ANTIFLU Capsules/ Suspension (Oseltamivir phosphate)

Composition

ANTIFLU Capsules
Each capsule contains:
Oseltamivir Phosphate equivalent to
Oseltamivir ...... 75 mg
Approved colours used in empty capsule shells

ANTIFLU Suspension
Each ml (on reconstitution) contains:
Oseltamivir Phosphate equivalent to
Oseltamivir ...... 12 mg

Dosage Form/s
Oral capsule and powder for oral suspension

Pharmacology

Pharmacodynamics

Oseltamivir is an antiviral drug. It is an ethyl ester pro-drug, requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate.
The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.
Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.
The antiviral activity and neuraminidase inhibitory activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture and biochemical assays. The concentrations of oseltamivir carboxylate required for inhibition of the influenza virus 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 0.0008 microM to >35 microM and 0.004 microM to >100 microM, respectively (1 microM = 0.284 mcg/mL). The relationship between the antiviral activity in cell culture and the inhibition of the influenza virus replication in humans has not been established.
Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate. Reduced susceptibility of
influenza virus to inhibition by oseltamivir carboxylate may be conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins.

Reduced susceptibility isolates have been obtained during treatment with oseltamivir and from sampling during community surveillance studies. The clinical impact of this reduced susceptibility is unknown.

Hemagglutinin (HA) substitutions selected in cell culture and associated with reduced susceptibility to oseltamivir include (influenza virus subtype-specific numbering) A11T, K173G, and R453M in H3N2; and H99Q in influenza B virus (Yamagata lineage). In some cases, HA substitutions were selected in conjunction with known NA resistance substitutions and may contribute to reduced susceptibility to oseltamivir; however, the impact of HA substitutions on antiviral activity of oseltamivir in humans is unknown and likely to be strain dependent.

Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. The incidence of oseltamivir treatment-associated resistance in paediatric treatment studies has been detected at rates of 27% to 37% and 3% to 18% (3/11 to 7/19 and 1/34 to 9/50 post-treatment isolates, respectively) for influenza A/H1N1 and influenza A/H3N2, respectively. The frequency of resistance selection to oseltamivir and the prevalence of such resistant virus vary seasonally and geographically.

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance-associated substitution H275Y was found in >99% of US/ Europe circulating 2008 H1N1 influenza isolates. The 2009 H1N1 influenza ('swine flu') was almost uniformly susceptible to oseltamivir. Prescribers should consider available information from the Centers for Disease Control and Prevention (CDC) on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir.

Cross-resistance

Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitutions observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated substitutions observed in influenza B, confer reduced susceptibility to zanamivir but not oseltamivir. The R292K oseltamivir resistance-associated substitution observed in N2, and the I222T, D198E/N, R371K, or G402S oseltamivir resistance-associated substitutions observed in influenza B neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. In general, amino acid substitutions at neuraminidase catalytic residues confer cross-resistance to other neuraminidase inhibitors while substitutions at framework residues may or may not confer cross-resistance. 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 interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with oseltamivir did not impair normal humoral antibody response to infection.

Pharmacokinetics

**Adults**

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted, predominantly by hepatic esterases, to oseltamivir carboxylate (active metabolite).
At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing as described in table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oseltamivir</th>
<th>Oseltamivir Carboxylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>65 (26)</td>
<td>348 (18)</td>
</tr>
<tr>
<td>AUC$_{0-12h}$ (ng·h/mL)</td>
<td>112 (25)</td>
<td>2,719 (20)</td>
</tr>
</tbody>
</table>

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

Co-administration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6,218 ng·h/mL under fasted conditions and 6,069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

The volume of distribution ($V_{ss}$) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 to 26 litres, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome (CY) P450 isoforms. No phase 2 conjugates of either compound have been identified in vivo.

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to 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 in the urine. Peak plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration.

Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds the 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 radiolabelled dose is eliminated in the faeces.

**Paediatric**

**Infants and Children, 1 Year of Age and Older**

The pharmacokinetics of oseltamivir has been evaluated in single-dose pharmacokinetic studies in children aged 1 to 16 years. Multiple-dose pharmacokinetics was studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, 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). Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age is similar to those in adults.

**Infants Less Than 1 Year of Age**

The pharmacokinetics, pharmacodynamics and safety of oseltamivir have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 0 - 12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious with a safety profile comparable to that of adults.
seen in older children and adults using the approved dose. The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

**Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic**

Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile. No clinical studies of prophylaxis in infants aged <1 have been performed.

**Renal Impairment**

Administration of 100 mg of oseltamivir 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 below. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis.

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

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 3fold 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_{min} (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 patients with mild or moderate hepatic impairment.

**Geriatric**

Exposure to oseltamivir carboxylate at the steady state was 25 to 35% higher in geriatric patients (age range: 65 to 78 years) compared with young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric patients 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 unless there is evidence of moderate or severe renal impairment (creatinine clearance <60 ml/min).

**Pregnant Women**

A pooled population pharmacokinetic analysis indicates that the oseltamivir dosage regimen results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women (n=59) compared to non-pregnant women (n=33). The lower predicted exposure however, remains above inhibitory concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza.
**Indications**

- **Treatment of Influenza**

  ANTIFLU is indicated for the treatment of acute, uncomplicated illness due to influenza A and B infection in patients (adults and children including full term neonates) who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms.

- **Prophylaxis of Influenza**

  ANTIFLU is indicated for post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. However, during a pandemic influenza outbreak, ANTIFLU is indicated for post-exposure prevention of influenza in infants less than 1 year of age. The appropriate use of ANTIFLU for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals aged 1 year or older.

- **Limitations of Use**

  ANTIFLU is not a substitute for early influenza vaccination on an annual basis as recommended by the CDC’s Advisory Committee on Immunization Practices. There is no evidence for the efficacy of ANTIFLU in any illness caused by agents other than influenza viruses Types A and B.

  The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (e.g. changes in viral virulence) might also diminish the clinical benefit of antiviral drugs. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season, and the impact of the disease in different geographical areas and patient populations. ANTIFLU is not recommended for patients with end-stage renal disease not undergoing dialysis.

**Dosage And Administration**

ANTIFLU Suspension and ANTIFLU Capsules are bioequivalent formulations.

- **Treatment of Influenza**

  Treatment with ANTIFLU should begin within the first 2 days of the onset of symptoms of influenza.

  **Adults and Adolescents (13 to 17 Years of Age)**

  The recommended oral dose of ANTIFLU for treatment of influenza in adults and adolescents aged 13 years and older is 75 mg twice daily for 5 days.

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Recommended dose for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg twice daily</td>
</tr>
</tbody>
</table>

  **Paediatric (Infants and Children 1 to 12 Years of Age)**

  The recommended oral dose of ANTIFLU for the treatment of influenza in paediatric patients, 1 to 12 years of age, based
Children weighing >40 kg and who are able to swallow capsules may receive treatment with the adult dosage of ANTIFLU Capsules twice daily for 5 days as an alternative to the recommended dose of ANTIFLU Suspension.

**Paediatric (Infants 0-12 months of age)**
The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults.

The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

<table>
<thead>
<tr>
<th>Body Weight*</th>
<th>Recommended dose for 5 days</th>
<th>Volume of Oral Suspension (12 mg/mL) for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 kg</td>
<td>9 mg twice daily</td>
<td>0.75 ml twice daily</td>
</tr>
<tr>
<td>3.5 kg</td>
<td>10.5 mg twice daily</td>
<td>0.9 ml twice daily</td>
</tr>
<tr>
<td>4 kg</td>
<td>12 mg twice daily</td>
<td>1.0 ml twice daily</td>
</tr>
<tr>
<td>4.5 kg</td>
<td>13.5 mg twice daily</td>
<td>1.12 ml twice daily</td>
</tr>
<tr>
<td>5 kg</td>
<td>15 mg twice daily</td>
<td>1.25 ml twice daily</td>
</tr>
<tr>
<td>5.5 kg</td>
<td>16.5 mg twice daily</td>
<td>1.37 ml twice daily</td>
</tr>
<tr>
<td>6 kg</td>
<td>18 mg twice daily</td>
<td>1.5 ml twice daily</td>
</tr>
<tr>
<td>6 - 7 kg</td>
<td>21 mg twice daily</td>
<td>1.75 ml twice daily</td>
</tr>
<tr>
<td>7 - 8 kg</td>
<td>24 mg twice daily</td>
<td>2.0 ml twice daily</td>
</tr>
<tr>
<td>8 - 9 kg</td>
<td>27 mg twice daily</td>
<td>2.25 ml twice daily</td>
</tr>
<tr>
<td>&gt; 9 - 10 kg</td>
<td>30 mg twice daily</td>
<td>2.5 ml twice daily</td>
</tr>
</tbody>
</table>

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient.
This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.
Prophylaxis of Influenza

Initiate post-exposure prophylaxis within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with ANTIFLU during a community outbreak.

**Adults and Adolescents (13 to 17 Years of Age)**
The recommended oral dose of ANTIFLU for the prophylaxis of influenza in adults and adolescents aged 13 years and older following close contact with an infected individual is 75 mg once daily for at least 10 days.

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Recommended dose for 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks. In immunocompromised patients, ANTIFLU may be continued for up to 12 weeks. The duration of protection lasts for as long as ANTIFLU dosing is continued.

**Paediatric (Infants and Children 1 to 12 Years of Age)**
The recommended oral dose of ANTIFLU for prophylaxis of influenza in paediatric patients, 1 to 12 years of age, based on body weight is given in the table below. Prophylaxis in paediatric patients following close contact with an infected individual is recommended for 10 days. For prophylaxis in paediatric patients during a community outbreak of influenza, dosing may be continued for up to 6 weeks.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Recommended Dose for 10 Days</th>
<th>Recommended Volumes for a 10-Day Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to 15 kg</td>
<td>30 mg once daily</td>
<td>2.5 mL (½ tsp)</td>
</tr>
<tr>
<td>&gt;15 kg to 23 kg</td>
<td>45 mg once daily</td>
<td>3.8 mL (¾ tsp)</td>
</tr>
<tr>
<td>&gt;23 kg to 40 kg</td>
<td>60 mg once daily</td>
<td>5.0 mL (1 tsp)</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>75 mg once daily</td>
<td>6.2 mL (1¼ tsp)</td>
</tr>
</tbody>
</table>

Children weighing >40 kg and who are able to swallow capsules may receive prophylaxis with a 75 mg dose of ANTIFLU Capsules once daily for 10 days as an alternative to the recommended dose of ANTIFLU Suspension.

**Paediatric (Infants Less Than 1 Year of Age)**
The recommended prophylaxis dose for infants aged less than 12 months during a pandemic influenza outbreak is half of the daily treatment dose (3 mg/kg once daily). This is based upon clinical data in children over 1 year of age and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following weight-adjusted dosing prophylaxis regimens are recommended for infants less than 1 year of age:

<table>
<thead>
<tr>
<th>Body Weight*</th>
<th>Recommended dose for 10 days</th>
<th>Volume of Oral Suspension (12 mg/mL) for Each Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 kg</td>
<td>9 mg once daily</td>
<td>0.75 ml once daily</td>
</tr>
<tr>
<td>3.5 kg</td>
<td>10.5 mg once daily</td>
<td>0.9 ml once daily</td>
</tr>
<tr>
<td>4 kg</td>
<td>12 mg once daily</td>
<td>1.0 ml once daily</td>
</tr>
<tr>
<td>Weight Range</td>
<td>Dose</td>
<td>Volume</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>4.5 kg</td>
<td>13.5 mg once daily</td>
<td>1.12 ml once daily</td>
</tr>
<tr>
<td>5 kg</td>
<td>15 mg once daily</td>
<td>1.25 ml once daily</td>
</tr>
<tr>
<td>5.5 kg</td>
<td>16.5 mg once daily</td>
<td>1.37 ml once daily</td>
</tr>
<tr>
<td>6 kg</td>
<td>18 mg once daily</td>
<td>1.5 ml once daily</td>
</tr>
<tr>
<td>&gt; 6 - 7 kg</td>
<td>21 mg once daily</td>
<td>1.75 ml once daily</td>
</tr>
<tr>
<td>&gt; 7 - 8 kg</td>
<td>24 mg once daily</td>
<td>2.0 ml once daily</td>
</tr>
<tr>
<td>&gt; 8 - 9 kg</td>
<td>27 mg once daily</td>
<td>2.25 ml once daily</td>
</tr>
<tr>
<td>&gt; 9 - 10 kg</td>
<td>30 mg once daily</td>
<td>2.5 ml once daily</td>
</tr>
</tbody>
</table>

* This table is not intended to contain all possible weights for this population. This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

**Hepatic Impairment**

No dose adjustment is recommended for treatment or for prevention in patients with mild or moderate hepatic impairment. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated. No studies have been carried out in paediatric patients with hepatic disorder.

**Renal Impairment**

* Adults and Adolescents (13 to 17 years of age)*

Following are the dosage recommendations for the treatment and prophylaxis of influenza in adults and adolescents (13 to 17 years of age) with various stages of renal impairment (estimated creatinine clearance of less than or equal to 90 mL per minute).

Dosage modifications are recommended in adults with an estimated creatinine clearance less than or equal to 60 mL per minute.

*Treatment of Influenza*

Dose adjustment is recommended for adult patients and adolescents (13 to 17 years of age) with moderate or severe renal impairment receiving ANTIFLU for the treatment of influenza. Recommended doses are detailed in the table below.

<table>
<thead>
<tr>
<th>Renal Impairment Creatinine Clearance</th>
<th>Recommended Dose for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&gt;60-90 mL/min)</td>
<td>75 mg twice daily for 5 days</td>
</tr>
<tr>
<td>Moderate (&gt;30 to 60 mL/min)</td>
<td>30 mg twice daily for 5 days</td>
</tr>
<tr>
<td>Severe (&gt;10 to 30 mL/min)</td>
<td>30 mg once daily for 5 days</td>
</tr>
<tr>
<td>≤10 mL/min/ ESRD patients not on dialysis</td>
<td>Not recommended (no data available)</td>
</tr>
<tr>
<td>Haemodialysis patients (≤10 mL/min)</td>
<td>30 mg immediately after each haemodialysis cycle (treatment duration not to exceed 5 days)</td>
</tr>
</tbody>
</table>
Peritoneal dialysis patients* (≤10 ml/min)
30 mg single dose administered immediately

* Data derived from studies in CAPD patients; the clearance of oseltamivir carboxylate is expected to be higher when the automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

**Prophylaxis of Influenza**

For the prophylaxis of influenza, dose adjustment is recommended for adult patients and adolescents (13 to 17 years of age) with moderate or severe renal impairment receiving ANTIFLU as detailed in the table below.

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Recommended Dose for Prevention†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&gt;60-90ml/min)</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Moderate (&gt;30 to 60 ml/min)</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>Severe (&gt;10 to 30 ml/min)</td>
<td>30 mg once daily every second day</td>
</tr>
<tr>
<td>≤10 ml/min/ ESRD patients not on dialysis</td>
<td>Not recommended (no data available)</td>
</tr>
<tr>
<td>Haemodialysis patients(≤10 ml/min)</td>
<td>30 mg immediately and then 30 mg after every second haemodialysis session</td>
</tr>
<tr>
<td>Peritoneal dialysis patients*(≤10 ml/min)</td>
<td>30 mg immediately and then 30 mg once weekly</td>
</tr>
</tbody>
</table>

* Data derived from studies in CAPD patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

† 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).

**Paediatric**

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

**Immunocompromised Patients**

Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised subjects.

**Geriatric Use**

No dose adjustment is required for geriatric patients, unless there is evidence of moderate or severe renal impairment.

**Administration**

ANTIFLU may be taken with or without food. However, when taken with food, tolerability may be enhanced in some patients. Adults, adolescents or children (>40 kg) who are able to swallow capsules may receive appropriate doses of ANTIFLU capsules. ANTIFLU for oral suspension may be used by patients (adults and paediatric) who have difficulties swallowing capsules or where lower doses are needed.

**Direction for Preparing the Suspension**

Shake the bottle to loosen the powder.
Slowly add boiled and cooled water up to the blue arrow mark on the label.
Replace the cap and shake the bottle vigorously.
Adjust the volume up to the blue arrow mark by adding more water if necessary and shake again. Keep the reconstituted suspension under refrigeration at 2° to 8°C. Do not freeze. Shake the bottle well before each use. Use the reconstituted suspension within 10 days of preparation. An oral dosing dispensing device (oral syringe provided with pack) that measures the appropriate volume in mL should be utilized with the oral suspension. For patients less than 1 year of age, provide an appropriate dosing device (oral syringe or dropper) that can accurately measure and administer small volumes.

**Contraindications**

ANTIFLU is contraindicated in patients with a known serious hypersensitivity to oseltamivir or any of the components of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme.

**Warnings And Precautions**

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses. This product is not a substitute for influenza vaccination. Use of oseltamivir must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as oseltamivir is administered. Oseltamivir should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable. Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use oseltamivir. Cases of anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, have been reported in postmarketing experience with oseltamivir. Oseltamivir should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected. Influenza can be associated with a variety of neurologic and behavioural symptoms, which can include events such as hallucinations, delirium and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. There have been postmarketing reports (mostly from Japan) of delirium and abnormal behaviour leading to injury (including self-injury) and, in some cases, resulting in fatal outcomes, in patients with influenza who were receiving oseltamivir. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on oseltamivir usage data. The reports were primarily among paediatric patients and often had an abrupt onset and rapid resolution. The contribution of the drug to these events has not been established. Influenza can be associated with a variety of neurologic and behavioural symptoms that can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient. Serious bacterial infections may begin with influenza-like symptoms, or may coexist with, or occur as complications during the course of influenza. Oseltamivir has not been shown to prevent such complications. Efficacy of oseltamivir 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.
No information is available regarding the treatment of influenza in patients with any medical condition sufficiently severe
or unstable to be considered at imminent risk of requiring hospitalization.
Efficacy of oseltamivir for treatment or prophylaxis has not been established in immuno-compromised patients. Safety of
oseltamivir for prophylaxis of influenza has been demonstrated for up to 12 weeks in immunocompromised patients.
Oseltamivir has no influence on the ability to drive and use machines.

Drug Interactions

Influenza Vaccines
The concurrent use of oseltamivir with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated.
However, because of the potential for interference between these products, LAIV should not be administered within 2
weeks before or 48 hours after administration of oseltamivir, unless medically indicated.
Inactivated influenza vaccine can be administered at any time relative to the use of oseltamivir.

Overall Drug Interaction Profile
Information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant
drug interactions are unlikely.
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 CYP450 mixed-
function oxidases or for glucuronyl transferases.
Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known
safety margin for most of these drugs, the elimination characteristics of oseltamivir carboxylate (glomerular filtration
and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when
prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g.
chlorpropamide, methotrexate, phenylbutazone).

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-
administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an
approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that
oseltamivir interaction with this pathway is weak.

Additional Information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering
oseltamivir with paracetamol (acetaminophen), acetylsalicylic acid (aspirin), cimetidine, antacids (magnesium and
aluminium hydroxides and calcium carbonates), rimantadine, amantadine or warfarin (in subjects stable on warfarin and
without influenza).

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-associated adverse reactions. Dose adjustment is
recommended for both treatment and prevention in adult patients and adolescents (13 to 17 years of age) with moderate or severe renal impairment (a serum creatinine clearance between 10 and 60 mL/minute). Dose adjustment is recommended for patients with end-stage renal disease (ESRD) undergoing routine hemodialysis or continuous peritoneal dialysis treatment. Oseltamivir is not recommended for patients with ESRD not undergoing dialysis. There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation. Refer to DOSAGE AND ADMINISTRATION.

Hepatic Impairment

No dosage adjustment is required in patients with mild-to-moderate hepatic impairment. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated. No studies have been carried out in paediatric patients with hepatic disorder.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with oseltamivir in pregnant women. Available published epidemiological/post-marketing data suggest that oseltamivir, 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 dose, which preclude a definitive assessment of the risk. In animal studies, there was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in offspring of rats and rabbits exposed at maternally toxic doses 100 and 50 times human exposures, respectively. Oseltamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant women may receive oseltamivir, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Lactation

Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a sub-therapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Paediatric Use

No data allowing a dose recommendation for premature children (less than 36 weeks post-menstrual age) are currently available. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions. Refer to Dosage and Administration.

Geriatric Use

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.

Undesirable Effects

Summary of the Safety Profile

The overall safety profile of oseltamivir is based on data from 6,049 adult/adolescent and 1,473 paediatric patients treated with oseltamivir or placebo for influenza, and on data from 3,990 adult/adolescent and 253 paediatric patients
receiving oseltamivir or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children — 10 on oseltamivir and 8 on placebo) received oseltamivir or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these adverse reactions were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1 to 2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these adverse reactions did not lead to discontinuation of oseltamivir.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding, and neuropsychiatric disorders.

The adverse reactions listed in the tables below fall into the following categories: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000). Adverse reactions are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reactions According to Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Common</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Agitation</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
</tbody>
</table>

In adult/adolescent treatment and prevention studies, adverse reactions that occurred the most frequently at the recommended dose (75 mg b.i.d. for 5 days for treatment and 75 mg o.d. for up to 6 weeks for prophylaxis) are shown below.

The safety profile reported in subjects who received the recommended dose of oseltamivir for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Headache</th>
<th>Insomnia</th>
<th>Altered level of consciousness Convulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Visual disturbance</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough Sore throat, Rhinorrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Vomiting Abdominal pain (including upper abdominal pain) Dyspepsia</td>
<td>Gastrointestinal bleeding Haemorrhagic colitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Elevated liver enzymes</td>
<td>Fulminant hepatitis Hepatic failure Hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Eczema Dermatitis Rash Urticaria</td>
<td>Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pain Dizziness (including vertigo) Fatigue Pyrexia Pain in limb</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment and Prevention of Influenza in Children

A total of 1,473 children (including otherwise healthy children aged 1 to 12 years and asthmatic children aged 6 to 12 years) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of oseltamivir once daily in a post-exposure prophylaxis study in households, a 6-week paediatric seasonal prophylaxis study, and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects.

The table below shows the most frequently reported adverse reactions from paediatric clinical trials.

Adverse Reactions in Studies Investigating Oseltamivir for Treatment and Prevention of Influenza in Children (Age/Weight-Based Dosing)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reactions According to Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Otitis media</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
</tbody>
</table>
### Description of Selected Adverse Reactions

#### Psychiatric Disorders and Nervous System Disorders
Influenza can be associated with a variety of neurologic and behavioural symptoms, which can include events such as hallucinations, delirium and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. In patients with influenza who were receiving oseltamivir, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases, resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

#### Hepato-Biliary Disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness, have been reported. These cases include fatal fulminant hepatitis/hepatic failure.

#### Other Special Populations

**Paediatric Population (Infants Less Than 1 Year of Age)**
Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than 1 year of age is similar to the established safety profile of children aged 1 year and older, with vomiting, diarrhoea and diaper rash being the most frequently reported adverse reactions.

**Elderly Patients and Patients with Chronic Cardiac and/or Respiratory Disease**
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients ‘at risk’ (patients 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 patients ‘at risk’ was

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th>Conjunctivitis (including red eyes, eye discharge and eye pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Earache</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough, Nasal congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Dermatitis (including allergic and atopic dermatitis)</td>
</tr>
</tbody>
</table>
qualitatively similar to that in otherwise healthy adults/adolescents. Those events reported numerically more frequently in subjects taking oseltamivir compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo. 

**Immunocompromised Patients**

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children who were 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in oseltamivir prophylaxis clinical studies.

**Children with Pre-existing Bronchial Asthma**

In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

### Additional

Other adverse reactions identified during post-approval use of oseltamivir include swelling of the face or tongue, allergy, hypothermia, seizure, and aggravation of diabetes. 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 oseltamivir exposure.

### Overdosage

Reports of overdoses with oseltamivir have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported. Adverse events reported following overdose were similar in nature to those observed with therapeutic doses of oseltamivir.

No specific antidote is known.

Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing oseltamivir oral suspension and when administering oseltamivir products to children.

### Storage And Handling Instructions

**ANTIFLU Capsules**

Store in a cool, dry place.

**ANTIFLU Suspension**

*Dry Powder:* Store in a cool, dry place. Protect from light.

*Reconstituted Suspension:* Use the reconstituted suspension within 10 days of preparation. Store reconstituted suspension under refrigeration at 2° to 8°C. Do not freeze. Shake the bottle well before each use.

### Packaging Information

**ANTIFLU Capsules** ......................................................... Blisters of 10 capsules

**ANTIFLU Suspension** .................................................. Bottle of 75 ml

Last reviewed: **July 2017**

Last updated: **July 2017**

**ANTIFLU Capsules/ Suspension**

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