Additional prescribing information for antivirals

1) Oseltamivir phosphate (Tamiflu®) capsules (30mg, 45mg, 75mg) and for oral suspension (12mg/mL) (capsules may be used for emergency compounding of an oral suspension; directions available at http://www.rocheusa.com/products/tamiflu/pi.pdf) (Adapted from Oseltamivir [package insert], Roche 2008 and CDC recommendations)

Indications and usage:
- Treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days
- Prophylaxis of influenza in patients 1 year and older

Mechanism of action:
Oseltamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to active form, oseltamivir carboxylate. The proposed mechanism of action is inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Contraindications:
Known hypersensitivity to any of the components of the product

Precautions:
- Efficacy in patients who begin treatment after 40 hours of symptoms has not been established
- Efficacy in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population.
- No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.
- Safety and efficacy of repeated treatment or prophylaxis courses have not been studied
- Efficacy for treatment or prophylaxis has not been established in immunocompromised patients
- Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Tamiflu has not been shown to prevent such complications.
- The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated
- Dose adjustment is recommended for patients with a serum creatinine clearance <30mL/min
- Serious skin/hypersensitivity reactions: Rare cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in post-marketing experience.
- Neuropsychiatric events: There have been post marketing 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 Tamiflu. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution.

Pregnancy:
Category C

Nursing mothers:
In lactating rats, oseltamivir and oseltamivir carboxylate are excreted in the milk. It is not known whether oseltamivir or oseltamivir carboxylate is excreted in human milk.

Drug interactions:
- Live attenuated influenza vaccine should not be administered within 2 weeks before or 48 hours after administration of Tamiflu, unless medically indicated.
- Clinically significant drug interactions are unlikely (No pharmacokinetic interactions have been observed when co-administering oseltamivir with amoxicillin, acetaminophen, cimetidine or with antacids (magnesium and aluminum hydroxides and calcium carbonates).

Adverse reactions:
**Adult:** Most frequent: nausea, vomiting
Also: diarrhea, bronchitis, abdominal pain, dizziness, headache, cough, insomnia, vertigo, fatigue

**Pediatric:** Most frequent: vomiting, diarrhea, otitis media
Also: abdominal pain, asthma (including aggravated), nausea, epistaxis, pneumonia, ear disorder, sinusitis, bronchitis, conjunctivitis, dermatitis, lymphadenopathy, tympanic membrane disorder

**Post-marketing:** Body as a whole: dermatitis, rash, eczema, urticaria, erythema multiform, Stevens-Johnson Syndrome, toxic epidermal necrolysis; Digestive: hepatitis, liver function tests abnormal; Cardiac: arrhythmia; Gastrointestinal disorders: gastrointestinal bleeding, hemorrhagic colitis, Neurologic: seizure; Metabolic: aggravation of diabetes; Psychiatric: delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares

**Dosage and administration:**
- Treatment in adults and adolescents 13 years and older: 75mg orally twice daily for 5 days (Treatment should begin within 2 days of onset of symptoms of influenza)
- Prophylaxis in adults and adolescents 13 years and older following close contact with an infected individual: 75mg orally once daily for at least 10 days (Therapy should begin within 2 days of exposure)

**- Treatment in pediatric patients 1 year and older (oral suspension or capsules)**

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Body weight (lbs)</th>
<th>Recommended dose for 5 days</th>
<th>Number of bottles needed to obtain recommended dose for a 5 day regimen</th>
<th>Number of capsules needed to obtain recommended doses for a 5 day regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15</td>
<td>≤ 33</td>
<td>30mg twice daily</td>
<td>1</td>
<td>10 x 30mg capsules</td>
</tr>
<tr>
<td>&gt;15-23</td>
<td>&gt;33-51</td>
<td>45mg twice daily</td>
<td>2</td>
<td>10 x 45mg capsules</td>
</tr>
<tr>
<td>&gt;23-40</td>
<td>&gt;51-88</td>
<td>60mg twice daily</td>
<td>2</td>
<td>20 x 30mg capsules</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&gt;88</td>
<td>75 mg twice daily</td>
<td>3</td>
<td>10 x 75mg capsules</td>
</tr>
</tbody>
</table>

- Prophylaxis in pediatric patients 1 year and older (oral suspension or capsules)
(Prophylaxis in patients 1-12 years of age has not been evaluated for longer than 10 days duration. Therapy should begin within 2 days of exposure.)

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Body weight (lbs)</th>
<th>Recommended dose for 10 days</th>
<th>Number of bottles needed to obtain recommended dose for a 10 day regimen</th>
<th>Number of capsules needed to obtain recommended doses for a 10 day regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15</td>
<td>≤ 33</td>
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</tbody>
</table>
Treatment for children younger than 1 year **If an EUA is issued by the FDA**

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended treatment dose for 5 days</th>
<th>Number of bottles needed to obtain recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>And info on &lt; 3 months</td>
<td>12mg twice daily</td>
<td>1</td>
</tr>
<tr>
<td>3-5 months</td>
<td>20mg twice daily</td>
<td>1</td>
</tr>
<tr>
<td>6-11 months</td>
<td>25mg twice daily</td>
<td>1</td>
</tr>
</tbody>
</table>

Prophylaxis for children younger than 1 year **If an EUA is issued by the FDA**

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended prophylaxis dose for 10 days</th>
<th>Number of bottles needed to obtain recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>Not recommended unless situation judged critical due to limited data on use in this age group</td>
<td></td>
</tr>
<tr>
<td>3-5 months</td>
<td>20mg once daily</td>
<td>1</td>
</tr>
<tr>
<td>6-11 months</td>
<td>25mg once daily</td>
<td>1</td>
</tr>
</tbody>
</table>

Dose adjustments:

*Geriatric:* none

*Hepatic impairment:* No dose adjustment for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9)

*Renal:* CrCl 10-30mL/min

- Treatment: 75mg orally once daily for 5 days
- Prophylaxis: 75mg orally every other day OR 30mg once daily

*Hemodialysis/ peritoneal dialysis* - no recommendations

2) Zanamivir (Relenza®) for inhalation (Adapted from Zanamivir [package insert], GSK 2008)

*Indications and usage:*

- Treatment of uncomplicated acute illness due to influenza A and B virus in adult and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days
- Prophylaxis of influenza in adult patients and pediatric patients 5 years of age and older

*Important limitations on use of Relenza:*

- Not recommended treatment or prophylaxis of influenza in individuals with underlying airway disease (such as asthma or chronic obstructive pulmonary disease)
- Has not been proven effective for treatment of influenza in individuals with underlying airways disease
- Has not been proven effective for prophylaxis of influenza in the nursing home setting

*Mechanism of action:*

The mechanism of action is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

*Contraindications:*

- Do not use in patients with history of allergic reaction to any ingredient of Relenza including lactose (which contains milk proteins)

*Warnings*
Relenza is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with Relenza in patients with and without underlying airways disease. Many of these cases were reported during post-marketing and causality was difficult to assess.

Relenza should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

**Precautions**

- Efficacy in patients who begin treatment after 48 hours of symptoms has not been established
- Safety and efficacy of repeated treatment courses have not been studied
- Allergic-like reactions. Including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in post-marketing experience
- Neuropsychiatric events: There have been post marketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including Relenza.
- No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization
- Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Relenza has not been shown to prevent such complications

**Pregnancy**

Category C

**Nursing mothers**

In lactating rats zanamivir was excreted in the milk. It is not known whether zanamivir is excreted in human milk.

**Drug interactions:**

- Live attenuated influenza vaccine should not be administered within 2 weeks before or 48 hours after administration of Relenza, unless medically indicated (trivalent inactivated influenza vaccine can be administered at any time relative to use of Relenza)
- Clinically significant drug interactions are unlikely

**Adverse reactions**

**Adult:** Diarrhea, nausea, vomiting, headaches, respiratory (nasal signs and symptoms, bronchitis, cough, sinusitis, ear, nose and throat infections); dizziness

**Pediatric:** Respiratory (ear, nose and throat infections/hemorrhage; asthma, cough); Digestive (vomiting, diarrhea, nausea)

**Post-marketing:** Allergic reactions: Allergic or allergic-like reaction including oropharyngeal edema; Psychiatric: delirium, including symptoms such as altered level of consciousness, confusion abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares; Cardiac: arrhythmias, syncope; Neurologic: seizures; Respiratory: bronchospasm, dyspnea; Skin: facial edema, rash (including serious cutaneous reactions)

**Dosage and administration**

- Treatment in adults and pediatric patients 7 years and older: 2 inhalations (one 5mg blister per inhalation for a total dose of 10mg) twice daily (approximately 12 hours apart) for 5 days
  
  Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses

  **Dose adjustments:** none

  **Prophylaxis:**
Household setting: in adults and pediatric patients 5 years of age and older: 10mg once daily for 10 days
(There is no data on the effectiveness of prophylaxis with Relenza in a household setting when initiated more than 1.5 days after the onset of signs and symptoms in the index case.)
Community outbreaks: in adults and adolescents: 10mg once daily for 28 days. (There is no data on the effectiveness of prophylaxis with Relenza in a community outbreak when initiated more than 5 days after the outbreak was identified in the community.)

Patient instructions
**Patients should be instructed in the use of delivery system**
Instructions should include a demonstration whenever possible.
If relenza is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional.

3) Rimantadine hydrochloride (tablets 100mg; Flumadine syrup 50mg/5mL) (Adapted from Rimantadine [package insert], Sandoz 2007)

Indications and usage:
Prophylaxis and treatment of illness caused by various strains of influenza A virus in adults
(for adults who develop an influenza-like illness during known or suspected influenza A infection in the community. When administered within 48 hours after onset of signs and symptoms of infection caused by influenza A virus strains, rimantadine hydrochloride has been shown to reduce the duration of fever and systemic symptoms.)
Prophylaxis against influenza virus in children
(in controlled studies of children over the age of 1 year, healthy adults and elderly patients, rimantadine hydrochloride has been shown to be safe and effective in preventing signs and symptoms of infection caused by various strains of influenza A virus.)

Mechanism of action:
The mechanism of rimantidine is not fully understood. Rimantadine appears to exert is inhibitory effect early in the viral replicative cycle, possibly inhibiting the uncoating of the virus.

Contraindications:
Known hypersensitivity to drugs of the adamantane class, including rimantadine and amantadine

Precautions
General: Increased incidence of seizures has been reported in patients with a history of epilepsy who received the related drug amantadine. In clinical trials of rimantadine hydrochloride, the occurrence of seizure-like activity was observed in a small number of patients with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine hydrochloride. If seizures develop, rimantadine hydrochloride should be discontinued.
Safety and pharmacokinetics of rimantadine in renal and hepatic insufficiency have only been evaluated after single dose administration.

Pregnancy
Category C

Nursing mothers
Rimantadine hydrochloride should NOT be administered to nursing mothers because of the adverse effects noted in offspring of rats treated with rimantadine during the nursing period.

Adverse reactions
**Most frequent:** those involving nervous system (insomnia, dizziness, headache, nervousness, fatigue) and gastrointestinal system (nausea, vomiting, anorexia, dry mouth, abdominal pain);

**Body as a whole:** asthenia

**Dosage and administration**

- **Treatment in adults:** 100mg twice daily for 7 days from initial onset of symptoms

**Dose adjustments:**

In patients with severe hepatic dysfunction, renal failure (CrCl ≤ 10 mL/min) and elderly nursing home patients, a dose reduction to 100mg daily is recommended

- **Prophylaxis in adults:** 100mg twice daily

**Dose adjustments:**

In patients with severe hepatic dysfunction, renal failure (CrCl ≤ 10 mL/min), elderly nursing home patients and patients over 64 years of age, a dose reduction to 100mg daily is recommended

- **Prophylaxis in children:**
  - Ages 1 to 10 years: 5mg/kg, but not exceeding 150mg
  - Age 10 years and older: 100mg twice daily

4) **Amantadine hydrochloride** (capsules, tablets 100mg; syrup 50mg/5mL)

**Indications and usage:**

Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus

**Mechanism of action:**

The mechanism by which amantadine exerts its antiviral activity is not clearly understood. It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein. In certain cases, amantadine is also known to prevent assembly during virus replication.

**Contraindications:**

Known hypersensitivity to amantadine hydrochloride or to any of the other ingredients in amantadine hydrochloride capsules

**Warnings:**

Deaths (Deaths have been reported from overdose with amantadine. The lowest reported acute lethal dose was 1 gram. Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension.)

Suicide attempts (Suicide attempts, some of which have been fatal, have been reported in patients treated with amantadine, many of whom received short courses for influenza treatment or prophylaxis. The incidence of suicide attempts is not known and the pathophysiologic mechanism is not understood. Suicide attempts and suicidal ideation have been reported in patients with and without prior history of psychiatric illness.)

CNS effects (Patients with a history of epilepsy or other “seizures” should be observed closely for possible increased seizure activity. Patients receiving amantadine hydrochloride capsules who note central nervous system effects of blurring of vision should be cautioned against driving or working in situations where alertness and adequate motor coordination are important.)

Other (Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving amantadine hydrochloride capsules. Because amantadine hydrochloride capsules has anticholinergic effects and may cause mydriasis, it should not be given to patients with untreated angle closure glaucoma.)
Precautions:
Neuroleptic malignant syndrome (NMS): Sporadic cases of possible NMS have been reported in association with dose reduction or withdrawal of amantadine therapy. (Therefore, patients should be observed carefully when the dosage of amantadine is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.)
Renal (Because amantadine is mainly excreted in the urine. It accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals who are 65 years of age or older.)
Liver disease (Care should be exercised when administering amantadine to patients with liver disease. Rare instances of reversible elevation of liver enzymes have been reported in patients receiving amantadine, though a specific relationship between the drug and such changes has not been established.)
Other (The dose of amantadine may need careful adjustment in patients with congestive heart failure, peripheral edema or orthostatic hypotension. Care should be exercised when administering amantadine to patients with a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents.)
Drug interactions
CNS stimulants
Quinine or quinidine
Live attenuated influenza vaccine
Pregnancy
Category C
Nursing mothers
Amantadine is excreted in human milk. Use is not recommended in nursing mothers.
Adverse reactions
Most frequent: nausea, dizziness, insomnia
Less frequent: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue
Dosage and administration
-Prophylaxis and treatment in adults: 200mg once daily or 100mg twice daily for 7 days from initial onset of symptoms (If central nervous system effects develop in once-a-day dosage, a split dosage schedule may reduce such complications.)
-Dose adjustments:
In patients ≥65 years of age: 100mg once daily
In patients with impaired renal function

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 50</td>
<td>200mg first day, then 100mg each day after</td>
</tr>
<tr>
<td>15 to 29</td>
<td>200mg first day followed by 100mg on alternate days</td>
</tr>
<tr>
<td>&lt;15 or hemodialysis</td>
<td>200mg every 7 days</td>
</tr>
</tbody>
</table>

-Prophylaxis and treatment in children:
Ages 1 to 9 years: 4.4-8.8mg/kg per day; not to exceed 150mg/day
Ages 9 to 12 years: 100mg orally twice daily