



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

Warnings and Precautions (5.4) —RECENT MAJOR CHANGES— 06/2016

Indications and Usage — 06/2016

Dosage Forms and Strengths — 06/2016

Contraindications — 06/2016

Warnings and Precautions — 06/2016

Adverse Reactions — 06/2016

Drug Interactions — 06/2016

Use in Specific Populations — 06/2016

How Supplied/Storage and Handling — 06/2016

Patent Information — 06/2016

How to Obtain Patient Counseling Information — 06/2016

Other information — 06/2016

See full prescribing information for Osetamivir Phosphate Capsules

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Treatment of Influenza
1.2 Prophylaxis of Influenza
1.3 Limitations of Use
2 DOSAGE AND ADMINISTRATION
2.1 Dosage and Administration Overview
2.2 Recommended Dosage for Treatment of Influenza
2.3 Recommended Dosage for Prophylaxis of Influenza
2.4 Dosage in Patients with Renal Impairment
2.6 Emergency Preparation of Oral Suspension from 75 mg Osetamivir Phosphate Capsules
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Skin/Hypersensitivity Reactions
5.2 Neuropsychiatric Events
5.3 Risk of Bacterial Infections
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Influenza Vaccines
7.2 Drugs Without Clinically Significant Drug Interaction with Osetamivir Phosphate Capsules

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 of age 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 and older (see Dosage and Administration (2.2)) or for prophylaxis of influenza in patients 1 year of age and older (see Dosage and Administration (2.3)) using:
• Osetamivir phosphate capsules
The capsules may be taken with or without food; however, tolerability may be enhanced if osetamivir phosphate capsules are 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 capsules are used, they should 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 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 (13 years of age and older)
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 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 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)).

PATIENT INFORMATION
Osetamivir Phosphate (OH-sel-TAM-i-VR) Capsules, for oral use
What is osetamivir phosphate capsule?
Osetamivir phosphate capsule is a prescription medicine used to:
• treat the flu (influenza) in people 2 weeks of age and older who have had flu symptoms for no more than two days.
• prevent the flu in people who are 1 year of age and older.
It is not known if osetamivir 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 flu in people who have weakened immune systems (immunocompromised).
• 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.
Osetamivir phosphate capsules do not treat or prevent illness that is caused by infections other than the influenza virus.
Osetamivir phosphate capsules do not prevent bacterial infections that may happen with the flu.
Osetamivir phosphate capsules are not recommended for people with end-stage renal disease (ESRD) who are not receiving dialysis.
Osetamivir phosphate capsules do not take the place of receiving a flu vaccination. Talk to your healthcare provider about when you should receive an annual flu vaccination.
Who should not take osetamivir phosphate capsules?
Do not take osetamivir phosphate capsules if you are allergic to osetamivir phosphate or any of the ingredients in osetamivir phosphate capsules. See the end of this leaflet for a complete list of ingredients in osetamivir phosphate capsules.
What should I tell my healthcare provider before taking osetamivir phosphate capsules?
Before you take osetamivir phosphate capsules, tell your healthcare provider if you:
• have problems swallowing osetamivir phosphate capsules.
• have kidney problems.
• have any other medical conditions.
• are pregnant or plan to become pregnant. Available information indicates that osetamivir phosphate capsules do not increase the risk of birth defects.
• are breastfeeding or plan to breastfeed. Osetamivir phosphate can 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 supplements.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.
How should I take osetamivir phosphate capsules?
Take osetamivir phosphate capsules exactly as your healthcare provider tells you to.
• Take osetamivir phosphate capsules with food or without food. There is less chance of stomach upset if you take osetamivir phosphate capsules with food.
• If you miss a dose of osetamivir 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 osetamivir phosphate capsules at your scheduled time. Do not take 2 doses at the same time.
• If osetamivir phosphate for oral suspension is not available or you cannot swallow osetamivir phosphate capsules, your healthcare provider or pharmacist may instruct you to open osetamivir 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 or pharmacist has instructed you to take osetamivir phosphate for oral suspension or open your osetamivir phosphate capsules, 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 osetamivir phosphate capsules?
Osetamivir phosphate capsules may cause serious side effects, including:
• Serious skin and allergic reactions. Osetamivir phosphate capsules can cause serious skin and allergic reactions. Stop taking osetamivir phosphate capsules and get medical help right away if you get any of the following symptoms:
o skin rash or hives
o swelling of your face, eyes, lips, tongue, or throat
o your skin blisters and peels
o trouble breathing
o blisters or sores in your mouth
o chest pain or tightness
o itching
• Change in behavior. People, especially children, who have the flu can develop nervous system problems and abnormal behavior that can lead to death. During treatment with osetamivir phosphate capsules, tell your healthcare provider right away if you or your child have confusion, speech problems, shaky movements, seizures, or start hearing voices or seeing things that are not really there (hallucinations).

Renally impaired adult patients (creatinine clearance >30 to 60 mL/min): Reduce to 30 mg once daily (2.4)
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)
Capsules: 30 mg, 45 mg, 75 mg (3)
CONTRAINDICATIONS
Patients with known serious hypersensitivity to osetamivir or any of the components of osetamivir phosphate capsules (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)

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 Helena Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or 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 capsules use, unless medically indicated. (7.2)
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2017

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Use in Patients with Chronic Conditions
8.9 Immunocompromised Patients
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Treatment of Influenza
14.2 Prophylaxis of Influenza
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

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) |
|-----------------------------------------------------------|-----------------------------|--------------------------------|----------------------------------------------------|--------------------------------------------------|-------------------------------------------|
| Patients from 2 Weeks to less than 1 Year of Age | | | | | |
| Any weight | 3 mg/kg twice daily | Not applicable | 0.5 mL/kg/5 | 1 bottle | Not applicable |
| Patients 1 to 12 Years of Age Based on Body Weight | | | | | |
| 15 kg or less | 30 mg twice daily | 45 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 or 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 capsules 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 30 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 Populations (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 mL/minute) | 75 mg twice daily for 5 days | 75 mg once daily |
| Moderate (>30-60 mL/minute) | 30 mg twice daily for 5 days | 30 mg once daily |
| Severe (>10-30 mL/minute) | 30 mg once daily for 5 days | 30 mg every other day |
| 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 not on Dialysis | Osetamivir phosphate is not recommended | Osetamivir phosphate is not recommended |

† Capsules or oral suspension 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, commercial 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 Capsules Dose

| Osetamivir Phosphate Capsules 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 capsules 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) (Padlock 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 (Humco®) OR Ora-Sweet® SF (Padlock 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):
a. Place the specified amount of water into a polyethylene terephthalate (PET) or glass bottle (see Table 4). Constitution in either bottle type is not recommended because there is no stability data with either bottle type.
b. 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.
c. Gently swirl the suspension to ensure adequate wetting of the osetamivir phosphate powder for at least 2 minutes.
d. Slowly add the specified amount of vehicle to the bottle.
e. 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.
f. Put an ancillary label on the bottle indicating "Shake Well Before Use."
g. 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.
h. 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.
i. 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)).
j. Store the prepared oral suspension in glass or PET bottles either:
• In a refrigerator (2° to 8°C or 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.

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 capsules. Stop osetamivir phosphate capsules and initiate appropriate treatment if allergic-like reaction occurs or is suspected. The use of osetamivir phosphate capsules is contraindicated in patients with known serious hypersensitivity to osetamivir phosphate capsules (see Contraindications (4) and Adverse Reactions (5.1)).
5.2 Neuropsychiatric Events
There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving osetamivir phosphate capsules (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. 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 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 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.
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 to 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.

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 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.
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 to 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.

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 capsules. Stop osetamivir phosphate capsules and initiate appropriate treatment if allergic-like reaction occurs or is suspected. The use of osetamivir phosphate capsules is contraindicated in patients with known serious hypersensitivity to osetamivir phosphate capsules (see Contraindications (4) and Adverse Reactions (5.1)).
5.2 Neuropsychiatric Events
There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving osetamivir phosphate capsules (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. 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 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 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.
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 to 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.

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 capsules. Stop osetamivir phosphate capsules and initiate appropriate treatment if allergic-like reaction occurs or is suspected. The use of osetamivir phosphate capsules is contraindicated in patients with known serious hypersensitivity to osetamivir phosphate capsules (see Contraindications (4) and Adverse Reactions (5.1)).
5.2 Neuropsychiatric Events
There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving osetamivir phosphate capsules (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. 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 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 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.
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 to 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 Capsules 75 mg twice daily (n = 2646) | Placebo (n = 1977) | Osetamivir Phosphate Capsules 75 mg twice daily (n = 1943) | Placebo (n = 1566) |
| Gastrointestinal Disorders | | | | |
| Nausea | 10% | 6% | 8% | 4% |
| Vomiting | 8% | 3% | 2% | 1% |
| Nervous System Disorders | | | | |
| Headache | 2% | 1% | 17% | 16% |
| Pain | <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 capsules 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 capsules (16%) compared to placebo (6%).
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 doses ranging from 2 to 3.5 mg per kg of the formulation for oral suspension twice daily orally 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 236 subjects receiving osetamivir phosphate capsules 75 mg once daily was consistent with that previously observed in other osetamivir phosphate prophylaxis clinical trials (see Clinical Studies (14.2)).

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of osetamivir phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to osetamivir phosphate therapy.
General disorders and administration site conditions: Swelling of the face or tongue, allergy, anaphylaxis/calcium antagonists, reactions, hypotension.
Skin and subcutaneous tissue disorders: Rash, dermatitis, urticaria, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme (see Warnings and Precautions (5.1)).
Gastrointestinal Disorders: Gastrointestinal bleeding, hemorrhagic colitis.
Cardiac Disorders: Arrhythmia.
Hepatobiliary Disorders: Hepatitis, abnormal liver function tests.
Nervous System Disorders: Seizure.
Metabolism and Nutrition Disorders: Aggravation of diabetes.
Psychiatric Disorders: Abnormal behavior, delirium, including symptoms such as hallucinations, agitation, anxiety, altered level of consciousness, confusion, nightmares, delusions (see Warnings and Precautions (5.2)).

7 DRUG INTERACTIONS
7.1 Influenza Vaccines
Live Attenuated Influenza Vaccine
The concurrent use of osetamivir phosphate with the live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for osetamivir phosphate to inhibit replication of live vaccine virus and possibly reduce the efficacy of LAIV, avoid administration of LAIV within 2 weeks before or 48 hours after osetamivir phosphate capsules administration, unless medically indicated.
Inactivated Influenza Vaccine
Inactivated influenza vaccine can be administered at any time relative to use of osetamivir phosphate.

7.2 Drugs Without Clinically Significant Drug Interaction with Osetamivir Phosphate Capsules
No dose adjustments are needed for either osetamivir or the concomitant drug when coadministering osetamivir with amoxicillin, acetyaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonate), antidiarrheals, amantadine, or varfarin (see Clinical Pharmacology (12.3)).

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Risk Summary
There are no adequate and well-controlled studies with osetamivir phosphate in pregnant women. Available published epidemiological data suggest that osetamivir phosphate, taken in any trimester, is not associated with an increased risk of birth defects. However, these studies individually are limited by small sample sizes, use of different comparison groups, and some lacked information on those, which preclude a definitive assessment of

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)).

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 367 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 4,603 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 of 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 established in immunocompromised patients (see Clinical Studies (14.2)). Safety of oseltamivir phosphate for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients (see Adverse Reactions (6.1)).

10 OVERDOSAGE

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

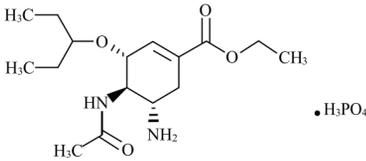
Oseltamivir phosphate, an influenza neuraminidase inhibitor (NAI), is available as:

- 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, pregelatinized starch, sodium stearoyl fumarate and talc. The 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide and red iron oxide. The 45 mg capsule shell contains gelatin, titanium dioxide and black iron oxide. The 75 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide and red iron oxide. Each capsule is printed with white ink, which includes shellac, propylene glycol, strong ammonia solution and FD&C Blue No. 2 as the colorant.

The botanical source for pregelatinized starch is maize starch.

Oseltamivir phosphate USP is a white to off-white powder with the chemical name [2R-(2S,4S,5a)]-Ethyli 4-(acetyl amino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1). The molecular formula is C₂₁H₃₂N₂O₈·H₂PO₄. The relative molecular mass is 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 capsules 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 _{max} (ng/mL) | 65 (26) | 348 (18) |
| AUC _{0-12h} (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 (C₅₅₁ ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (C_{12h} ng•h/mL under fasted conditions and 6069 ng•h/mL under fed conditions) of oseltamivir carboxylate.

Distribution

The volume of distribution (V_d) of oseltamivir carboxylate, following intravenous administration in 24 subjects (oseltamivir phosphate is not available as an IV formulation), ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%), (37.2%) 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) |
|-----------------------------------------|--------------------------------------------------|-----------------------------------------------|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------|
| Recommended Treatment Regimens | | | | | |
| PK exposure parameter | 75 mg twice daily | 75 mg twice daily | 30 mg twice daily | 30 mg once daily | 30 mg every 10 cycle |
| C _{max} (ng/mL) | 145 | 253 | 180 | 219 | 221 |
| C _{min} (ng/mL) | 298 | 464 | 306 | 477 | 1170 |
| AUC _{0-6h} (ng•h/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 _{max} (ng/mL) | 313 | 602 | 57 | 70 | 42 |
| C _{min} (ng/mL) | 29 | 311 | 209 | 377 | 903 |
| AUC _{0-6h} (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_{max} (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_{min} 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 indicated that the oseltamivir phosphate dosage regimen resulted in lower exposure to the active metabolite in pregnant women (n=50) compared to non-pregnant women (n=33). However, this predicted exposure is expected to have actively 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=8) 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 older patients and does not require a 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 oxidase or for glucuronyl transferases.

Coadministration of probenecid results in an approximate two-fold increase in exposure to oseltamivir carboxylate due to a decrease in 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, acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonate), 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 IC₅₀ values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and influenza B clinical strains were 2.5 nM (n=14), 0.18 nM (n=74), and 0.36 nM (range 0.13 to 7.35 nM, n=774), and 60 nM (20 to 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 (EC₅₀ and EC₉₀) were in the range of 0.008 micromolar to greater than 35 micromolar and 0.004 micromolar to greater than 100 micromolar, respectively (1 micromolar=0.284 micromoles 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 was 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) H1N1, K1736, and R453M in H3N2; and H99D in influenza B virus (Yamagata lineage). In some cases, HA substitutions were selected in conjunction with known HA 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* |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Influenza A N1 (N1 numbering in brackets) |
| H117V (H117V), E119V (E119V), R152K (R152K), Y155H (Y155H), F173V (F174V), D198E (D198E/N), I222K/R/T/V (I222K/R/T/V), S246N (S247N), G248R/266V (G249R/267V), H274Y (H275Y), N294S (N295S), Q312R/H271 (Q313R/H427T), N325K (N325K), R371R (R368K) |
| Influenza A N2 |
| E41G, E119V, D151V, I222L/V, Q226H, S462G245-248 deletion, S247F, R292K, N294S |
| Influenza B (B numbering in brackets) |
| E119A (E117A), P141S (P139S), G142R (G140R), R152K (R150K), D198E/NY (D197E/NY), I222L/T/V (I221L/T/V), A246D/S/T (A245D/S/T), H274Y (H273Y), N294S (N294S), R371R (R374A), G402S (G407S) |

*All numbering is N2, except where indicated

Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. The incidence of oseltamivir resistance in pediatric treatment-associated resistance in influenza A/H1N1 has been detected at rates of 27 to 37% and 3 to 18% (2/11 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 H272Y 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 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The D135K and K150I zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the G250E zanamivir resistance-associated substitutions observed in influenza B virus neuraminidase, confer reduced susceptibility to zanamivir but not oseltamivir. The R329K oseltamivir resistance-associated substitution observed in N2 and the I222T, D198E/R, S274K, 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 infectious agents.

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 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 1500 mg/kg/day administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy, males for 2 weeks before mating, during mating, and for 2 weeks after mating, there were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose in this study was approximately 100 times the human systemic exposure (AUC_{0-12h}) 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 patients between 18 and 65 years old, one in the U.S. and one outside the U.S., for the treatment of 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, headache, 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 treated for 10 days.

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. Patients were reassessed 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." Then improvement in symptoms was known to be circulating in the community. Of 688 subjects enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected subjects, 67% were infected with influenza A and 3% with influenza B.

Efficacy in this trial was determined by the time to alleviation or resolution of influenza signs and symptoms, measured by a composite endpoint that required the following four individual conditions to be met: i) alleviation of cough, ii) alleviation of cornea, iii) resolution of fever, and iv) parental opinion of a return to normal health after influenza. Oseltamivir phosphate treatment of 2 mg per kg twice daily, started within 48 hours of onset of symptoms, reduced the total composite time to freedom from illness by 1.5 days compared to placebo. Subgroup analyses by gender showed no differences in the treatment effect of oseltamivir phosphate in male and female pediatric subjects.

Geriatric Subjects

Three double-blind placebo-controlled treatment trials were conducted in subjects who were at least 65 years of age in three consecutive seasons. The enrollment criteria were similar to that of adult trials with the exception of fever being defined as higher than 97.5°F. Of 741 subjects enrolled, 476 (65%) subjects were influenza-infected. Of these, 95% were infected with influenza type A and 5% with influenza type B. In the pooled analysis, there was a 1-day reduction in the median time to improvement in influenza-infected subjects who received oseltamivir phosphate 75 mg twice daily for 5 days compared to those who received placebo (see Use in Specific Populations (8.5)). Some seasonal variability was noted in the clinical efficacy outcomes.

Pediatric Subjects (1 year to 12 years of age)

One double-blind placebo-controlled treatment trial was conducted in pediatric subjects aged 1 year to 12 years (median age 5 years) who had fever (at least 100°F) plus one respiratory symptom (cough or cornea). Then improvement in symptoms was known to be circulating in the community. Of 688 subjects enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected subjects, 67% were infected with influenza A and 3% with influenza B.

Efficacy in this trial was determined by the time to alleviation or resolution of influenza signs and symptoms, measured by a composite endpoint that required the following four individual conditions to be met: i) alleviation of cough, ii) alleviation of cornea, iii) resolution of fever, and iv) parental opinion of a return to normal health after influenza. Oseltamivir phosphate treatment of 2 mg per kg twice daily, started within 48 hours of onset of symptoms, reduced the total composite time to freedom from illness by 1.5 days compared to placebo. Subgroup analyses by gender showed no differences in the treatment effect of oseltamivir phosphate in male and female pediatric subjects.

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

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

Of the 136 subjects under the age of 1 year enrolled and dosed in the trials, the majority of the subjects were male (55%), white (79%), non-Hispanic (74%), full term (76%) and infected with influenza A (80%). Pharmacokinetic data indicated that a dose of 3 mg per kg twice daily in pediatric subjects 2 weeks to less than 1 year of age provided oseltamivir phosphate concentrations similar to or higher than those observed in older pediatric subjects and adults receiving the approved dose and provided the basis for approval (see Adverse Reactions (6.1) and Use in Specific Populations (8.4)).

14.2 Prophylaxis of Influenza

Adult and Adolescent Subjects (13 years of age and older)

In a randomized, placebo-controlled, double-blind trial in household contacts occurring influenza illness has been demonstrated in three 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 the following criteria (all signs and symptoms must have been recorded within 24 hours):

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

In a pooled analysis of two seasonal prophylaxis trials in healthy unvaccinated adults (aged 18 to 65 years), oseltamivir phosphate 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory-confirmed clinical influenza from 5% (25/519) for the placebo group to 1% (6/520) for the oseltamivir phosphate group.

In the seasonal (community outbreak) prophylaxis trial in elderly residents of skilled nursing homes, about 80%, 43%, and 14% of the subjects were vaccinated, had cardiac disorders, and had chronic airway obstructive disorders, respectively. In this trial, subjects were randomized to oseltamivir phosphate 75 mg once daily or placebo taken orally for 42 days. The incidence of laboratory-confirmed clinical influenza was 4% (1/272) in the placebo-treated subjects compared to less than 1% (1/276) in the oseltamivir phosphate-treated subjects.

In the post-exposure prophylaxis trial in household contacts (aged 13 years or older) and in an index influenza case, oseltamivir phosphate 75 mg once daily or placebo taken orally was administered within 48 hours of onset of symptoms in the index case and continued for 7 days (index cases did not receive oseltamivir phosphate treatment). The incidence of laboratory-confirmed clinical influenza was 12% (24/200) in the placebo-treated subjects compared to 1% (2/205) in the oseltamivir phosphate-treated subjects.

Pediatric Subjects (1 year to 12 years of age)