

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use OSELTAMIVIR PHOSPHATE CAPSULES safely and effectively. See full prescribing information for OSELTAMIVIR PHOSPHATE CAPSULES.**  
**OSELTAMIVIR PHOSPHATE capsules for oral use**  
**Initial U.S. Approval: 1999**

### INDICATIONS AND USAGE

Osetamivir phosphate capsules are an influenza neuraminidase inhibitor (NAI) indicated for:

- Treatment of acute, uncomplicated influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours. (1.1)
- Prophylaxis of influenza A and B in patients 1 year and older. (1.2)

### Limitations of Use:

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

### DOSAGE AND ADMINISTRATION

#### Treatment of influenza

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

#### Prophylaxis of influenza

- Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days (2.3)
  - Community outbreak: 75 mg once daily for up to 6 weeks (2.3)
- Pediatric patients 1 to 12 years of age: Based on weight once daily for 10 days (2.3)
  - Community outbreak: Based on weight once daily for up to 6 weeks (2.3)
- Renally impaired adult patients (creatinine clearance >30 to 60 mL/min): Reduce to 30 mg once daily (2.4)

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Treatment of Influenza

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

#### 1.2 Prophylaxis of Influenza

Osetamivir phosphate capsules are indicated for the prophylaxis of influenza A and B in patients 1 year and older.

#### 1.3 Limitations of Use

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage and Administration Overview

Administer osetamivir phosphate capsules for the treatment of influenza in patients 2 weeks of age or older (see *Dosage and Administration* (2.2)) or for prophylaxis of influenza in patients 1 year and older (see *Dosage and Administration* (2.3)) using:

#### Osetamivir phosphate capsules

The capsules may be taken with or without food; however, tolerability may be enhanced if osetamivir phosphate capsules is taken with food.

Adjust the osetamivir phosphate capsules dosage in patients with moderate or severe renal impairment (see *Dosage and Administration* (2.4)).

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

#### 2.2 Recommended Dosage for Treatment of Influenza

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

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

The recommended oral dosage of osetamivir phosphate capsules for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily (one 75 mg capsule or 12.5 mL of oral suspension twice daily) for 5 days.

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

Table 1 displays the recommended oral dosage of osetamivir phosphate capsules 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 post-exposure prophylaxis with osetamivir phosphate capsules within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with osetamivir phosphate capsules during a community outbreak.

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

The recommended dosage of osetamivir phosphate capsules for prophylaxis of influenza in adults and adolescents 13 years and older is 75 mg orally once daily (one 75 mg capsule or 12.5 mL of oral suspension once daily) for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, osetamivir phosphate capsules may be continued for up to 12 weeks (see *Use in Specific Populations* (8.9)). The duration of protection lasts for as long as osetamivir phosphate capsules dosing is continued.

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

Table 1 displays the recommended oral dosage of osetamivir phosphate capsules for prophylaxis of influenza in pediatric patients 1 year to 12 years of age based on body weight and provides information about prescribing the capsule or the formulation for oral suspension. Prophylaxis in pediatric patients is recommended for 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak (see *Use in Specific Populations* (8.4) and *Clinical Studies* (14.2)).

### Table 1 Osetamivir phosphate Dosage Recommendations in Pediatric Patients for Treatment and Prophylaxis of Influenza

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

\*The recommended duration for post-exposure prophylaxis is 10 days and the recommended duration for community outbreak (seasonal/pre-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients). The amount supplied (e.g., number of bottles or capsules) for seasonal prophylaxis may be greater than for post-exposure prophylaxis.

†Use an oral dosing dispensing device that measures the appropriate volume in mL with the oral suspension.

‡Osetamivir phosphate for oral suspension is the preferred formulation for patients who cannot swallow capsules.

§For patients less than 1 year of age, provide an appropriate dosing device that can accurately measure and administer small volumes.

#### 2.4 Dosage in Patients with Renal Impairment

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

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

Renal Impairment (Creatinine Clearance)	Recommended Treatment Regimen*	Recommended Prophylaxis Regimen†
Mild (>60 to 90 mL/minute)	75 mg twice daily for 5 days	75 mg once daily
Moderate (>30 to 60 mL/minute)	30 mg twice daily for 5 days	30 mg once daily
Severe (>10 to 30 mL/minute)	30 mg once daily for 5 days	30 mg every other day

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

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

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

### ADVERSE REACTIONS

Most common adverse reactions (>1% and more common than with placebo):

- Treatment studies – Nausea, vomiting, headache. (6.1)
- Prophylaxis studies – Nausea, vomiting, headache, pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novado Pharmaceuticals LLC at 1-855-668-2369 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

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

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

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Renal Impairment (Creatinine Clearance)	Recommended Treatment Regimen*	Recommended Prophylaxis Regimen†
ESRD Patients on Hemodialysis (≤10 mL/minute)	30 mg immediately and then 30 mg after every hemodialysis cycle (treatment duration not to exceed 5 days)	30 mg immediately and then 30 mg after alternate hemodialysis cycles
ESRD Patients on Continuous Ambulatory Peritoneal Dialysis‡ (≤10 mL/minute)	A single 30 mg dose administered immediately	30 mg immediately and then 30 mg once weekly
ESRD Patients <b>not</b> on Dialysis	Osetamivir phosphate capsule is not recommended	Osetamivir phosphate capsule is not recommended

\*Capsules can be used for 30 mg dosing.

†The recommended duration for post-exposure prophylaxis is at least 10 days and the recommended duration for community outbreak (seasonal/pre-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients).

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

#### 2.6 Emergency Preparation of Oral Suspension from 75 mg osetamivir phosphate Capsules

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

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

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

#### Table 3 Emergency Preparation: Volume of Prepared Oral Suspension (6 mg per mL) Based Upon osetamivir phosphate Dose

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

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

**Step #2:** Preparation must be performed with only one of the following vehicles (other vehicles have not been studied): Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), or simple syrup.

Determine the number of capsules and the amount of water and vehicle needed to prepare the total volume (see Table 3) of prepared oral suspension (6 mg per mL) for a complete treatment or prophylaxis course (see Table 4).

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

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

\*Includes overage to ensure all doses can be delivered

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

- Place the specified amount of water into a polyethylene terephthalate (PET) or glass bottle (see Table 4). Constitution in other bottle types is not recommended because there is no stability data with those bottle types.
- Carefully separate the capsule body and cap and pour the contents of the required number of osetamivir phosphate 75 mg capsules into the PET or glass bottle.
- Gently swirl the suspension to ensure adequate wetting of the osetamivir phosphate powder for at least 2 minutes.
- Slowly add the specified amount of vehicle to the bottle.
- Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. The active drug, osetamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of osetamivir phosphate capsules which are insoluble in these vehicles.
- Put an ancillary label on the bottle indicating "Shake Well Before Use."
- Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
- Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations. Place an appropriate expiration date on the label according to storage conditions below.
- Include the recommended dosage on the pharmacy label as per Tables 1 and 2 (see *Dosage and Administration* (2.2, 2.3, and 2.4)).
- Store the prepared oral suspension in glass or PET bottles either:
  - In a refrigerator (2° to 8°C (36° to 46°F)): Stable for 5 weeks when stored in a refrigerator.
  - At room temperature (25°C (77°F)): Stable for 5 days when stored at room temperature.

### 3 DOSAGE FORMS AND STRENGTHS

Osetamivir phosphate capsules, USP:

- 30-mg (30 mg free base equivalent of the phosphate salt). Size "4" hard gelatin capsules with light yellow opaque colour body with black colour band, imprinted with "M" and light yellow opaque cap imprinted with "30 mg".
- 45-mg (45 mg free base equivalent of the phosphate salt). Size "4" hard gelatin capsules with grey opaque colour body with black colour band, imprinted with "M" and grey opaque colour cap imprinted with "45 mg".
- 75-mg (75 mg free base equivalent of the phosphate salt). Size "2" hard gelatin capsules with grey opaque colour body with black colour band, imprinted with "M" and light yellow opaque colour cap imprinted with "75 mg".

### 4 CONTRAINDICATIONS

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Serious Skin/Hypersensitivity Reactions

Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience with osetamivir phosphate. Stop osetamivir phosphate and institute

appropriate treatment if an allergic-like reaction occurs or is suspected. The use of osetamivir phosphate is contraindicated in patients with known serious hypersensitivity to osetamivir phosphate (see *Contraindications* (4) and *Adverse Reactions* (6.2)).

#### 5.2 Neuropsychiatric Events

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

#### 5.3 Risk of Bacterial Infections

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

#### 5.4 Fructose Intolerance in Patients with Hereditary Fructose Intolerance

Fructose can be harmful to patients with hereditary fructose intolerance. One dose of 75 mg osetamivir phosphate for oral suspension delivers 2 grams of sorbitol. This is above the daily maximum limit of sorbitol for patients with hereditary fructose intolerance, and may cause dyspepsia and diarrhea.

### 6 ADVERSE REACTIONS

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

- Serious skin and hypersensitivity reactions (see *Warnings and Precautions* (5.1))
- Neuropsychiatric events (see *Warnings and Precautions* (5.2))

#### 6.1 Clinical Trials Experience

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

#### Adverse Reactions from Treatment and Prophylaxis Trials in Adult and Adolescent Subjects (13 years of age and older)

The overall safety profile of osetamivir phosphate is based on data from 2,646 adult and adolescent subjects that received the recommended dosage of 75 mg orally twice daily for 5 days for treatment of influenza and 1,943 adult and adolescent subjects that received the recommended dosage of 75 mg orally once daily for up to 6 weeks for prophylaxis of influenza in clinical trials.

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

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

System Organ Class Adverse Reaction	Treatment Trials		Prophylaxis Trials	
	Osetamivir phosphate 75 mg twice daily (n=2646)	Placebo (n=1977)	Osetamivir phosphate 75 mg once daily (n=1943)	Placebo (n=1586)
Gastrointestinal Disorders Nausea Vomiting	10 % 8 %	6 % 3 %	8 % 2 %	4 % 1 %
Nervous System Disorders Headache General Disorders	2 %	1 %	17 %	16 %
	<1 %	<1 %	4 %	3 %

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

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

A total of 1,481 pediatric subjects (including otherwise healthy pediatric subjects aged 1 year to 12 years and asthmatic pediatric subjects aged 6 to 12 years) participated in clinical trials of osetamivir phosphate for the treatment of influenza. A total of 859 pediatric subjects received treatment with osetamivir phosphate for oral suspension either at a 2 mg per kg twice daily for 5 days or weight-band dosing. Vomiting was the only adverse reaction reported at a frequency of ≥1% in subjects receiving osetamivir phosphate (16%) compared to placebo (8%).

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

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

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

#### Adverse Reactions from the Prophylaxis Trial in Immunocompromised Subjects

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

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## 8.4 Pediatric Use

### Treatment of Influenza

The safety and efficacy of oseltamivir phosphate for the treatment of influenza in pediatric patients 2 weeks old to 17 years of age has been established [*see Dosage and Administration (2.2), Clinical Pharmacology (12.3), and Clinical Studies (14.1)*] and is based on:

- 13 to 17 years of age: Safety and efficacy in adolescent patients 13 to 17 years of age was supported by adequate and well-controlled trials in adults and adolescents and younger pediatric patients and safety data in adolescents treated with oseltamivir phosphate in a study of treatment and prophylaxis.
- 1 year to 12 years of age: Safety and efficacy in pediatric patients 1 year to 12 years of age was supported by results of one double-blind, placebo-controlled trial in 452 pediatric patients with influenza in whom oseltamivir phosphate 2 mg per kg twice daily or placebo was administered within 48 hours of symptom onset [*see Clinical Studies (14.1)*]. Additional safety information was provided in a double-blind, placebo-controlled trial in pediatric patients 6 to 12 years of age with known asthma. Efficacy could not be established in pediatric patients with asthma.
- 2 weeks to less than 1 year of age: Safety and efficacy in pediatric patients 2 weeks to less than 1 year of age is supported by adequate and well-controlled trials in adults and older pediatric patients and two open-label trials of oseltamivir phosphate (2 to 3.5 mg per kg twice daily for 5 days) in 136 pediatric subjects 2 weeks to less than 1 year of age. In these two trials, the oseltamivir plasma concentrations in these subjects were similar to or higher than the oseltamivir plasma concentrations observed in older pediatric subjects and adults [*see Clinical Pharmacology (12.3) and Clinical Studies (14.1)*].

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

### Prophylaxis of Influenza

The safety and efficacy of oseltamivir phosphate for the prophylaxis of influenza in pediatric patients 1 year to 17 years old has been established [*see Dosage and Administration (2.3), Clinical Pharmacology (12.3), and Clinical Studies (14.2)*] and is based on:

- 13 to 17 years of age: Prophylaxis in adolescent patients 13 to 17 years of age is supported by one randomized, placebo-controlled post-exposure household prophylaxis trial of oseltamivir phosphate 75 mg taken orally once daily for 7 days in household contacts including 207 adolescents [*see Clinical Studies (14.2)*].
- 1 year to 12 years of age: Oseltamivir phosphate for prophylaxis in pediatric patients 1 year to 12 years of age is supported by one randomized, open-label, post-exposure household prophylaxis trial including pediatric subjects 1 year to 12 years of age who received 30 to 60 mg of oseltamivir phosphate for oral suspension (supplied as powder) taken orally once daily for 10 days [*see Clinical Studies (14.2)*]. Additional safety information was provided in a 6-week seasonal prophylaxis (community outbreak) safety study in 49 patients 1 year to 12 years of age.

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

## 8.5 Geriatric Use

### Treatment of Influenza

Of the 4,765 adults in clinical trials of oseltamivir phosphate for the treatment of influenza, 948 (20%) were 65 years and older, while 329 (7%) were 75 years and older. In three double-blind, placebo-controlled trials in the treatment of influenza in patients at least 65 years old, that enrolled 741 subjects (374 received placebo and 362 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 responses between the elderly and younger subjects [*see Clinical Studies (14.1)*].

### Prophylaxis of Influenza

Of the 4,803 adults in clinical trials of oseltamivir phosphate for the prophylaxis of influenza, 1,046 (23%) were 65 years and older, while 719 (16%) were 75 years and older. In a randomized, placebo-controlled trial in elderly residents of nursing homes who took oseltamivir phosphate for up to 42 days for the prophylaxis of influenza (oseltamivir phosphate *n*=276, placebo *n*=272), no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects [*see Clinical Studies (14.2)*].

## 8.6 Renal Impairment

Patients with renal impairment had higher blood levels of oseltamivir carboxylate compared to patients with normal renal function which may increase the risk of oseltamivir phosphate-associated adverse reactions. Therefore, dosage adjustment is recommended for patients with a serum creatinine clearance between 10 and 60 mL/minute 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 is not recommended for patients with ESRD not undergoing dialysis [*see Indications and Usage (1.3) and Clinical Pharmacology (12.3)*].

## 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 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 (14.1)*].

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

## 8.9 Immunocompromised Patients

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

## 10 OVERDOSAGE

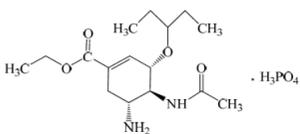
Reports of overdoses with oseltamivir phosphate have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse reactions were reported. Adverse reactions reported following overdose were similar in nature to those observed with therapeutic doses of oseltamivir phosphate [*see Adverse Reactions (6)*].

## 11 DESCRIPTION

Oseltamivir phosphate, USP an influenza neuraminidase inhibitor (NAI), is available as:

- Capsules containing 30 mg, 45 mg, or 75 mg of oseltamivir for oral use, in the form of oseltamivir phosphate
- In addition to the active ingredient, each capsule contains croscarmellose sodium, povidone K30, pregelatinized starch, sodium stearyl fumarate and talc. The 30 mg capsule shell contains gelatin, iron oxide red, iron oxide yellow, and titanium dioxide. The 45 mg capsule shell contains gelatin, iron oxide black and titanium dioxide. The 75 mg capsule shell contains gelatin, iron oxide black, iron oxide red, iron oxide yellow, and titanium dioxide. Each capsule is printed with black ink, which includes shellac, propylene glycol,black iron oxide and potassium hydroxide.

Oseltamivir phosphate, USP is a white to off white powder with the chemical name (3*R*,4*R*,5*S*)-4-acetylamino-5-amino 3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The molecular formula is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>P (free base). The molecular weight is 312.4 for oseltamivir free base and 410.40 for oseltamivir phosphate salt. The structural formula is as follows:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

#### Absorption and Bioavailability

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

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

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

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

Coadministration with food had no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

#### Distribution

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

#### Elimination

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

#### Metabolism

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

#### Excretion

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

#### Specific Populations

#### Renal Impairment

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

Population-derived pharmacokinetic parameters were determined for patients with varying degrees of renal function including ESRD patients on hemodialysis. Median simulated exposures of oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in Table 7. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis [*see Indications and Usage (1.3), and Use in Specific Populations (8.6)*].

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

Renal Function/ Impairment	Normal Creatinine Clearance 90-140 mL/min (n=57)	Mild Creatinine Clearance 60-90 mL/min (n=45)	Moderate Creatinine Clearance 30-60 mL/min (n=13)	Severe Creatinine Clearance 10-30 mL/min (n=11)	ESRD Creatinine Clearance <10 mL/min on Hemodialysis (n=24)
<b>Recommended Treatment Regimens</b>					
<b>PK exposure parameter</b>	<b>75 mg twice daily</b>	<b>75 mg twice daily</b>	<b>30 mg twice daily</b>	<b>30 mg once daily</b>	<b>30 mg every HD cycle</b>
C <sub>max</sub> (ng/mL)	145	253	180	219	221

Renal Function/ Impairment	Normal Creatinine Clearance 90-140 mL/min (n=57)	Mild Creatinine Clearance 60-90 mL/min (n=45)	Moderate Creatinine Clearance 30-60 mL/min (n=13)	Severe Creatinine Clearance 10-30 mL/min (n=11)	ESRD Creatinine Clearance <10 mL/min on Hemodialysis (n=24)
C <sub>max</sub> (ng/mL)	298	464	306	477	1170
AUC <sub>0-24</sub> (ng·hr/mL)	11224	18476	12008	16818	23200

#### Recommended Prophylaxis Regimens

PK exposure parameter	75 mg once daily	75 mg once daily	30 mg once daily	30 mg every other day	30 mg alternate HD cycle
C <sub>max</sub> (ng/mL)	39	62	57	70	42
C <sub>min</sub> (ng/mL)	213	311	209	377	903
AUC <sub>0-24</sub> (ng·h/mL)	5294	8336	6262	9317	11200

AUC normalized to 48 hours

In continuous ambulatory peritoneal dialysis (CAPD) patients, the peak concentration of oseltamivir carboxylate following a single 30 mg dose of oseltamivir or once weekly oseltamivir was approximately 3-fold higher than in patients with normal renal function who received 75 mg twice daily. The plasma concentration of oseltamivir carboxylate on day 5 (147 ng/mL) following a single 30 mg dose in CAPD patients is similar to the predicted C<sub>max</sub> (160 ng/mL) in patients with normal renal function following 75 mg twice daily. Administration of 30 mg once weekly to CAPD patients resulted in plasma concentrations of oseltamivir carboxylate at the 168-hour blood sample of 63 ng/mL, which were comparable to the C<sub>min</sub> in patients with normal renal function receiving the approved regimen of 75 mg once daily (40 ng/mL).

#### Hepatic Impairment

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

#### Pregnant Women

A pooled population pharmacokinetic analysis indicates that the oseltamivir phosphate dosage regimen resulted in lower exposure to the active metabolite in pregnant women (n=59) compared to non-pregnant women (n=33). However, this predicted 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 (8.1)*].

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

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

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

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

#### Geriatric Patients

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

#### Drug Interaction Studies

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low. *In vitro* studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

Coadministration of probenecid results in an approximate two-fold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when coadministering with probenecid.

No clinically relevant pharmacokinetic interactions have been observed when coadministering oseltamivir with amoxicillin, acetaaminophen, aspirin, dinitroben, antacids (magnesium and aluminum hydroxides and calcium carbonates), rimantadine, amantadine, or warfarin.

## 12.4 Microbiology

### Mechanism of Action

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

#### Antiviral Activity

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub>) were in the range of 0.0083 micromolar to greater than 35 micromolar and 0.004 micromolar to greater than 100 micromolar, respectively (1 micromolar=0.284 microgram per mL). The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.

#### Resistance

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

Clinical studies: Reduced susceptibility isolates have been obtained during treatment with oseltamivir and from sampling during community surveillance studies. Changes in the viral neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are summarized in Table 8. The clinical impact of this reduced susceptibility is unknown. Hemagglutinin (HA) substitutions selected in cell culture and associated with reduced susceptibility to oseltamivir include (influenza virus subtype-specific numbering) A11T, K173G, and R453M in H3N2; and H99Q in influenza B virus (Yamagata lineage). In some cases, HA substitutions were selected in conjunction with known NA resistance substitutions and may contribute to reduced susceptibility to oseltamivir; however, the impact of HA substitutions on antiviral activity of oseltamivir in humans is unknown and likely to be strain-dependent.

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

Amino Acid Substitution
<b>Influenza A N1 (N1 numbering in brackets)</b>
I117V (I117V), E119V (E119V), R152K (R152K), Y155H (Y155H), F173V (F174V), D198G/N (D199G/N), I222K/R/T/V (I223K/R/T/V), S246G/N (S247G/N), G248R+I266V (G249R+I267V), H274Y (H275Y), N294S (N295S), Q312R+H277I (Q313R+H277I), N325K (N325K), R371K (R368K)
<b>Influenza A N2</b>
E41G, E119V, D151V, I222L/V, Q226H, SASG245-248 deletion, S247P, R292K, N294S
<b>Influenza B (B numbering in brackets)</b>
E119A (E117A), P141S (P139S), G142R (G140R), R152K (R150K), D198E/NV (D197E/NV), I222L/T/V (I221L/T/V), A246D/S/T (A245D/S/T), H274Y (H273Y), N294S (N294S), R371K (R374K), G402S (G407S)

\* All numbering is N2, except where indicated.

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

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

#### Cross-resistance

Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitutions observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S260G zanamivir resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to zanamivir but not oseltamivir. The R292K oseltamivir resistance-associated substitution observed in N2, and the I222T, D198E/N, R371K, or G402S oseltamivir resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. These examples do not represent an exhaustive list of cross resistance-associated substitutions and prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate.

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

#### Immune Response

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats given daily oral doses of the prodrug oseltamivir phosphate up to 400 mg/kg and 500 mg/kg, respectively, the prodrug and the active form oseltamivir carboxylate induced no statistically significant increases in tumors over controls. The mean maximum daily exposures to the prodrug in mice and rats were approximately 130- and 320-fold, respectively, greater than those in humans at the recommended clinical dose based on AUC comparisons. The respective safety margins of the exposures to the active oseltamivir carboxylate were 15- and 50-fold.

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

In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1,500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during mating, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose in this study was approximately 115 times the human systemic exposure (AUC<sub>0-24h</sub>) of oseltamivir carboxylate that occurs after administration of the maximum recommended human dose.

## 14 CLINICAL STUDIES

### 14.1 Treatment of Influenza

#### Adults

Two randomized, placebo-controlled, double-blind clinical trials of oseltamivir phosphate were conducted in adults between 18 and 65 years old, one in the U.S. and one outside the U.S., for the treatment of acute uncomplicated influenza. Eligible subjects had

fever of at least 100°F, accompanied by at least one respiratory symptom (cough, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue, or headache), and influenza virus was known to be circulating in the community. Subjects were randomized to receive oral oseltamivir phosphate or placebo for 5 days. All enrolled subjects were allowed to take fever-reducing medications.

Of 1,355 subjects enrolled in these two trials, 849 (63%) subjects were influenza-infected (median age 34 years; 52% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected subjects, 95% were infected with influenza A, 3% with influenza B, and 2% with influenza of unknown type.

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

In the treatment of influenza, no 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 or older) with chronic cardiac (excluding chronic idiopathic hypertension) or respiratory diseases, as measured by time to alleviation of all symptoms. However, in patients treated with oseltamivir phosphate there