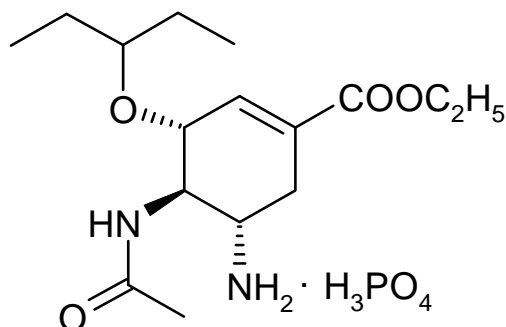


NAME OF THE MEDICINE

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 C₁₆H₂₈N₂O₄ (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 – 1.3 nM and for influenza B from 2.6 – 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

Reduced sensitivity of viral neuraminidase

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or resistance to oseltamivir has been examined in clinical studies (see Table 1). All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no worsening of the underlying symptoms.

Table 1: Emergence of Influenza Viruses with Reduced Susceptibility or Resistance to Oseltamivir in Clinical Studies

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Genotyping and Phenotyping*
Adults and Adolescents	4/1245 (0.32%)	5/1245 (0.4%)
Children (1 – 12 years)	19/464 (4.1%)	25/464 (5.4%)

* Full genotyping was not performed in all studies.

In clinical studies conducted in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prophylaxis of influenza in immunocompetent persons, there was no evidence for emergence of drug resistance associated with the use of TAMIFLU. There was no resistance observed during a 12-week seasonal prophylaxis study in immunocompromised subjects.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. For example, in 2008 the oseltamivir resistance-associated substitution H275Y was found in > 99 % of circulating 2008 H1N1 influenza isolates in Europe, while the 2009 H1N1 influenza (“swine flu”) was almost uniformly susceptible to oseltamivir. Resistant strains have also been isolated from both immunocompetent and immunocompromised patients treated with oseltamivir. The susceptibility to oseltamivir and the prevalence of such viruses appears to vary seasonally and geographically. Oseltamivir resistance has also been reported in patients with pandemic H1N1 influenza in connection with both therapeutic and prophylactic regimens.

The rate of emergence of resistance may be higher in the youngest age groups, and in immunocompromised patients. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral subtype specific.

Prescribers should consider available information on influenza virus drug susceptibility patterns for each season when deciding whether to use TAMIFLU (for the latest information, please refer to WHO and/or local government websites).

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 – 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 – 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 5 days, to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to renal function.

A population pharmacokinetic model describing the impact of creatinine clearance (CrCL) on oseltamivir and oseltamivir carboxylate pharmacokinetics was developed and qualified for simulation using 80 subjects with varying degrees of renal function. Subjects had dense pharmacokinetic profiles and were identified from three clinical studies; a study in subjects with either normal renal function or mild, moderate or severe renal impairment (WP15648) and two studies in healthy subjects receiving a range of single (WP15517) or multiple doses of oseltamivir (WP15525). Simulations were performed and suitable regimens using available capsule formulations were selected on the basis to provide oseltamivir carboxylate exposures considered safe and efficacious in clinical trials.

Refer to DOSAGE AND ADMINISTRATION for recommended dosing for patients with severe, moderate and mild renal impairment.

Two clinical studies were performed to evaluate the pharmacokinetic, safety and tolerability of oseltamivir and oseltamivir carboxylate in end stage renal disease patients undergoing haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). In study PP15974 patients undergoing either CAPD or HD received a single 75 mg capsule of oseltamivir, whereas in study NP16472 patients received 30 mg oseltamivir oral suspension for 6.5 weeks, with CAPD patients receiving a single dose per week and HD patients a dose after alternate dialysis sessions. In order to assist in determining appropriate dosing recommendations in HD, a population pharmacokinetic model for HD was constructed and qualified for simulation. Suitable regimens using available capsule formulations were selected on their basis to achieve oseltamivir carboxylate plasma trough levels in subjects with normal renal function dosed at 75 mg twice daily for treatment, or 75 mg oseltamivir given orally once daily for prophylaxis.

Refer to DOSAGE AND ADMINISTRATION for recommended dosing for patients with end stage renal disease undergoing haemodialysis and continuous ambulatory peritoneal dialysis.

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_{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 65 – 78 years old) 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 \geq 1 year of age

The pharmacokinetics of TAMIFLU have been evaluated in pharmacokinetic studies in children aged 1 – 16 years old. Multiple dose pharmacokinetics were studied in a small number of children aged 3 – 12 years old enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in younger children, than in adults, resulting in lower exposure in these children for a given mg/kg dose. Doses of 2 mg/kg and unit doses of 30 and 45 mg, administered to children in the appropriate categories according to the recommendation in the DOSAGE AND ADMINISTRATION section yield oseltamivir carboxylate exposures comparable to those 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 1355 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 – 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 2 and 3.

Table 2: Median Time (hours) to Alleviation of All Symptoms in the ITTI and ITT Populations

Study		Placebo (95% CI)	TAMIFLU 75 mg bd (95% CI)	<i>p</i> -value*
WV15671	ITTI	<i>n</i> = 129 103.3 (92.6 - 118.7)	<i>n</i> = 124 71.5 (60.0 - 83.2)	<0.0001
	ITT	<i>n</i> = 200 97.0 (86.3 - 113.6)	<i>n</i> = 204 76.3 (66.3 - 89.2)	0.004
WV15670	ITTI	<i>n</i> = 161 116.5 (101.5 - 137.8)	<i>n</i> = 158 87.4 (73.3 - 104.7)	0.0168
	ITT	<i>n</i> = 235 116.1 (99.8 - 129.5)	<i>n</i> = 240 97.6 (79.1 - 115.3)	0.0506

ITT Intent-to-treat

ITTI Intent-to-treat infected

* Difference between medians

Table 3: Summary of Secondary Efficacy Results (Median and 95% Confidence Interval) from the Studies in the Treatment of Naturally Acquired Influenza

Study (Protocol Number(s)) Treatment group	AUC of total symptom score (h)	Time to become afebrile (h)	AUC of virus titer (log ₁₀ TCID ₅₀ -h/mL)	Duration of virus shedding (h)
Study WV15671				
• Placebo (n = 129)	962.6 [#]	64.6 (59.2 - 76.3)	126.7 [#]	70.2 (68.0 - 71.4)
• TAMIFLU 75 mg twice daily (n = 124)	597.1 [#]	41.5 (34.0 - 48.0)	111.4 [#]	66.8 (64.6 - 68.8)
<i>p</i> -value*	<0.0001	Not calculated	0.2951	0.0332
Study WV15670				
• Placebo (n = 161)	943.0 [#]	73.5 (64.0 - 86.4)	130.8 [#]	71.0 (70.2 - 73.5)
• TAMIFLU 75 mg twice daily (n = 158)	773.3 [#]	43.6 (36.0 - 54.4)	78.2 [#]	70.2 (67.5 - 71.4)
<i>p</i> -value*	0.0073	Not calculated	0.0259	0.0917

n = number of subjects in the intent to treat infected population

* Comparison of placebo with TAMIFLU

95% confidence interval not calculated

Studies WV15670 and WV15671

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 ≥ 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 5 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 of 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 patients (13 – 80 years), 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 ≥ 37.2 °C /99.0 °F 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 – 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 Infants and Children

One double-blind placebo controlled treatment trial was conducted in children, aged 1 – 12 years old (mean age 5.3 years old), 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 – 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 Infants and Children – 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, children and infants aged 1 – 12 years old, 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 ≥ 13 years old 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 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 4).

Table 4: Incidence of Influenza Infection among Paediatric Contacts

Population	Number of Contacts 1-12 years	Influenza-infected Contacts			Index Case Infected	% Protective efficacy of oseltamivir	p-value
		P	T	Total			
Overall ITT	215	7 (7%)	21 (19%)	28	24	64.4	0.01
ITTII	129	6 (11%)	18 (24%)	24	24	55.2	0.089
ITTIINAB	117	2 (4%)	15 (24%)	17	24	80.1	0.0206

P = prophylaxis

T = treatment

ITTII = intent-to-treat index-infected

ITTIINAB = intent-to-treat index-infected, not infected at baseline.

Prophylaxis of Influenza in Immunocompromised Patients

A double-blind, placebo controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects, including 18 children 1 – 12 years old. Laboratory-confirmed clinical influenza, as defined by RT-PCR plus oral temperature ≥ 37.2 °C/99.0 °F plus cough and/or coryza, all recorded within 24 hours, was evaluated. Among subjects who were not already shedding virus at baseline, TAMIFLU reduced the incidence of laboratory-confirmed clinical influenza from 3.0% (7/231) in the group not receiving prophylaxis to 0.4% (1/232) in the group receiving prophylaxis (see Table 5).

Table 5: Incidence of Influenza Infection in Immunocompromised Patients

Population	Placebo <i>n/N</i> (%)	TAMIFLU 75 mg once daily <i>n/N</i> (%)	Treatment effect ^a	95% CI for difference in proportions between treatments ^b	<i>p</i> -value ^c
Overall ITT	7/238 (2.9%)	5/237 (2.1%)	28.3%	-2.3% to 4.1%	0.772
ITTII	7/238 (2.9%)	2/237 (0.8%)	71.3%	-0.6% to 5.2%	–
ITTIINAB	7/231 (3.0%)	1/232 (0.4%)	85.8%	0.1% to 5.7%	–

^a Treatment effect = $(1 - \text{Relative Risk}) \times 100\%$

^b Calculated using Newcombe's method of combining Wilson score intervals without continuity correction

^c Comparison of Placebo versus TAMIFLU using Fisher's exact test

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.

Use in Renal Impairment

For dose adjustments in patients with renal impairment refer to the PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections.

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

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 – 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.

While no controlled clinical trials have been conducted on the use of TAMIFLU in pregnant women, limited data available from post-marketing and retrospective observational surveillance do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development.

Use in Lactation

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking TAMIFLU and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk at very low levels. TAMIFLU should be used in lactating mothers only if the potential benefit for the lactating mother justifies the potential risk of exposure of the medicine to the nursing infant.

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 Toxicology).

No studies have been carried out in paediatric patients with hepatic impairment.

Use in Elderly Patients

Limited numbers of subjects aged ≥ 65 years old 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).

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 $\mu\text{g}/\text{mL}$ for the prodrug and 9.4 $\mu\text{g}/\text{mL}$ for the active metabolite, and maximum brain concentrations of 10.7 $\mu\text{g}/\text{g}$ for the prodrug and 0.54 $\mu\text{g}/\text{g}$ 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.

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 $\text{AUC}_{0-24\text{h}}$, 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.

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.

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. As a result, 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 administered 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, antacids (magnesium and aluminium hydroxides and calcium carbonates), warfarin, rimantadine or amantadine.

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

Elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir.

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

The overall safety profile of TAMIFLU is based on data from 2647 adults/adolescents and 858 paediatric patients with influenza, and on data from 1945 adult/adolescent and 148 paediatric patients receiving TAMIFLU for the prophylaxis of influenza in clinical trials. In adult/adolescent treatment studies, the most frequently reported adverse drug reactions (ADRs) were nausea, vomiting and headache. The majority of these ADRs were reported on a single occasion, occurred on either the first or second treatment day and resolved spontaneously within 1 – 2 days. In adult/adolescent prophylaxis studies, the most frequently reported ADRs were nausea, vomiting, headache and pain. In children, the most commonly reported ADR was vomiting. In the majority of patients, these events did not lead to discontinuation of TAMIFLU.

Treatment and Prophylaxis of Influenza in Adults and Adolescents

In adult/adolescent treatment and prophylaxis studies, ADRs that occurred the most frequently ($\geq 1\%$) at the recommended dose (75 mg twice daily for 5 days for treatment and 75 mg once daily for up to 6 weeks for prophylaxis), and whose incidence is at least 1% higher on TAMIFLU compared to placebo, are shown in Table 5.

The population included in the influenza treatment studies 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 qualitatively similar to that in otherwise healthy adults/adolescents.

The safety profile reported in the subjects that received the recommended dose of TAMIFLU for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies (see Table 6), despite a longer duration of dosing in the prophylaxis studies.

Table 6: Percentage of patients with ADRs that occurred in $\geq 1\%$ of the adults and adolescents in the oseltamivir group in studies investigating TAMIFLU for treatment or prophylaxis of influenza (difference to placebo $\geq 1\%$)

System Organ Class Adverse Drug Reaction	Treatment Studies		Prophylaxis		Frequency category ^a
	TAMIFLU (75 mg twice daily) <i>n</i> = 2647	Placebo <i>n</i> = 1977	TAMIFLU (75 mg twice daily) <i>n</i> = 1945	Placebo <i>n</i> = 1588	
<i>Gastrointestinal Disorders</i>					
Nausea	10%	6%	8%	4%	very common
Vomiting	8%	3%	2%	1%	common
<i>Neurological and Nervous System Disorders</i>					
Headache	2%	1%	17%	16%	very common
<i>General Disorders</i>					
Pain	< 1%	< 1%	4%	3%	common

^aFrequency category is reported only for the TAMIFLU group. Standard names to describe each of the frequency categories follow this convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$).

Adverse events reported in $\geq 1\%$ of the adults and adolescents taking TAMIFLU in the treatment studies (*n* = 2647) and in the prophylaxis studies (*n* = 1945), which occurred more frequently in the patients on placebo or where the difference between the TAMIFLU and placebo arm was $< 1\%$, were the following:

Gastrointestinal Disorders (TAMIFLU versus placebo)

- Treatment: diarrhoea (6% vs. 7%), abdominal pain (incl. upper abdominal pain, 2% vs. 3%)
- Prophylaxis: diarrhoea (3% vs. 4%), upper abdominal pain (2% vs. 2%), dyspepsia (1% vs. 1%)

Infections and Infestations (TAMIFLU vs. placebo)

- Treatment: bronchitis (3% vs. 4%), sinusitis (1% vs. 1%), herpes simplex (1% vs. 1%)
- Prophylaxis: nasopharyngitis (4% vs. 4%), upper respiratory tract infections (3% vs. 3%), influenza (2% vs. 3%)

General Disorders (TAMIFLU vs. placebo)

- Treatment: dizziness (incl. vertigo, 2% vs. 3%),

- Prophylaxis: fatigue (7% vs. 7%), pyrexia (2% vs. 2%), influenza like illness (1% vs. 2%), dizziness (1% vs. 1%), pain in limb (1% vs. <1%)

Neurological and Nervous System Disorders (TAMIFLU vs. placebo)

- Treatment: insomnia (1% vs. <1%)
- Prophylaxis: insomnia (1% vs. <1%)

Respiratory, Thoracic and Mediastinal Disorders (TAMIFLU vs. placebo)

- Treatment: cough (2% vs. 2%), nasal congestion (1% vs. 1%)
- Prophylaxis: nasal congestion (7% vs. 7%), sore throat (5% vs. 5%), cough (5% vs. 6%), rhinorrhea (1% vs. 1%)

Musculoskeletal, Connective Tissue and Bone Disorders (TAMIFLU vs. placebo)

- Prophylaxis: back pain (2% vs. 3%), arthralgia (1% vs. 2%), myalgia (1% vs. 1%)

Disorders of the Reproductive System and Breast (TAMIFLU vs. placebo)

- Prophylaxis: dysmenorrhoea (3% vs. 3%)

Treatment and Prophylaxis of Influenza in Elderly

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 (aged up to 65 years).

Prophylaxis of Influenza in Immunocompromised Patients

A 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 – 12 years old, showed that the safety profile in the 238 subjects receiving TAMIFLU was consistent with that previously observed in TAMIFLU prophylaxis clinical trials.

Treatment and Prophylaxis of Influenza in Paediatrics

A total of 1480 paediatric patients (including 698 otherwise healthy children aged 1 – 12 years old and asthmatic children aged 6 – 12 years old) participated in clinical studies investigating the use of TAMIFLU in the treatment of influenza. A total of 858 paediatric patients received treatment with TAMIFLU suspension.

The ADRs that occurred in $\geq 1\%$ of children aged 1 – 12 years receiving TAMIFLU in the clinical trials for treatment of naturally acquired influenza ($n = 858$), and whose incidence is at least 1% higher on TAMIFLU compared to placebo ($n = 622$), is vomiting (16% on oseltamivir vs. 8% on placebo). Amongst the 148 children who received the recommended dose of TAMIFLU once daily in a post-exposure prophylaxis study in households ($n = 99$), and in a separate 6-week paediatric prophylaxis study ($n = 49$), vomiting was the most frequent ADR (8% on TAMIFLU vs. 2% in the no prophylaxis group). TAMIFLU was well tolerated in these studies and the adverse events noted were consistent with those previously observed in paediatric treatment studies.

Adverse events reported in $\geq 1\%$ of the children taking TAMIFLU in the treatment studies ($n = 858$) or $\geq 5\%$ of the children in the prophylaxis studies ($n = 148$), which occurred more frequently in the children on placebo/no prophylaxis or where the difference between the oseltamivir and placebo/no prophylaxis arm was $< 1\%$, were the following:

Gastrointestinal Disorders (TAMIFLU versus placebo)

- Treatment: diarrhoea (9% vs. 9%), nausea (4% vs. 4%), abdominal pain (incl. upper abdominal pain, 3% vs. 3%)

Infections and Infestations (TAMIFLU vs. placebo)

- Treatment: otitis media (5% vs. 8%), bronchitis (2% vs. 3%), pneumonia (1% vs. 3%), sinusitis (1% vs. 2%)

Respiratory, Thoracic and Mediastinal Disorders (TAMIFLU vs. placebo)

- Treatment: asthma (including aggravated asthma, 3% vs. 4%), epistaxis (2% vs. 2%)
- Prophylaxis: cough (12% vs. 26%), nasal congestion (11% vs. 20%)

Skin and Subcutaneous Tissue Disorders (TAMIFLU vs. placebo)

- Treatment: dermatitis (including allergic and atopic dermatitis, 1% vs. 2%)

Disorders of Ear and Labyrinth (TAMIFLU vs. placebo)

- Treatment: earache (1% vs. < 1%)

Disorders of the Eye (TAMIFLU vs. placebo)

- Treatment: conjunctivitis (including red eyes, eye discharge and eye pain, 1% vs. < 1%)

Additional adverse events reported from paediatric treatment studies, which previously qualified to be presented above, however in larger datasets did not fulfill the criteria for inclusion in previous sections anymore, are given below:

Disorders of Blood and Lymphatic system (TAMIFLU vs. placebo)

- Treatment: lymphadenopathy (< 1% vs. 1%)

Disorders of Ear and Labyrinth (TAMIFLU vs. placebo)

- Treatment: tympanic membrane disorder (< 1% vs. 1%)

Post-Marketing Experience

The following adverse events have been identified during post-marketing use of TAMIFLU. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency and/or establish a causal relationship to TAMIFLU exposure.

Skin and subcutaneous tissue disorders: hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema and urticaria, erythema multiforme, allergy, anaphylactic/anaphylactoid reactions, face oedema, Stevens-Johnson-Syndrome and toxic epidermal necrolysis have been reported.

Hepatobiliary disorders: 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, however, 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. Three separate large epidemiological studies confirmed that influenza-infected patients receiving TAMIFLU are at no higher risk of developing neuropsychiatric events in comparison to influenza-infected patients not receiving antivirals.

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

Gastrointestinal disorders: gastrointestinal 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 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 oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

Infants and Children $\geq 1 - < 13$ years of age

The recommended dose of TAMIFLU for paediatric patients ≥ 1 year old is:

Body weight in kg	Recommended dose for 5 days
≤ 15 kg	30 mg twice daily
$> 15 - 23$ kg	45 mg twice daily
$> 23 - 40$ kg	60 mg twice daily
> 40 kg	75 mg twice daily

Paediatric patients ≥ 1 year old who are able to swallow capsules may receive treatment with 30 mg, 45 mg or 75 mg capsules twice daily. A 75 mg dose may be achieved with a 75 mg capsule twice daily or one 30 mg capsule plus one 45 mg capsule twice daily.

Paediatric patients ≥ 1 year old who are unable to swallow capsules may receive the appropriate dose of TAMIFLU oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

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

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.

Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive the appropriate dose of TAMIFLU oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

Infants and Children ≥ 1 – < 13 years of age

The recommended prophylactic oral dose of TAMIFLU for infants and children ≥ 1 year old is:

Body weight in kg	Recommended dose for 10 days
≤ 15 kg	30 mg once daily
$> 15 - 23$ kg	45 mg once daily
$> 23 - 40$ kg	60 mg once daily
> 40 kg	75 mg once daily

Paediatric patients ≥ 1 year old who are able to swallow capsules may receive treatment with 30 mg, 45 mg or 75 mg capsules. A 75 mg dose may be achieved with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once daily.

Paediatric patients ≥ 1 year old who are unable to swallow capsules may receive the appropriate dose of TAMIFLU oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

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

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.

No studies have been carried out in paediatric patients with hepatic impairment.

Renal Impairment

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 – 60 mL/min, it is recommended that the dose be reduced to 30 mg of TAMIFLU twice daily for 5 days. In patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose is reduced to 30 mg of TAMIFLU once daily, for 5 days. In patients undergoing routine haemodialysis, an initial dose of 30 mg of TAMIFLU can be administered prior to the start of dialysis if influenza symptoms develop during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session. For peritoneal dialysis, a dose of 30 mg of TAMIFLU administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see PHARMACOKINETICS). The pharmacokinetics of oseltamivir have not been studied in patients with end stage renal disease (i.e. creatinine clearance of < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation can not be provided for this group.

Prophylaxis of influenza

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 – 60 mL/min, it is recommended that the dose be reduced to 30 mg of TAMIFLU once daily. In patients with creatinine clearance between 10 – 30 mL/min receiving TAMIFLU it is recommended that the dose be reduced to 30 mg of TAMIFLU every other day. In patients undergoing routine haemodialysis, an initial dose of 30 mg of TAMIFLU can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis, an initial dose of 30 mg of TAMIFLU administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see PHARMACOKINETICS). The pharmacokinetics of oseltamivir have not been studied in patients with end stage renal disease (i.e. creatinine clearance of < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation can not be provided for this group.

Immunocompromised Patients

Seasonal prophylaxis in immunocompromised patients \geq 1 year of age is recommended for 12 weeks. No dose adjustment is necessary.

Infants < 1 year of age

The safety and efficacy of TAMIFLU have not been established in infants < 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 \geq 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.

Patients Unable to Swallow Capsules

When commercially manufactured TAMIFLU powder for oral suspension is not readily available, adults, adolescents, children and infants who are unable to swallow capsules may receive appropriate doses of TAMIFLU prepared at home by parents or caregivers or prepared by a pharmacist.

Home-prepared TAMIFLU for adults, adolescents, children and infants ≥ 1 year of age

This procedure describes the preparation of a **15 mg/mL** solution.

Adults, adolescents, children and infants 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.

Recommended dose	Amount of TAMIFLU 15 mg/mL mixture for one dose
30 mg	2 mL
45 mg	3 mL
60 mg	4 mL

- 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.
- 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.

Pharmacy-compounded TAMIFLU for adults, adolescents, children and infants ≥ 1 year of age

This procedure describes the preparation of a **15 mg/mL** suspension, which will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a suspension (15 mg/mL) from TAMIFLU 30 mg, 45 mg or 75 mg capsules using water containing 0.1% w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume of compounded TAMIFLU 15 mg/mL suspension required is determined by the weight of the patient according to the recommendation in the table below:

Body Weight (kg)	Total Volume to Compound per Patient Weight (mL)
≤ 15 kg	30 mL
$> 15 - 23$ kg	40 mL
$> 23 - 40$ kg	50 mL
> 40 kg	60 mL

Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above: 30 mL, 40 mL, 50 mL or 60 mL) of compounded TAMIFLU 15 mg/mL suspension as shown in the table below:

Total Volume of Compounded Suspension to be Prepared	Required Number of TAMIFLU Capsules (mg of oseltamivir)			Required Volume of Vehicle
	75 mg	45 mg	30 mg	
30 mL	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	29 mL
40 mL	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	38.5 mL
50 mL	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	48 mL
60 mL	12 capsules (900 mg)	20 capsules (900 mg)	30 capsules (900 mg)	57 mL

*No integral number of capsules can be used to achieve the target concentration; therefore, please use either the 30 mg or 75 mg capsules.

Third, follow the procedure below for compounding the suspension (15 mg/mL) from TAMIFLU capsules:

- Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU capsules into a clean mortar.
- Triturate the granules to a fine powder.
- Add one-third (1/3) of the specified amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) and triturate the powder until a uniform suspension is achieved.
- Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
- Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
- Repeat the rinsing (Step 5) with the remainder of the vehicle.
- Close the bottle using a child-resistant cap.
- Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension.
(Note: Undissolved residue may be visible but is comprised of inert ingredients of TAMIFLU capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.)
- Put an ancillary label on the bottle indicating "Shake Gently Before Use".
- Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this information be provided by affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
- Place an appropriate expiration date label according to storage condition (see PRESENTATION AND STORAGE CONDITIONS).

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, medicine name and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions for

pharmacy-compounded 15 mg/mL suspension from TAMIFLU capsules for infants and children ≥ 1 year old.

Body Weight (kg)	Dose (mg)	Volume per Dose 15 mg/ml	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤ 15 kg	30 mg	2 mL	2 mL twice daily	2 mL once daily
$> 15 - 23$ kg	45 mg	3 mL	3 mL twice daily	3 mL once daily
$> 23 - 40$ kg	60 mg	4 mL	4 mL twice daily	4 mL once daily
> 40 kg	75 mg	5 mL	5 mL twice daily	5 mL once daily

Note: This compounding procedure results in a 15 mg/mL suspension, which is different from the commercially available TAMIFLU powder for oral suspension.

Dispense the suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (2 mL, 3 mL, 4 mL or 5 mL) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Preparation of Oral Suspension

It is recommended that TAMIFLU **12 mg/mL** 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 - 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 overdose.

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 - 8 °C) for up to 17 days. TAMIFLU Oral Suspension should not be frozen.

After pharmacy compounding of TAMIFLU capsules the 15 mg/mL suspension can be stored at room temperature (below 25 °C) for up to 3 weeks (21 days) or in a refrigerator (2 - 8 °C) for up to 6 weeks. Pharmacy-compounded TAMIFLU suspension should not be frozen.

Home-prepared TAMIFLU mixture must be swallowed immediately after preparation.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE OF THE MEDICINE



Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
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Dee Why NSW 2099
AUSTRALIA

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