NAME OF THE MEDICINE

TAMIFLU®
oseltamivir phosphate

(CAS registry number: 204255-11-8)

The chemical name (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C_{16}H_{28}N_{2}O_{4} (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.

DESCRIPTION

Oseltamivir phosphate is a white crystalline solid, highly soluble in water (> 500 mg/mL).

TAMIFLU (oseltamivir phosphate) is available as hard capsules for oral use. Each 75 mg hard capsule of TAMIFLU contains 98.5 mg oseltamivir phosphate, equivalent to 75 mg of oseltamivir. Each 45 mg hard capsule of TAMIFLU contains 59.1 mg oseltamivir phosphate, equivalent to 45 mg of oseltamivir. Each 30 mg hard capsule of TAMIFLU contains 39.4 mg of oseltamivir phosphate, equivalent to 30 mg of oseltamivir.

The hard capsules contain the following excipients: starch – pregelatinised maize, talc, povidone K 30, croscarmellose sodium and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide, iron oxide red CI77491, iron oxide yellow CI77492, iron oxide black CI77499, shellac and indigo carmine CI73015.

TAMIFLU is also available as powder for oral suspension. Each bottle, with 30 g powder for oral suspension contains 1.182 g of oseltamivir phosphate and when reconstituted with water results in a concentration of 12 mg/mL of oseltamivir. Each bottle contains the following excipients: xanthan gum, sodium dihydrogen citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide and Tutti-Frutti flavouring.
**PHARMACOLOGY**

**Pharmacodynamics**

**Mechanism of Action**

Oseltamivir phosphate is a pro-drug of the active metabolite, oseltamivir carboxylate. The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. A study in cultured tracheobronchial epithelial cells and primary nasal epithelial cells has shown that oseltamivir may also suppress virus entry to cells.

**In Vitro Susceptibility Tests**

Antiviral susceptibility and development of resistance to oseltamivir is usually discussed in the context of cell culture experiments involving Madin-Darby Canine Kidney (MDCK) virus reduction assay and/or neuraminidase inhibition assay (NA IC₅₀). The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. Oseltamivir carboxylate showed antiviral activity in the low nano-molar range in all these cell assays.

*In vitro* neuraminidase enzyme IC₅₀ (NA IC₅₀) values for oseltamivir susceptible clinical isolates of influenza A ranged from 0.1 nM to 1.3 nM and for influenza B from 2.6 nM to 8.7 nM.

Reduced susceptibility to oseltamivir carboxylate has been recovered *in vitro* by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. *In vitro* NA IC₅₀ assays showed that the degree of reduced sensitivity (IC₅₀) differs markedly for different mutations from 2-fold for resistant variant with the I222V mutation in influenza A N1 to 30,000-fold for resistant variant with the R292K mutation in influenza A N2.

The relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

**Viral Resistance**

Resistance to neuraminidase inhibitors *in vitro* can occur by neuraminidase mutations or haemagglutinin mutations. Haemagglutinin mutations generally reduce haemagglutinin binding affinity to sialic acid and thus reduce viral dependence on neuraminidase activity *in vitro*, resulting in neuraminidase inhibitor resistance indirectly. Neuraminidase mutations generally reduce binding affinity of neuraminidase inhibitors to the neuraminidase enzyme and thus confer resistance to neuraminidase inhibitors. To date, haemagglutinin mutations have not been described to confer resistance *in vivo* or in clinical studies, whereas neuraminidase mutations can confer resistance *in vivo* and have been observed to be selected at low frequency in clinical treatment studies.

Neuraminidase mutations have been observed to be selected *in vitro* after several passages in Madin-Darby Canine Kidney (MDCK) cells in the presence of increasing concentrations of
Oseltamivir carboxylate for influenza A virus isolates. Genetic analysis of resistant isolates obtained in vitro and in clinical studies, showed that reduced susceptibility to oseltamivir carboxylate is associated with presence of resistance mutations N294S; E119V; R292K and in one instance each N294S and SASG245-248del in N2 neuraminidase of influenza A virus isolates and resistance mutation H274Y in influenza A N1 (including H5N1). In influenza B neuraminidase one instance of G402S giving a 4-fold decrease in sensitivity has been reported and one instance of D198N (10-fold decrease) in an immunocompromised child has been reported. Also, influenza virus isolated from an 8 month old infant girl (B/Perth/211/2001) carried neuraminidase with approximately 10-fold reduced sensitivity to oseltamivir. Sequencing indicated carrying a D197E mutation (D198E in N2 numbering) was associated with the reduced sensitivity.

Viruses with resistant neuraminidase genotypes have varying degrees of loss of fitness and transmissibility compared to wild-type. Infectivity, pathogenicity and transmission studies in mice and ferrets indicate R292K mutation in N2 was associated with compromised growth and transmissibility, where as the growth and transmissibility of viruses carrying the E119V mutation in N2 or D198N in influenza B were similar to wild-type virus. H274Y in N1 and N294S in N2 appear intermediate, although growth and transmissibility may depend on the genetic background in which these mutations occur.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In clinical studies in naturally acquired infection (irrespective of treatment dose) the incidence of patients found to carry oseltamivir-resistant virus for adults and adolescents was 0.32% (4/1245) by phenotyping alone, 0.4% (5/1245) by genotyping and phenotyping (full genotyping was not performed on all studies) and 4.1% (19/464) or 5.4% (25/464) respectively, for children aged 1-12. All these patients were found to carry oseltamivir carboxylate resistant virus only transiently. The patients cleared the virus normally and showed no clinical deterioration.

In clinical studies conducted in post-exposure (7 days), post exposure within household groups (10 days) and seasonal (42 days) prophylaxis of influenza, there was no evidence for emergence of drug resistance associated with the use of TAMIFLU.

Insufficient information is available to date to fully characterise the risk of emergence of resistance to neuraminidase inhibitors in clinical use.

Cross-Resistance

Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed in vitro. Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, two of the three oseltamivir-induced mutations (E119V, H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same amino acid residues as two of the three mutations (E119G/A/D, R152K and R292K) observed in zanamivir-resistant virus.
Pharmacokinetics

Absorption

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is converted predominantly by hepatic esterases to the active metabolite. In multiple dose studies the peak concentration of the active metabolite occurs 2 to 3 hours after dosing. Following an oral dose of 75 mg twice daily, the peak concentration (C_{max}) of the active metabolite is approximately 350 - 400 ng/mL. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5% relative to the active metabolite. Plasma concentrations of the active metabolite are unaffected by co-administration with food (see DOSAGE AND ADMINISTRATION).

Distribution

The active metabolite reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit. In these studies, anti-viral concentrations of the active metabolite were seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea, following oral administration of oseltamivir phosphate.

The mean volume of distribution (V_{ss}) of the active metabolite is approximately 23 L in humans.

The binding of the active metabolite to human plasma protein is negligible (approximately 3%).

Metabolism

Oseltamivir is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. Thus interactions mediated by competition for these enzymes are unlikely.

Elimination

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to the active metabolite. Peak plasma concentrations of the active metabolite decline with a half-life of 6 hours to 10 hours in most subjects. The active metabolite is not further metabolised and 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 the anionic pathway) in addition to glomerular filtration occurs. Less than 20% of an oral radiolabelled dose is eliminated in faeces.

Special Populations

Renal impairment

Administration of 100 mg of TAMIFLU twice daily, for five days, to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely
proportional to renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose is reduced to 75 mg of TAMIFLU once daily for 5 days. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance \( \leq 10 \) mL/min (see DOSAGE AND ADMINISTRATION - Special Patient Populations).

Prophylaxis of influenza

In patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg of suspension once daily. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance \( \leq 10 \) mL/min (see DOSAGE AND ADMINISTRATION - Special Patient Populations).

Hepatic impairment

Based on *in vitro* and animal studies, significant increases in exposure to oseltamivir or its metabolite are not expected and this has been confirmed in clinical studies in patients with mild or moderate hepatic impairment. The pharmacokinetics of a single oral dose of oseltamivir 75 mg have been established in moderately hepatic impaired (Child-Pugh score 7-9) patients. Results of the study showed that \( C_{\text{max}} \) and AUC of active metabolite of oseltamivir in the 12 hepatic impaired patients fell within the therapeutic margin of safety and efficacy. The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied (see DOSAGE AND ADMINISTRATION).

Elderly

Exposure to the active metabolite at steady-state was approximately 25% higher in elderly patients (age range between 65 and 78) compared to young adults given comparable doses of TAMIFLU. Half-lives observed in elderly patients were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients for either treatment or prophylaxis of influenza unless there is co-existent renal impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Paediatrics

The pharmacokinetics of TAMIFLU have been evaluated in pharmacokinetic studies in children aged 1 to 16 years old. Younger children cleared both the pro-drug and the active metabolite faster than adults, resulting in lower exposure for a given mg/kg dose. Doses of 2 mg/kg gave comparable exposure to that achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). With advancing age, the difference in exposure between children and adults (per mg/kg dose) lessened to the extent that the exposure in children over
12 years of age was similar to that in adults (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

TAMIFLU should not be used in children under 1 year of age (see PRECAUTIONS - Toxicology).

**CLINICAL TRIALS**

**Treatment of Influenza in Adults**

A total of 1,355 patients were included in two phase III multicentre, placebo-controlled trials in naturally acquired influenza which were conducted in the Northern Hemisphere influenza season of 1997 to 1998 (Studies WV15670 & WV15671). An identical trial (Study WV15730) followed in the Southern Hemisphere winter of 1998 where 60 patients were recruited. The population used in the primary analyses was the intent-to-treat infected (ITTI) population. This population included only subjects who received at least one dose of study treatment and had laboratory confirmed influenza. The intent-to-treat (ITT) population included all subjects who took at least one dose of study medication, regardless of whether they proved to have influenza. The results for the two pivotal studies are shown in Tables 1 and 2.

**Table 1:** Median Time (hours) to Alleviation of All Symptoms in the ITTI and ITT Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (95% CI)</th>
<th>TAMIFLU 75 mg bd (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WV15671 ITTI</td>
<td>n = 129 103.3 (92.6 - 118.7)</td>
<td>n = 124 71.5 (60.0 - 83.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ITT</td>
<td>n = 200 92.0 (86.3 - 113.6)</td>
<td>n = 204 76.3 (66.3 - 89.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>WV15670 ITTI</td>
<td>n = 161 116.5 (101.5 - 137.8)</td>
<td>n = 158 87.4 (73.3 - 104.7)</td>
<td>0.0168</td>
</tr>
<tr>
<td>ITT</td>
<td>n = 235 116.1 (99.8 - 129.5)</td>
<td>n = 240 97.6 (79.1 - 115.3)</td>
<td>0.0506</td>
</tr>
</tbody>
</table>

ITTI Intent-to-treat infected
ITT Intent-to-treat

* Difference between medians
### Study WV15671

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>AUC of total symptom score (h)</th>
<th>Time to become afebrile (h)</th>
<th>AUC of virus titer (log_{10}TCID_{50}/mL)</th>
<th>Duration of virus shedding (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo ($n = 129$)</td>
<td>962.6$^#$</td>
<td>64.6 (59.2 - 76.3)</td>
<td>126.7$^#$</td>
<td>70.2 (68.0 - 71.4)</td>
</tr>
<tr>
<td>TAMIFLU 75 mg bd ($n = 124$)</td>
<td>597.1$^#$</td>
<td>41.5 (34.0 - 48.0)</td>
<td>111.4$^#$</td>
<td>66.8 (64.6 - 68.8)</td>
</tr>
</tbody>
</table>

$p$-value* $<0.0001$ Not calculated 0.2951 0.0332

### Study WV15670

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>AUC of total symptom score (h)</th>
<th>Time to become afebrile (h)</th>
<th>AUC of virus titer (log_{10}TCID_{50}/mL)</th>
<th>Duration of virus shedding (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo ($n = 161$)</td>
<td>943.0$^#$</td>
<td>73.5 (64.0 - 86.4)</td>
<td>130.8$^#$</td>
<td>71.0 (70.2 - 73.5)</td>
</tr>
<tr>
<td>TAMIFLU 75 mg bd ($n = 158$)</td>
<td>773.3$^#$</td>
<td>43.6 (36.0 - 54.4)</td>
<td>78.2$^#$</td>
<td>70.2 (67.5 - 71.4)</td>
</tr>
</tbody>
</table>

$p$-value* 0.0073 Not calculated 0.0259 0.0917

$n = $ number of subjects in the intent to treat infected population
$p$-value* $<0.0001$ Not calculated 0.2951 0.0332

Studies WV15670 and WV15671 were multicentre, double blind, randomised, parallel group studies with the objective of assessing the safety and antiviral efficacy of TAMIFLU. Subjects who enrolled in these studies presented with symptoms of influenza defined as:

- **fever** (defined as body temperature $\geq 38$ °C)
- **plus one respiratory symptom** [cough, sore throat, nasal symptoms (rhinorrhoea/congestion)]
- **plus one constitutional symptom** [headache, malaise (feeling unwell), myalgia (aches and pains), sweats/chills (feeling feverish), prostration (fatigue)].

Subjects were randomised to receive either 75 mg TAMIFLU twice daily, 150 mg TAMIFLU twice daily or placebo twice daily for a period of five days, commencing up to 36 hours, later amended to 48 hours after the reported onset of symptoms.

**Primary efficacy parameter:** Time to alleviation of all symptoms was significantly reduced by up to 30 hours in both the 75 mg and 150 mg active treatment groups compared with placebo, demonstrating a more rapid recovery for subjects on TAMIFLU. Treatment with TAMIFLU resulted in a reduced median time to alleviation all of the seven defined influenza symptoms. No increase in efficacy was demonstrated in subjects who received TAMIFLU 150 mg twice daily compared to 75 mg twice daily.
Secondary efficacy parameters: Both doses of TAMIFLU significantly reduced the median total symptom score AUC (measure of extent and severity of illness) by up to 40% compared to placebo. The duration of virus shedding was also reduced in subjects treated with TAMIFLU.

Temperature AUC was reduced in TAMIFLU-treated subjects compared with placebo. Fewer subjects reported fever following dosing with TAMIFLU, despite a lower consumption of symptom relief medication (paracetamol) by the TAMIFLU groups compared to the placebo group. This was in addition to a marked reduction in the time taken for subjects on TAMIFLU to return to an afebrile state during the treatment interval compared with placebo.

The overall incidence of secondary illnesses (such as bronchitis, otitis media, sinusitis and pneumonia) requiring antibiotic medication was reduced by 50% in TAMIFLU treated subjects when compared with placebo. Subjects treated with TAMIFLU rated their health, activity and quality of sleep to be better than patients on placebo during the dosing period. Moreover, treatment with TAMIFLU was associated with a reduction in time taken to return to normal (pre-influenza) health status and ability to perform daily activity.

Treatment of Influenza in Adolescents, Adults and Elderly – Study M76001

In a recent study which included adolescents, adults and elderly (13 to 80 years) patients, time to alleviation of all symptoms was significantly reduced by up to 24.2 hours in patients treated with TAMIFLU. There was a significant reduction of the median total symptom score AUC in the treatment group compared to placebo. Consistent with other studies, temperature AUC, number of patients with fever and the time to afebrile state were reduced in TAMIFLU treated subjects compared with placebo. There was also a reduced need for patients receiving TAMIFLU to take symptom relief medication (paracetamol).

Treatment of Influenza in High Risk Populations – Study WV15758/872

In a separate study, patients aged > 13 years with influenza and co-existing chronic cardiac and/or respiratory disease received TAMIFLU 75 mg or placebo twice daily. No difference in the median time to alleviation of all symptoms was seen between patients taking TAMIFLU or placebo. However, the duration of febrile illness was reduced by approximately one day in the TAMIFLU treatment group. The number of patients shedding virus on days 2 and 4 was also markedly reduced in those treated with TAMIFLU. There was no difference in the safety profile of TAMIFLU in the at-risk populations compared to the general adult population.

Prevention of Influenza in Adults and Adolescents

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a post-exposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature ≥ 99.0 °F/37.2 °C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a 4-fold increase in virus antibody titres from baseline.
In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 18 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

In a seasonal prophylaxis study in elderly residents of nursing homes, TAMIFLU 75 mg once daily taken for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders and 43% had cardiac disorders.

In a post-exposure prophylaxis study, household contacts (aged ≥ 13 years) who had no laboratory evidence of influenza at baseline, and who were living with an index case who was subsequently shown to have had influenza infection, were randomised to treatment (the intent-to-treat index-infected, not infected at baseline [ITTIINAB] population). In this population, TAMIFLU 75 mg administered once daily within 2 days of onset of symptoms in the index case and continued for 7 days, reduced the incidence of laboratory confirmed clinical influenza in the contacts from 12% (24/200) in the placebo group to 1% (2/205) for the TAMIFLU group (risk reduction 91.9%, \( p < 0.001 \)). For the study population as a whole (the ITT population), including contacts of index cases in whom influenza infection was not confirmed, the incidence of laboratory confirmed clinical influenza was reduced from 7.4% (34/462) in the placebo group to 0.8% (4/493) for the TAMIFLU group (risk reduction 89%, \( p < 0.001 \)). Index cases did not receive TAMIFLU in the study. In the ITT population, 13.9% of contacts in the placebo group and 11.4% of contacts in the TAMIFLU group had been vaccinated.

**Treatment of Influenza in Paediatric Patients**

One double-blind placebo controlled treatment trial was conducted in children, aged 1 to 12 years (mean age 5.3 years), who had fever (≥ 37.8 °C) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected with influenza A and 33% with influenza B.

The primary endpoint in this study was the time to freedom from illness, a composite endpoint which required 4 individual conditions to be met. These were: alleviation of cough, alleviation of coryza, resolution of fever, and parental opinion of a return to normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom from illness by 1.5 days compared to placebo. The median time to freedom from illness in the intent-to-treat infected (ITTI) population was 5.7 days in the placebo group and 4.2 days in patients treated with TAMIFLU. In the intent-to-treat population (ITT), the median time to freedom from illness was 5.2 days in the placebo group and 4.4 days in patients treated with TAMIFLU. The median time to freedom from illness was significantly reduced in the subgroup of patients infected with influenza A and treated with TAMIFLU, compared to patients infected with influenza B and treated with TAMIFLU (not statistically significant). The proportion of patients developing acute otitis media was reduced by 40% in children receiving TAMIFLU compared to placebo. Subgroup analyses of this study by gender showed no differences in the treatment effect of TAMIFLU in males and females.
A second study was conducted in 334 asthmatic children aged 6 to 12 years of age, 53.6% of whom were influenza-positive. The median time to freedom from illness was reduced by 8% in patients treated with TAMIFLU compared to placebo (not statistically significant). By day 6 (the last day of treatment) FEV1 had increased by 10.8% in the TAMIFLU-treated group compared to 4.7% in the placebo group ($p = 0.0148$) although there was no difference in the use of asthma medication between groups.

**Prevention of Influenza in Paediatric Patients – Study WV16193**

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days (prophylactic efficacy in adults and adolescents $\geq 13$ years has previously been demonstrated with a 7 day dosing regimen [see above]).

In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction, [95% CI 26.0 - 81.2]; $p = 0.0042$). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention (58.5% reduction, [95% CI 15.6 - 79.6]; $p = 0.0114$).

According to subgroup analysis in children at 1-12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19% (21/111) in the group not receiving prevention to 7% (7/104) in the group receiving (64.4% reduction, [95% CI 15.8 - 85.0]; $p = 0.01$; ITT). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21% (15/70) in the group not receiving prevention to 4% (2/47) in the group receiving prevention (80.1% reduction, [95% CI 22.0 - 94.9]; $p = 0.0206$; ITTIINAB) (see Table 3).
Table 3: Incidence of Influenza Infection among Paediatric Contacts

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of Contacts 1-12 years</th>
<th>Influenza-infected Contacts</th>
<th>Index Case Infected</th>
<th>% Protective efficacy of oseltamivir</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ITT</td>
<td>215</td>
<td>7 (7%)</td>
<td>21 (19%)</td>
<td>28</td>
<td>64.4</td>
</tr>
<tr>
<td>ITTII</td>
<td>129</td>
<td>6 (11%)</td>
<td>18 (24%)</td>
<td>24</td>
<td>55.2</td>
</tr>
<tr>
<td>ITTIINAB</td>
<td>117</td>
<td>2 (4%)</td>
<td>15 (24%)</td>
<td>17</td>
<td>80.1</td>
</tr>
</tbody>
</table>

P = prophylaxis
T = treatment
ITTII = intent-to-treat index-infected
ITTIINAB = intent-to-treat index-infected, not infected at baseline.

**INDICATIONS**

TAMIFLU is indicated for the treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection.

TAMIFLU is indicated for the prevention of influenza in adults and children aged 1 year and older. Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

**CONTRAINDICATIONS**

TAMIFLU is contraindicated in patients with known hypersensitivity to any of the components of the product.

**PRECAUTIONS**

TAMIFLU is a specific treatment for infections due to influenza A or B viruses. Use should be limited to patients who have characteristic symptoms of influenza when influenza A or B virus infections have been documented locally. Data on the treatment of influenza B are limited.

There is no current evidence for the safety or efficacy of oseltamivir in persons with complications of an acute influenza episode such as viral or bacterial pneumonia. Such patients may require extensive supportive and adjunctive care. Antiviral therapy has not been shown to reduce the need for such care and monitoring.

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac diseases/or respiratory diseases has not been established.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.
TAMIFLU powder for oral suspension contains sorbitol. One dose of 45 mg TAMIFLU oral suspension administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance, this is above the recommended daily maximum limit of sorbitol.

**Driving and Operating Machinery**

There have been no reported effects of TAMIFLU on driving performance or the ability to operate machinery. Adverse effects on such activities are not predicted from the pharmacology of TAMIFLU.

**Paediatric Use**

The safety and efficacy of TAMIFLU in paediatric patients have not been established in children aged less than 1 year of age. TAMIFLU should not be used in children under 1 year of age (see PRECAUTIONS - Toxicology)

**Toxicology**

In unweaned rats a single oral dose of oseltamivir phosphate 500 mg/kg (free base equivalent) to 7-day old pups resulted in deaths associated with high exposure to the prodrug. However, at 1520 mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occurred at 300 mg/kg administered to 7-day old rats. This dose level resulted in maximum plasma concentrations of 42.4 μg/mL for the prodrug and 9.4 μg/mL for the active metabolite, and maximum brain concentrations of 10.7 μg/g for the prodrug and 0.54 μg/g for the active metabolite. Based on the correlation between mortality and plasma exposure across the dose-range, the prodrug, but not the active metabolite, appears to underlie the toxicity in 7-day old juvenile rats.

**Use in Elderly Patients**

Limited numbers of subjects aged 65 and over have been included in the clinical trials. However, on the basis of drug exposure and tolerability, dose adjustments are not required for elderly patients unless there is co-existent renal impairment (see PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**Use in Renal Impairment**

Dose adjustment is recommended for patients with creatinine clearance of 10 - 30 mL/min for the treatment and prevention of influenza. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance < 10 mL/min. Therefore, caution should be taken when administering TAMIFLU to those patients (see PHARMACOLOGY and DOSAGE AND ADMINISTRATION).
Carcinogenicity

A two-year carcinogenicity study with oseltamivir phosphate in rats was negative at oral doses up to 500 mg/kg/day, resulting in respective relative systemic exposures (based on AUC_{0-24h}, maximum clinical dose of 75 mg twice daily) to oseltamivir phosphate and its active metabolite of 352 times and 52 times, respectively.

A two-year carcinogenicity study with oseltamivir phosphate in mice was negative at oral doses up to 400 mg/kg/day, resulting in respective relative systematic exposures (based on AUC_{0-24h}, maximum clinical dose of 75 mg twice daily) to oseltamivir phosphate and its active metabolite of 130 times and 15 times, respectively.

A 26-week dermal carcinogenicity study of oseltamivir carboxylate in FVB/Tg.AC transgenic mice was negative when tested at doses up to 780 mg/kg/day.

Mutagenicity

Oseltamivir phosphate was found to be non-genotoxic in the Ames test and the human lymphocyte chromosome assay, with or without metabolic activation, and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. The active metabolite of oseltamivir phosphate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay and negative in the SHE cell transformation test.

Effects on Fertility

No effect on male or female fertility was observed in rats exposed to oseltamivir phosphate. The highest dose has approximately 180 times the human systemic exposure (AUC) to the active metabolite.

Use in Pregnancy – Category B1

There are insufficient human data upon which to base an evaluation of risk of TAMIFLU to the pregnant woman or developing foetus. Studies for effects on embryo-foetal development were conducted in rats (at doses up to 1500 mg/kg/day) and rabbits (at doses up to 500 mg/kg/day) by the oral route. Relative exposures in these studies were 180 times human exposure (AUC_{0-24h} of the active metabolite) in the rat and 50 times human exposure in the rabbit. Foetal exposure in both species was approximately 15% to 20% of that of the mother. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. The duration of parturition was increased in rats at oral doses of 1500 mg/kg/day of oseltamivir phosphate, 180 times human exposure (AUC_{0-24h}), but it was not affected at 500 mg/kg/day (approximately 40 times human exposure). Oseltamivir phosphate was not teratogenic in these studies.

Because animal reproductive studies may not be predictive of human response, and there are no adequate and well-controlled studies in pregnant women, TAMIFLU should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Use in Lactation

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Offspring development was not affected at maternal doses of 1500 mg/kg/day in rats. It is not known whether oseltamivir or the active metabolite are excreted in human milk. TAMIFLU should therefore be used only if the potential benefit for the lactating mother justifies the potential risk for the nursing infant.

Drug Interactions

Information derived from pharmacology and pharmacokinetic studies of oseltamivir phosphate suggest that clinically significant drug interactions are unlikely.

Oseltamivir phosphate is rapidly converted to the active metabolite by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in the literature. These esterases have been shown not to be saturable at concentrations of oseltamivir 100 times those which occur during treatment. Therefore, drug interactions caused by competition for these enzymes are highly unlikely.

*In vitro* studies demonstrated that neither oseltamivir phosphate nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases. Thus, drug interactions involving P450 isozymes are unlikely.

Oseltamivir is a weak substrate *in vitro* for the P-glycoprotein transport system; however, no adverse event for oseltamivir or the concomitant administrated drug which could be due to an interaction at the P-glycoprotein level has been detected.

Cimetidine has no effect on plasma levels of oseltamivir or its active metabolite.

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 the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways.

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid (aspirin), cimetidine or with antacids (magnesium and aluminium hydroxides and calcium carbonates).

There is no mechanistic basis for an interaction with oral contraceptives.

Drug interaction studies have not been undertaken with oseltamivir and a number of drugs and drug classes, including erythromycin and macrolide antibiotics, theophylline derivatives and antihistamines.

Co-administration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic pathway is weak.
Effects on Laboratory Tests

TAMIFLU has not been found to cause any clinically relevant changes in a range of biochemistry and haematology tests.

Pharmaceutical Precautions

Direct contact of oseltamivir phosphate with the skin and eyes should be avoided as it is a potential skin sensitiser and eye irritant.

ADVERSE EVENTS

Experience from Clinical Trials

Adult Treatment Studies

In adult phase III treatment studies, the adverse event profile was found to be similar across all four treatment studies (i.e. Studies WV15670, WV15671, WV15730 and WV15707) with comparable frequency and type(s) of adverse event(s) being recorded. Being essentially of similar design these studies were subsequently pooled to better estimate the frequency of adverse events reported during 5 days of treatment with TAMIFLU (75 mg twice daily). A summary of adverse events in adults (including elderly patients) with an incidence of > 1% (irrespective of causality) and occurring more frequently in subjects taking TAMIFLU is presented in Table 4.

Table 4: Summary of Adverse Events in the Treatment of Naturally Acquired Influenza With Dose of 75 mg TAMIFLU Twice Daily (Excluding Nausea Associated With Vomiting) (Studies WV15670, WV15671, WV15730 and WV15707)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n = 475</th>
<th>75 mg TAMIFLU bd n = 496</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>15 (3.2%)</td>
<td>59 (11.9%)</td>
</tr>
<tr>
<td>Nausea (without vomiting)*</td>
<td>25 (5.3%)</td>
<td>52 (10.5%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (0.6%)</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (2.3%)</td>
<td>13 (2.6%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11 (2.3%)</td>
<td>12 (2.4%)</td>
</tr>
</tbody>
</table>

* Table excludes reports of nausea associated with vomiting i.e. nausea reported within 1 day of report of vomiting

Nausea and vomiting were transient events and generally occurred with the first dose.

Other clinical adverse events of any intensity, which occurred with an incidence of > 1% in patients receiving 75 mg TAMIFLU twice daily in adult phase III treatment clinical studies, were diarrhoea and dizziness. These events were considered at least remotely related to
treatment with TAMIFLU. The excess reporting of headache and abdominal pain in the 75 mg twice daily TAMIFLU group compared with placebo was numerically marginal.

**Adult Prevention Studies**

A total of 3434 subjects (adolescents, healthy adults and elderly) participated in phase III prevention studies with 1480 receiving the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing. There were no clinically relevant differences in the safety profile of the 942 elderly subjects, who received TAMIFLU or placebo, compared with the younger population.

The most frequently reported adverse events in all prophylaxis studies of naturally acquired influenza are summarised in Table 5. The adverse events are listed in descending order of frequency and are events occurring more frequently in the TAMIFLU group compared with the placebo group.

| Table 5: Summary of Most Frequent Adverse Events in All Prophylaxis Studies in Naturally Acquired Influenza (Studies WV15799, WV15673, WV15697, WV15708 and WV15825) |
|---|---|
| **Placebo** | **75 mg TAMIFLU od** |
| n = 1434 | n = 1480 |
| Nausea | 62 (4.3%) | 118 (8.0%) |
| Headache | 251 (17.5%) | 298 (20.1%) |
| Vomiting | 15 (1.0%) | 31 (2.1%) |
| Diarrhoea | 38 (2.6%) | 48 (3.2%) |
| Pain | 43 (3.0%) | 53 (3.6%) |
| Fatigue | 107 (7.5%) | 117 (7.9%) |
| Rhinorrhoea | 16 (1.1%) | 23 (1.6%) |
| Abdominal pain | 23 (1.6%) | 30 (2.0%) |
| Insomnia | 14 (1.0%) | 18 (1.2%) |
| Dizziness (excluding vertigo) | 21 (1.5%) | 24 (1.6%) |
| Upper respiratory tract infection | 115 (8.0%) | 120 (8.1%) |
| Dyspepsia | 23 (1.6%) | 25 (1.7%) |

The adverse events reported in prophylaxis studies were consistent with the established safety profile for TAMIFLU in the treatment of influenza. Adverse events experienced more frequently by subjects taking TAMIFLU than placebo included nausea (8.0% vs. 4.3%), vomiting (2.1% vs. 1.0%), diarrhoea (3.2% vs. 2.6%) and abdominal pain (2.0% vs. 1.6%). Headache was the most frequently reported adverse event with an incidence of 17.5% in the placebo group and 20.1% in the group receiving TAMIFLU.
Paediatric Treatment Studies

A total of 1032 paediatric patients aged 1 - 12 years (including 698 otherwise healthy children aged 1 - 12 years and 334 asthmatic paediatric patients aged 6 - 12 years) participated in phase III studies investigating the use of TAMIFLU in the treatment of influenza. A total of 515 paediatric patients received treatment with TAMIFLU suspension.

Adverse events occurring in > 1% of paediatric patients receiving TAMIFLU treatment are listed in Table 6. The most frequently reported adverse event was vomiting. Other events reported more frequently by paediatric patients treated with TAMIFLU included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the majority of cases.

Table 6: Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza Adverse Events Occurring On Treatment in > 1% of Paediatric Patients Enrolled in Phase III Trials of TAMIFLU Treatment of Naturally Acquired Influenza

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment a</th>
<th>Treatment b</th>
<th>Prophylaxis b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Oseltamivir 2 mg/kg bd</td>
<td>Oseltamivir Unit dose c</td>
</tr>
<tr>
<td></td>
<td>n = 517</td>
<td>n = 515</td>
<td>n = 158</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48 (9.3%)</td>
<td>77 (15.0%)</td>
<td>31 (19.6%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>55 (10.6%)</td>
<td>49 (9.5%)</td>
<td>5 (3.2%)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>58 (11.2%)</td>
<td>45 (8.7%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20 (3.9%)</td>
<td>24 (4.7%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Asthma (including aggravated)</td>
<td>19 (3.7%)</td>
<td>18 (3.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (4.3%)</td>
<td>17 (3.3%)</td>
<td>10 (6.3%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13 (2.5%)</td>
<td>16 (3.1%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (3.3%)</td>
<td>10 (1.9%)</td>
<td>-</td>
</tr>
<tr>
<td>Ear disorder</td>
<td>6 (1.2%)</td>
<td>9 (1.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>13 (2.5%)</td>
<td>9 (1.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11 (2.1%)</td>
<td>8 (1.6%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (0.4%)</td>
<td>5 (1.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>10 (1.9%)</td>
<td>5 (1.0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>8 (1.5%)</td>
<td>5 (1.0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Tympanic membrane disorder</td>
<td>6 (1.2%)</td>
<td>5 (1.0%)</td>
<td>-</td>
</tr>
</tbody>
</table>

a Pooled data from phase III trials of TAMIFLU treatment of naturally acquired influenza.
b Uncontrolled study comparing treatment (twice-daily dosing for 5 days) with prophylaxis (once-daily dosing for 10 days).
c Unit dose = age-based dosing

Adverse events included are: all events reported in the treatment studies with frequency ≥ 1% in the oseltamivir 75 mg twice daily group.
Paediatric Prophylaxis Study

Paediatric patients aged 1 - 12 years participated in a post-exposure prophylaxis study in households, both as index cases ($n = 134$) and as contacts ($n = 222$). Gastrointestinal events, particularly vomiting, were the most frequently reported. TAMIFLU was well tolerated in this study; the adverse events noted being consistent with those previously observed (see Table 6).

Post-Marketing Experience

**Skin and subcutaneous tissue disorder:** rare cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema and urticaria, and very rare cases of erythema multiforme and Stevens-Johnson-Syndrome have been reported. Rare reports of toxic epidermal necrolysis. Allergy, anaphylactic/ anaphylactoid reactions and face oedema have also been reported rarely.

**Liver and biliary system disorder:** very rare reports of hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir.

**Psychiatric disorders/Nervous system disorders:** Convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety and nightmares) have been reported during TAMIFLU administration in patients with influenza, predominately in children and adolescents. These events often had an abrupt onset and rapid resolution. In rare cases, these events resulted in accidental injury, and some resulted in a fatal outcome. The contribution of TAMIFLU to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking TAMIFLU.

 Patients with influenza should be closely monitored for signs of abnormal behaviour throughout the treatment period.

**Gastro-intestinal disorders:** in rare cases gastro-intestinal bleeding was observed after the use of TAMIFLU. In particular, haemorrhagic colitis was reported and subsided when the course of influenza abated or treatment with TAMIFLU was interrupted.

**DOSAGE AND ADMINISTRATION**

TAMIFLU may be taken with or without food (see PHARMACOLOGY). However, taking with food may enhance tolerability in some patients.

**Treatment of Influenza**

Treatment should begin within the first or second day of onset of symptoms of influenza.

**Adults and Adolescents**

The recommended oral dose of TAMIFLU capsules in adults and adolescents 13 years of age and older is 75 mg twice daily, for 5 days. Adults and adolescents 13 years of age and older
who are unable to swallow capsules may receive the appropriate dose of TAMIFLU suspension.

**Paediatric Patients**
The recommended oral dose of TAMIFLU for paediatric patients 1 year and older who cannot swallow a 75 mg capsule is:

<table>
<thead>
<tr>
<th>Body weight in kg</th>
<th>Recommended dose for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 kg</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt; 15 - 23 kg</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt; 23 - 40 kg</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg twice daily</td>
</tr>
</tbody>
</table>

For the oral suspension an oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser.

Paediatric patients weighing > 40 kg who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily or one 30 mg capsule plus one 45 mg capsule twice a day as an alternative to the recommended dose of TAMIFLU suspension.

**Prophylaxis of Influenza**

**Adults and Adolescents**
The recommended oral dose of TAMIFLU for prevention of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Therapy should begin within two days of exposure. The recommended dose for prevention during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts for as long as dosing is continued.

**Paediatric Patients**
Children weighing > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once a day, for 10 days as an alternative to the recommended dose of TAMIFLU suspension (see below).

The recommended prophylactic oral dose of TAMIFLU for children ≥ 1 year of age is:

<table>
<thead>
<tr>
<th>Body weight in kg</th>
<th>Recommended dose for 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 kg</td>
<td>30 mg once daily</td>
</tr>
<tr>
<td>&gt; 15 to 23 kg</td>
<td>45 mg once daily</td>
</tr>
<tr>
<td>&gt; 23 to 40 kg</td>
<td>60 mg once daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

For the oral suspension, a dosing syringe marked with 30 mg, 45 mg and 60 mg dosing levels is provided.

It is recommended that TAMIFLU powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.
Patients unable to swallow capsules

Adults, adolescents and children who are unable to swallow capsules may receive their required 30 mg, 45 mg, 60 mg or 75 mg dose of TAMIFLU by following the instructions below.

1. Hold the TAMIFLU capsule(s), corresponding to the required dose, over a small bowl. Carefully pull the capsule(s) open and pour the powder into the bowl.
2. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey, light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste of the medication.
3. Stir the mixture well and give the entire contents to the patient. The mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture. It is not necessary to administer any undissolved white powder as this is inert material.

If the patient requires a dose of TAMIFLU, which is different to that available in capsule form, they may receive their appropriate dose of TAMIFLU by following the instructions below.

1. Hold one TAMIFLU 75 mg capsule over a small bowl. Carefully pull the capsule open and pour the powder into the bowl.
2. Using a graduated syringe, add 5 mL water to the powder. Stir for about two minutes.
3. Draw up into the syringe the correct amount of mixture from the bowl (see table below). The recommended dose is body weight dependent (see tables above).
   Push down on the plunger of the syringe, to empty its entire contents into a second bowl. Discard any unused mixture.

<table>
<thead>
<tr>
<th>Recommended dose</th>
<th>Amount of TAMIFLU mixture for one dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>2 mL</td>
</tr>
<tr>
<td>45 mg</td>
<td>3 mL</td>
</tr>
<tr>
<td>60 mg</td>
<td>4 mL</td>
</tr>
</tbody>
</table>

4. In the second bowl, add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to the mixture to mask the bitter taste of the medication.
5. Stir this mixture well and give the entire contents of the second bowl to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture.
Special Patient Populations

Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prevention of influenza (see PHARMACOLOGY). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Renal Impairment

*Treatment of influenza*

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose is reduced to 75 mg of TAMIFLU once daily, for 5 days. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see PHARMACOKINETICS and PRECAUTIONS).

*Prophylaxis of influenza*

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with creatinine clearance between 10 – 30 mL/min receiving TAMIFLU it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg of suspension once daily. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see PHARMACOKINETICS - Special Populations and PRECAUTIONS).

Paediatrics

The safety and efficacy of TAMIFLU have not been established in children aged less than 1 year of age. TAMIFLU should not be used in children under 1 year of age (see PRECAUTIONS - Toxicology)

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) in the treatment or prevention of influenza unless there is co-existent renal impairment (see PHARMACOLOGY and PRECAUTIONS).

Fructose Intolerance

A bottle of 30 g TAMIFLU powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg TAMIFLU oral suspension administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.
Preparation of Oral Suspension

It is recommended that TAMIFLU oral suspension be reconstituted by the pharmacist prior to dispensing to the patient:

1. Tap the closed bottle several times to loosen the powder.
2. Measure 52 mL of purified water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add the total amount of purified water to the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push bottle adapter into neck of the bottle.
5. Close bottle with cap tightly. This will make sure that the bottle adapter fits in the bottle in the right position.
6. Write the date of expiry of the reconstituted oral suspension on the bottle label. (The shelf life of the reconstituted oral suspension is 10 days if stored at room temperature [below 25 °C] or 17 days if stored in a refrigerator [between 2 °C and 8 °C]).

Note: Shake TAMIFLU oral suspension well before each use.

OVERDOSAGE

Treatment of overdose should consist of general supportive measures.

At present there has been no experience with overdose; however, the anticipated manifestations of acute overdose would be nausea, with or without accompanying emesis. Single doses of up to 1000 mg of TAMIFLU and twice daily doses of up to 500 mg of TAMIFLU for 7 days have been well tolerated. A complete pack with ten 30 mg, 45 mg or 75 mg capsules of TAMIFLU will contain a total of 300 mg, 450 mg or 750 mg of oseltamivir, respectively.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

TAMIFLU 30 mg, 45 mg and 75 mg capsules are available in blister packages of 10 capsules.

TAMIFLU 30 mg capsules are supplied as hard gelatin capsules with a light yellow/opaque cap and a light yellow/opaque body. "ROCHE" is printed in blue ink on the yellow body and "30 mg" is printed in blue ink on the light yellow cap.

TAMIFLU 45 mg capsules are supplied as hard gelatin capsules with a grey/opaque cap and a grey/opaque body. "ROCHE" is printed in blue ink on the grey body and "45 mg" is printed in blue ink on the grey cap.
TAMIFLU 75 mg capsules are supplied as hard gelatin capsules with a light yellow/opaque cap and a grey/opaque body. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap.

TAMIFLU 12 mg/mL Powder for Oral Suspension is available in a 100 mL bottle with 30 g of white to light yellow powder for reconstitution. TAMIFLU suspension is supplied with a plastic adapter, a plastic oral dispenser and a measuring plastic cup. After reconstitution with 52 mL of water, the usable volume of oral suspension allows the retrieval of 10 doses of 75 mg oseltamivir.

Store TAMIFLU capsules below 25 °C.

After reconstitution, TAMIFLU Oral Suspension can be stored at room temperature (below 25 °C) for up to 10 days or in a refrigerator (2 °C to 8 °C) for up to 17 days. TAMIFLU Oral Suspension should not be frozen.

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**NAME AND ADDRESS OF THE SPONSOR**

Roche Products Pty Limited  
ABN 70 000 132 865  
4–10 Inman Road  
Dee Why NSW 2099

**TGA Approval Date:** 4th June 2009