules for treatment of influenza in adults and adolescents 13 years and older in 75 mg twice daily (one 75 mg capsule twice daily) for 5 days.

Pediatric Patients (2 weeks of age through 12 years of age) [see Microbiology (12.4)]: Table 1 displays the recommended oral dosage of oseltamivir phosphate for treatment of influenza in pediatric patients 2 weeks of age through 12 years of age and provides information about prescribing the capsule or the formulation for oral suspension.

2.3 Recommended Dosage for Prophylaxis of Influenza

Initiate postexposure prophylaxis with oseltamivir phosphate capsules within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with oseltamivir phosphate capsules during a community outbreak.

Adults and Adolescents (13 years of age and older) [see Use in Specific Population (8.6 and 8.7), Microbiology (12.4)]: The recommended oral dosage of oseltamivir phosphate capsules for prophylaxis of influenza in adults and adolescents 13 years and older is 75 mg really once daily (one 75 mg capsule once daily) for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, oseltamivir phosphate capsules may be continued for up to 12 weeks [see Use in Specific Population (8.6 and 8.7), Microbiology (12.4)]. The duration of protection lasts for as long as oseltamivir phosphate capsules dosing is continued.

Pediatric Patients (1 to 12 years of age) [see Microbiology (12.4)]: Table 2 displays the recommended oral dosage of oseltamivir phosphate capsules for prophylaxis of influenza in pediatric patients 1 to 12 years of age based on body weight and provides information about prescribing the capsule or the formulation for oral suspension. Prophylaxis in immunocompromised 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 Population (8.6 and 8.7), Microbiology (12.4)].

2.4 Dosage in Patients with Renal Impairment

Table 3 displays the dosage recommendations for the treatment of prophylaxis of influenza in adults with various stages of renal impairment (estimated creatinine clearance of less than 30 mL per minute) [see Microbiology (12.4)]. Dosage modifications are recommended in adults with estimated creatinine clearance less than 30 mL per minute [see Use in Specific Population (8.4) and Clinical Pharmacology (2.6)].

2.5 Dosage in Patients with Liver Impairment

Table 4 displays the dosage recommendations for the treatment and prophylaxis of influenza in adults with various stages of hepatic impairment (Child-Pugh scores 5 to 15) [see Microbiology (12.4)]. Dosage modifications are recommended in adults with Child-Pugh scores 5 to 15 [see Use in Specific Population (8.5)].

2.6 Emergency Compounding of Oral Suspension from 75 mg Oseltamivir Phosphate Capsules

The following directions are provided for use during emergency situations and FDA-approved, commercially manufactured oseltamivir phosphate for oral suspension is not available from wholesalers or the manufacturer.

The following emergency preparation instructions will provide one patient with enough Oseltamivir Phosphate for a 5-day course of treatment of influenza or a 10-day course of prophylaxis.

Step 1: Determine the dosage of oseltamivir phosphate for the patient [see Dosage and Administration (2.2, 2.3, and 2.4)] then determine the total volume of oral suspension needed to be prepared [see Table 5].

Table 3 Emergency Preparation: Volume of Prepared Oral Suspension (8 mg per mL) Based Upon Oseltamivir Phosphate Capsule Dose

<table>
<thead>
<tr>
<th>Oseltamivir Phosphate Dose</th>
<th>Total Volume to Prepare per Patient (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg of loz</td>
<td>7.5 mL</td>
</tr>
<tr>
<td>30 mg of loz</td>
<td>15 mL</td>
</tr>
<tr>
<td>45 mg of loz</td>
<td>22.5 mL</td>
</tr>
<tr>
<td>60 mg of loz</td>
<td>30 mL</td>
</tr>
</tbody>
</table>

* If the oseltamivir phosphate dose is between the dosing limits, use the greater listed dose to determine the total volume of prepared suspension.

Step 2: Prepare treatment to be performed with only one of the following vehicles (other vehicle bases have not been studied): Cherry Syrup (Humco®), Oral-Sweet® SF (sugar-free/Paddock Laboratories), or simple syrup. Determine the number of capsules and the amount of sweetener and vehicle needed to prepare the oral volume (see Table 3) and prepare oral suspension (8 mg per mL) for a complete treatment or prophylaxis course (see Table 4).

Table 4 Emergency Preparation: Number of Oseltamivir Phosphate 75 mg Capsules and Amount

<table>
<thead>
<tr>
<th>Number of Oseltamivir Phosphate 75 mg Capsules</th>
<th>Amount of Capsules</th>
<th>Amount of Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>75 mg</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>150 mg</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>225 mg</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

* Capsules and oral suspension can be used for 30 days dosing.

‡ Assuming dosing in hemodialysis sessions is performed in the 5-day period. Treatment can be initiated immediately if influenza symptoms develop during the 48 hours between hemodialysis sessions; however, the post-hemodialysis dose should still be administered independently of time of administration of the initial dose. The recommended duration for post-exposure prophylaxis is at least 10 days and the recommended duration for community outbreak (seasonal) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients). The amount supplied (e.g., number of bottles or capsules) for seasonal prophylaxis may be greater than for post-exposure prophylaxis.

† Oseltamivir phosphate for oral suspension is not recommended for use in patients with end-stage renal disease (not undergoing dialysis) [see Microbiology (12.4)].
of Water and Vehicle Needed to Prepare the Total Volume of a Prepared Oral Suspension (6 mg per mL)

<table>
<thead>
<tr>
<th>Total Volume of Prepared Oral Suspension</th>
<th>7.2 mL</th>
<th>7.3 mL</th>
<th>10 mL</th>
<th>12.5 mL</th>
<th>15 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Oseltamivir Phosphate 75 mg Capsules (Total Strength)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Amount of Water</td>
<td>2.1 mL</td>
<td>5 mL</td>
<td>7 mL</td>
<td>9 mL</td>
<td>11 mL</td>
</tr>
<tr>
<td>Amount of Vehicle per mL</td>
<td>4.5 mL</td>
<td>0.4 mL</td>
<td>0.3 mL</td>
<td>0.3 mL</td>
<td>0.3 mL</td>
</tr>
</tbody>
</table>

* Includes enough to ensure all doses can be delivered

Step 3: Follow the instructions below for preparing the 75 mg oseltamivir phosphate capsules to produce the oral suspension (6 mg/mL).

1. Place the specified amount of water into a polyethylene terephthalate (PET) or glass bottle (see Table 4). Contribution in other bottle types is not recommended because there is no stability data with other bottle types.
2. Carefully separate the capsule body and cap and pour the contents of the required number of oseltamivir phosphate 75 mg capsules into the PET or glass bottle.
3. Gently swirl the suspension to achieve uniform mixing of the oseltamivir phosphate powder for at least 2 minutes.
4. Slowly add the specified amount of vehicle to the bottle.
5. Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogenous distribution of the dissolved drug in the resulting suspension. The active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by the ingress of oseltamivir phosphate capsules which are insoluble in these vehicles.
6. Place an auxiliary label on the bottle indicating "Shake Well Before Use.”
7. Instruct the parent or caregiver that any suspension remaining in the bottle following completion of therapy must be discarded by either allowing an auxiliary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place a pharmacy label on the bottle that includes the patient's name, dosing instruction, drug name and any other required information to be in compliance with all state and Federal Pharmacy Regulations. Place an appropriate expiration date on the label according to storage conditions below.
9. Include the recommended dosage and pharmacy label as per Tables 1 and 2 (see Dosage and Administration). (2.2, 2.3, and 2.4).
10. Store the prepared oral suspension in glass or PET bottles either:

- In a refrigerator (2°C to 8°C or 36°F to 46°F). Stable for 5 weeks when stored in a refrigerator.
- At room temperature (25°C [77°F]). Stable for 5 days when stored at room temperature.
- In a refrigerator (2°C to 8°C or 36°F to 46°F). Stable for 5 weeks when stored in a refrigerator.

3 DATION FORMS AND STRENGTHS

Oseltamivir Phosphate Capsules:

- 30-mg capsules (30 mg free base equivalent of the phosphate salt) WhiteOpaque/White Opaque Capsules, imprinted with black ink “N” on the body and black ink “1009” on the cap.
- 45-mg capsules (45 mg free base equivalent of the phosphate salt) Light Blue Grey Opaque/ Light Blue Grey Opaque Capsules, imprinted with black ink “N” on the body and black ink “1009” on the cap.
- 75-mg capsules (75 mg free base equivalent of the phosphate salt) White Opal/ Light Blue Grey Opaque Capsules, imprinted with black ink “N” on the body and black ink “1010” on the cap.

4 CONTRAINDICATIONS

Oxetamivir phosphate capsules are contraindicated in patients with known serious hypersensitivity to oxetamivir or any component of the product. Oxetamivir phosphate capsules have also been shown to prevent such complications. Prescribers should be alert to the potential for serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme (see Warnings and Precautions). (5.1)

5 WARNINGS AND PRECAUTIONS

2.1 Serious Skin/Hypersensitivity Reactions

Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported postmarketing with oseltamivir phosphate capsules. Stop oseltamivir phosphate capsules and institute appropriate treatment if an allergic-like reaction occurs or is suspected. The use of oseltamivir phosphate capsules in patients with known serious hypersensitivity to oseltamivir phosphate capsules is contraindicated (see Contraindications). (6.1, 6.2).

2.2 Neuro-psychiatric Events

There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving oseltamivir phosphate capsules (see Adverse Reactions). (6.1, 6.2). Because these events were 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. Oseltamivir phosphate capsules are contraindicated in patients with known serious hypersensitivity to oxetamivir phosphate capsules (see Contraindications). (6.1, 6.2).

2.3 Risk of Bacterial Infections

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

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere (see labeling):

- Serious skin/hypersensitivity reactions (see Warnings and Precautions). (5.1)
- Neuro-psychiatric events (see Warnings and Precautions). (5.2.1)

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.

3.7 Allergic Type Reactions

Across studies, a variety of allergic-type reactions were observed in adults and adolescents treated with oseltamivir phosphate capsules. These reactions included rash, pruritus, urticaria, flushing, injection site reactions, and angioedema. These reactions usually occurred within 24 hours of first administration of oseltamivir phosphate capsules and resolved within a few days.

3.8 Abnormalities in Laboratory Tests

Influenza Prophylaxis Trials: There were no unusual changes in laboratory tests in the following studies: average hemoglobin, white blood cell count, and platelet count were all within normal ranges. Changes in other tests, such as liver enzymes and kidney function tests, were no different than those observed in placebo-treated individuals.

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>Nervous System</td>
<td>Oseltamivir Phosphate 75 mg twice daily 4 weeks (n = 2466)</td>
<td>Oseltamivir Phosphate 75 mg once daily 10 weeks (n = 1941)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine 40 mg daily (n = 1977)</td>
<td>Paroxetine 20 mg twice daily (n = 1980)</td>
</tr>
</tbody>
</table>

* Adverse reactions that occurred in ≥1% of oseltamivir phosphate-treated adults and adolescents and ≥1% greater in oseltamivir phosphate-treated subjects compared to
Pharmacology (12.3)
The safety and efficacy of oseltamivir phosphate for the treatment of influenza in pediatric patients 2

8.4 Pediatric Use
Oseltamivir phosphate capsules are administered to a nursing woman. Low levels considered unlikely to lead to toxicity in the breastfed infant. Exercise caution when based on limited published data, oseltamivir and oseltamivir carboxylate are present in human milk at low levels up to 36 weeks post-conceptional age. Exercise caution when pediatric patients.

8.5 Pediatric Use

Clinical Considerations

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

8.5 Pregnancy

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

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (2 weeks to less than 1 year of age)

Assessment of adverse reactions in pediatric subjects up to 28 days old is based on case report information provided in a double-blind, placebo-controlled trial in children aged 6 months to 11 months and a study of 70 infants aged 28 days to 28 weeks. Adverse reactions in pediatric subjects in the two studies were similar except for upper respiratory tract infection, which occurred in 11% of oseltamivir phosphate-treated subjects and 2% of placebo-treated subjects.

8.5 Pregnancy

Clinical Considerations

8.5 Pregnancy

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

Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (2 weeks to less than 1 year of age)

Assessment of adverse reactions in pediatric subjects 2 weeks to less than 1 year of age was based on case report information provided in a double-blind, placebo-controlled trial in children aged 6 months to 11 months and a study of 70 infants aged 28 days to 28 weeks. Adverse reactions in pediatric subjects in the two studies were similar except for upper respiratory tract infection, which occurred in 11% of oseltamivir phosphate-treated subjects and 2% of placebo-treated subjects.

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Clinical Considerations

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Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (2 weeks to less than 1 year of age)

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Clinical Considerations

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8.5 Pregnancy

Clinical Considerations

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Adverse Reactions from Treatment and Prophylaxis Trials in Pediatric Subjects (2 weeks to less than 1 year of age)

Assessment of adverse reactions in pediatric subjects 2 weeks to less than 1 year of age was based on case report information provided in a double-blind, placebo-controlled trial in children aged 6 months to 11 months and a study of 70 infants aged 28 days to 28 weeks. Adverse reactions in pediatric subjects in the two studies were similar except for upper respiratory tract infection, which occurred in 11% of oseltamivir phosphate-treated subjects and 2% of placebo-treated subjects.
Absorption and Bioavailability

Oseltamivir is an antiviral drug with activity against influenza virus. The chemical name is C16H28N2O4 (free base). The molecular weight is 312.4 for oseltamivir free base and 568.5 for oseltamivir (2S,3R)-epxyprooxy-3-amino-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical name is C16H28N2O4.

Absorption of oseltamivir capsules is rapid and complete with peak plasma concentrations achieved within 2 hours after oral administration in both elderly and younger subjects. Approximately 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate and less than 5% of the dose is excreted unchanged in the urine. Oseltamivir is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 80% of the oseltamivir carboxylate dose is metabolized or excreted in the urine as glucuronides.

Distribution

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 oral dose reaches the systemic circulation as oseltamivir.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oseltamivir</th>
<th>Oseltamivir Carboxylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>65 (20)</td>
<td>348 (10)</td>
</tr>
<tr>
<td>AUC(0-12h) (mg h/L)</td>
<td>119 (35)</td>
<td>219 (30)</td>
</tr>
</tbody>
</table>

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg oseltamivir daily (about 6.7 times the maximum recommended oseltamivir phosphate capsules dosage) (see Dosage and Administration (2.2)). Coadministration with food has no significant effect on peak plasma concentration (55% mg/L under fed condition and 44% mg/L under fed condition) and the area under the plasma concentration time curve (0.2 to 24 h) under fed conditions and 0.2 to 5 h under fed conditions.

Efficacy of oseltamivir phosphate for prophylaxis of influenza has not been established for pediatric patients less than 1 year of age.

8.5 Geriatric Use

Treatment of Influenza

Oseltamivir phosphate capsules for the treatment of influenza, 75 mg or 75 mg twice daily for 5 days in household contacts including 207 post-exposure household prophylaxis trial of oseltamivir phosphate 75 mg taken orally once daily for 10 days (see Clinical Pharmacology (12.3) and Clinical Studies (14.2)).

Postmarketing Experience

Efficacy of oseltamivir phosphate capsules for the prophylaxis of influenza in patients with severe renal impairment (creatinine clearance 10 to 60 mL/minute and for patients with end-stage renal disease (ESRD) undergoing continuous renal replacement therapy (see Dosage and Administration (2.2)). Oseltamivir phosphate capsules are not recommended for use in patients with ESRD undergoing hemodialysis or continuous peritoneal dialysis treatment (see Dosage and Administration (2.2)).

8.6 Renal Impairment

The safety and efficacy of oseltamivir phosphate for treatment of influenza in patients with chronic renal impairment and/or respiratory disease was evaluated in one randomized, placebo-controlled clinical trial. Efficacy in this 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)).

8.7 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)).

8.8 Use in Patients with Chronic Conditions

Efficacy of oseltamivir phosphate capsules 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 this 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)).

9 Immunocompromised Patients

Efficacy of oseltamivir phosphate capsules for the treatment or prophylaxis of influenza has been established in immunocompromised patients (see Clinical Studies (14.2)). Safety of oseltamivir phosphate capsules for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients (see Adverse Reactions (6.1)).

10 OVERDOSAGE

Reports of overdoses with oseltamivir phosphate capsules have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdoses, no adverse reactions were reported. Adverse reactions reported following overdose were similar in nature to those observed in patients with therapeutic doses of oseltamivir phosphate capsules (see Clinical Pharmacology (12.3)).

11 DESCRIPTION

Oseltamivir Phosphate Capsules, USP, as influenza-neuraminidase inhibitors (NAIs), are available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir carboxylate. Each capsule contains povidone, croscarmellose sodium, and sodium stearyl fumarate. The 30 mg capsule shell contains titanium dioxide, and sodium lauryl sulfate, FD&C Blue 1, D&C Red 28, and FD&C Red 40. Each capsule contains oseltamivir phosphate 30 mg, 45 mg, or 75 mg.

Pharmacology (12.3)

Bioavailability of oseltamivir following oral administration is 75% under fasted conditions and 44% under fed conditions.

Pharmacokinetics in patients with severe hepatic impairment have not been evaluated (see Clinical Pharmacology (12.3)).

Efficacy in the treatment of influenza in patients with severe hepatic impairment has not been established, but no new safety signals were identified (see Clinical Studies (14.2)).

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Efficacy in the treatment of influenza in patients with severe hepatic impairment has not been established, but no new safety signals were identified (see Clinical Studies (14.2)).
The volume of distribution (Vd) 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 proteins is low (8%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Elimination
Absorbed oseltamivir is primarily (≥90%) eliminated by conversion to the active metabolite, oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1.3 to 3 hours in normoalbuminemic subjects. Oseltamivir carboxylate is not further metabolized and is eliminated entirely by urinary excretion. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration.

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

Dosage
Oseltamivir carboxylate is administered orally (≥95%) by oral route. Clinical trials have been conducted in the adult (≥12 years of age) and pediatric (≥1 year of age) populations with influenza A and B infections. Oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 8. The pharmacodynamics of oseltamivir have been studied in ESRD patients undergoing dialysis (see Indications and Usage (1.3) and Use in Specific Populations (8.7)).

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>PK Exposure Parameter</th>
<th>Recommended Prophylaxis Regimens</th>
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* All dosages: 10 mg for 48 hours.

In clinical studies oseltamivir exposure was not altered in subjects with mild to moderate hepatic impairment (see Use in Specific Populations (8.7)).

Pediatric Subjects
A pooled population pharmacokinetic analysis indicates that the oseltamivir phosphate capsules dosage regimens resulted in lower exposure in the active metabolite in pediatric subjects (oseltamivir carboxylate) compared to non-pediatric subjects (12). However, this predicted exposure is expected to have no activity against susceptible influenza virus strains, and there are no clinical pharmacokinetics and safety data to recommend a dose adjustment for pediatric patients (see Use in Specific Populations (8.4)).

Pediatric Subjects (1 year to 12 years of age)

In vitro studies demonstrated that neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms. The binding of oseltamivir carboxylate to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions. The volume of distribution (Vd) 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 proteins is low (8%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

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

Influenza A (HA numbering in brackets)

<table>
<thead>
<tr>
<th>Neuraminidase Amino Acid Substitutions</th>
<th>Influenza A N1 (N1 numbering in brackets)</th>
<th>Influenza A N2 (N2 numbering in brackets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A11T</td>
<td>R453M</td>
<td>A11T</td>
</tr>
<tr>
<td>A11T</td>
<td>A134G</td>
<td>A11T</td>
</tr>
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<td>A11T</td>
<td>K173G</td>
<td>A11T</td>
</tr>
<tr>
<td>A11T</td>
<td>H275Y</td>
<td>A11T</td>
</tr>
</tbody>
</table>

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

A double-blind, placebo-controlled, multicenter trial was unable to demonstrate efficacy of oseltamivir phosphate capsules in men and women. Study medication was started within 40 hours of onset of symptoms and administered twice daily for 5 days compared to subjects who received placebo. Subgroup analyses by gender showed no differences in the treatment effect of oseltamivir phosphate capsules in men and women. In 2-year carcinogenicity studies in mice and rats given daily oral doses of the prodrug oseltamivir carboxylate that occurs after administration of the maximum recommended human dose. There were no effects on fertility, mating performance or early embryonic development at any dose. Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse lymphoma assay with and without enzymatic activation and negative in the SCE cell transformation assay. Its fertility and early embryonic development studies in mice, doses of oseltamivir carboxylate 25 and 50 mg/kg were administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy. Males were dosed for 2 weeks before mating, during mating and 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose was approximately 100 times the human systemic exposure (AUC0-24h) of oseltamivir carboxylate that occurs after administration of the maximum recommended human dose.

3. NONCLINICAL TOXICOLOGY
3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Table 8 Neuraminidase Amino Acid Substitutions Associated with Reduced Susceptibility to Oseltamivir
Pediatric Subgroup (1 year to 12 years of age)

The efficacy of oseltamivir phosphate in preventing naturally occurring influenza illness has been demonstrated in seasonal prophylaxis (community outbreak) clinical trials and one post-exposure prophylaxis trial in household contacts. 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:

- A measured oral temperature greater than or equal to 99.0°F (37.2°C).
- At least one respiratory symptom (cough, sore throat, nasal congestion).
- At least one constitutional symptom (fever, fatigue, headache, chills, muscle aches), and
- Either a positive virus detection or a four-fold increase in virus antibody titer from baseline.

The post-exposure prophylaxis trial in household contacts (aged 13 years or older) of an index case, oseltamivir phosphate 75 mg once daily or placebo orally, was administered within 48 hours of onset of symptoms (index case and continued for 7 days (index cases did not receive oseltamivir phosphate capsules immediately). The incidence of laboratory-confirmed clinical influenza was 5% (15/276) in the placebo-treated subjects compared to less than 1% (0/40) in the oseltamivir phosphate-treated subjects.

In the post-exposure prophylaxis trial in household contacts (aged 1 year to 12 years of age), oseltamivir phosphate 75 mg once daily or placebo orally, was administered within 48 hours of onset of symptoms (index case and continued for 7 days). The incidence of laboratory-confirmed clinical influenza in the household, laboratory-confirmed clinical influenza was defined as meeting all of the following criteria:

- A measured oral temperature greater than or equal to 99.0°F (37.2°C).
- At least one respiratory symptom (cough, sore throat, nasal congestion).
- At least one constitutional symptom (fever, fatigue, headache, chills, muscle aches), and
- Either a positive virus detection or a four-fold increase in virus antibody titer from baseline or illness visit.

Among household contacts 1 year to 12 years of age not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was lower in the group who received oseltamivir phosphate prophylaxis (6.0% (5/83)) compared to the group who did not receive oseltamivir phosphate prophylaxis (17.1% (14/82)).

Immunocompromised Subjects

A double-blind, placebo-controlled trial was conducted for seasonal prophylaxis of influenza in 675 immunocompromised subjects (including 10 pediatric subjects 1 year to 12 years of age), who had received solid organ (388; liver, kidney, liver and kidney) or hematopoietic stem cell transplant recipients (287). Median time since transplantation for solid organ transplant recipients was 3,105 days for the placebo group and 1,379 days for the oseltamivir phosphate group. Median time since transplantation for hematopoietic stem cell transplant recipients was 42 days for the placebo group and 387 days for the oseltamivir phosphate group. Approximately 40% of subjects received influenza vaccine prior to entering the study. The primary efficacy endpoint was the incidence of confirmed clinical influenza prior to or at illness visit. The primary efficacy endpoint was the incidence of confirmed clinical influenza at each visit. The incidence of laboratory-confirmed clinical influenza was 3.5% (2/57) in the placebo group and 2.0% (1/50) in the oseltamivir phosphate group. The difference was not statistically significant. A secondary analysis was performed using the same clinical endpoint and RT-PCR for laboratory-confirmed influenza infection. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR-confirmed clinical influenza infection was 3% (2/73) in the placebo group and <1% (0/123) in the oseltamivir phosphate group.
Oseltamivir phosphate capsules: As prescribed by your doctor.

**What are Oseltamivir Phosphate Capsules?**

Oseltamivir phosphate capsules are a prescription medicine used to:

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

It is not known if oseltamivir phosphate capsules are:

- effective in people who start treatment after 2 days of developing flu symptoms.
- effective for the treatment of the flu in people with long-time (chronic) heart problems or breathing problems.
- effective for the treatment or prevention of the flu in people who have weakened immune system (immunosuppression).

- safe and effective for the treatment of the flu in children less than 2 weeks of age.
- safe and effective in the prevention of the flu in children less than 1 year of age.

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

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

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

**When should I take Oseltamivir Phosphate Capsules?**

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

- have problems swallowing oseltamivir phosphate capsules
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. Available information indicates that oseltamivir phosphate capsules do not increase the risk of birth defects
- are breastfeeding or plan to breast feed. Oseltamivir phosphate capsules pass into breast milk in small amounts.

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

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

**How should I take Oseltamivir Phosphate Capsules?**

Take oseltamivir phosphate capsules exactly as your healthcare provider tells you.

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

Oseltamivir phosphate capsules may cause serious side effects, including:

- Serious skin and allergic reactions. Oseltamivir phosphate capsules can cause serious skin and allergic reactions. Stop taking oseltamivir phosphate capsules and get medical help right away if you get any of the following symptoms:
  - skin rash or hives
  - your skin blisters and peels
  - hives or swelling 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 is not normal. During treatment with oseltamivir phosphate capsules, tell your healthcare provider right away if you or your child have confusion, sleep problems, uncontrolled noises or voices that are not really there (hallucinations).

The most common side effects of oseltamivir phosphate capsules when used for treatment of the flu include:

- nausea
- vomiting
- headache
- stomach pain
- diarrhea

The most common side effects of oseltamivir phosphate capsules when used for prevention of the flu include:

- nausea
- vomiting
- headache
- stuffy nose

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are all of the possible side effects of oseltamivir phosphate capsules.

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

**How should I store Oseltamivir Phosphate Capsules?**

- Store oseltamivir phosphate capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep oseltamivir phosphate capsules and all medicines out of the reach of children.

**General information about the safe and effective use of Oseltamivir Phosphate Capsules.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use oseltamivir phosphate capsules for a condition for which it was not prescribed. Do not give oseltamivir phosphate capsules to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about oseltamivir phosphate capsules that is written for health professionals. For more information, contact Zydus Pharmaceuticals at 1-877-993-8779.

**What are the ingredients in Oseltamivir Phosphate Capsules?**

**Active ingredient:** oseltamivir phosphate

**Inactive ingredients:**

Oseltamivir phosphate capsules: pregelatinized starch, gelatin, titanium dioxide, and sodium lauryl sulfate, FD&C Blue 1, D&C Red 28, and FD&C Red 40

Manufactured by: Zydus Pharmaceuticals USA LLC

Distributed by: Zydus Pharmaceuticals USA Inc.

This Patient Information has been approved by the U.S. Food and Drug Administration.
INSTRUCTIONS FOR USE
Oseltamivir phosphate capsules, USP, for oral use (os-el-TAM-ih-veer)

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

You will need:

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

Step 1. Open the contents of the prescribed dose of oseltamivir phosphate capsules into a small bowl.
Step 2. Add a small amount of the sweetened liquid to the capsule contents.
Step 3. Stir the mixture and give the entire dose of oseltamivir phosphate.

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