Tamiflu®

Oseltamivir

Composition

Active substance:

Oseltamivir (as oseltamivir phosphate).

Excipients:

Capsules: Excipients for capsules.

Powder for oral suspension: sorbitol (E 420), sodium dihydrogen citrate (E 331[a]), xanthan gum (E 415), sodium benzoate (E 211), saccharin sodium (E 954), titanium dioxide (E 171) and flavouring (tutti-frutti; contains ethyl vanillin).

Pharmaceutical form and quantity of active substance per unit

Tamiflu 30 mg: light-yellow opaque capsule containing 30 mg oseltamivir, corresponding to 39.4 mg oseltamivir phosphate

Tamiflu 45 mg: grey opaque capsule containing 45 mg oseltamivir, corresponding to 59.1 mg oseltamivir phosphate

Tamiflu 75 mg: capsule with grey body and light-yellow opaque cap containing 75 mg oseltamivir, corresponding to 98.5 mg oseltamivir phosphate

Tamiflu powder for oral suspension: Bottle containing 30 g powder for oral suspension. Oseltamivir 12 mg/ml after reconstitution with 52 ml of drinking water.

Indications and potential uses

Tamiflu is indicated for the treatment of influenza in adults and children ≥1 year. Tamiflu is effective against influenza A and B, but only few clinical data are available in the case of influenza B.

Tamiflu is indicated for the prevention of influenza A and B in adults and children aged ≥1 year.

Dosage and administration

Tamiflu may be taken with or without food (see *Pharmacokinetics*, *Absorption*). However, taking with food may enhance tolerability in some patients.

Treatment of influenza

Treatment should begin during the first or second day (ideally within 36 hours) after onset of symptoms of influenza.

Dosage instructions

Adults and adolescents

The recommended oral dose of Tamiflu capsules in adults and adolescents aged 13 years and above is 75 mg twice daily for 5 days. Adults and adolescents aged 13 years and above who have difficulty swallowing capsules may receive a dose of 75 mg Tamiflu suspension twice daily for 5 days.

Children ≥ 1 year

The following weight-based dosages of Tamiflu 30, 45, 75 mg capsules or suspension are recommended for children ≥1 year.

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

Children unable to swallow capsules receive the suspension. An oral dosing dispenser with 30 mg, 45 mg and 60 mg graduations is provided for the suspension. To ensure correct dosage, only this dispenser should be used.

Children weighing >40 kg or aged ≥8 years who are able to swallow capsules may also receive 75 mg Tamiflu capsules twice daily or one 30 mg capsule plus one 45 mg capsule twice daily for 5 days (see above).

If a patient cannot swallow the capsules and the oral suspension is not available, an appropriately dosed mixture can be prepared from capsules (see *Additional information*).

If neither the oral suspension nor the 30 mg or 45 mg capsules are available for children ≥1 year, an appropriately dosed mixture can be prepared from the 75 mg capsules (see *Additional information*).

Children <1 year

The safety and efficacy of Tamiflu have not yet been established in children under 1 year (see *Pharmacokinetics*).

However, based on limited pharmacokinetic and safety data, Tamiflu can be used for treatment of children aged 6 to 12 months during a pandemic influenza outbreak. The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.

Recommended oral dose of Tamiflu for children aged 6 to 12 months in a pandemic:

Limited pharmacokinetic data indicate that a dose of 3 mg/kg twice daily in children aged 6 to 12 months produces plasma levels of the active metabolite in the majority of patients that are similar to those shown to be clinically effective in older children and adults.

By contrast, insufficient clinical data are available to support a dosage recommendation for children under 6 months of age.

A magistral formula (10 mg/ml suspension) compounded in a pharmacy from Tamiflu capsules should be used for the treatment of influenza in children aged 6 to 12 months. For preparation of this magistral formula and its volumetric dosage, see *Additional information*.

Prevention of influenza

Adults and adolescents

The recommended oral dose of Tamiflu for prevention of influenza following close contact with an influenza-infected person is 75 mg once daily for 10 days. Treatment should begin within two days of exposure. The recommended dosage for prevention during an influenza epidemic is 75 mg once daily. Safety and efficacy have been demonstrated up to a duration of six weeks. The protective effect lasts for as long as the medicinal product is taken.

Children ³ 1 year

The following weight-based dosages of Tamiflu 30, 45, 75 mg capsules or suspension are recommended for children ≥1 year.

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

Children unable to swallow capsules receive the suspension. An oral dosing dispenser with 30 mg, 45 mg and 60 mg graduations is provided for the suspension. To ensure correct dosage, only this dispenser should be used.

Children weighing >40 kg or aged ≥8 years who are able to swallow capsules may also receive 75 mg Tamiflu capsules once daily or one 30 mg capsule plus one 45 mg capsule once daily for 10 days (see above).

If a patient cannot swallow the capsules and the oral suspension is not available, an appropriately dosed mixture can be prepared from capsules (see *Additional information*).

If neither the oral suspension nor the 30 mg or 45 mg capsules are available for children ≥1 year, an appropriately dosed mixture can be prepared from the 75 mg capsules (see *Additional information*).

Special dosage instructions

Patients with renal impairment

Treatment of influenza

No dose adjustment is necessary in patients with creatinine clearance above 30 ml/min. In patients with creatinine clearance between 10 and 30 ml/min it is recommended that the dose for treatment be reduced to 75 mg Tamiflu once daily for 5 days. Tamiflu is not recommended in patients with creatinine clearance £10 ml/min or in patients with severe renal failure undergoing regular hemodialysis or continuous peritoneal dialysis. No dosage recommendations exist for children with renal failure (see *Pharmacokinetics* and *Warnings and precautions*).

Prevention of influenza

No dose adjustment is necessary in patients with creatinine clearance above 30 ml/min. In patients with creatinine clearance between 10 and 30 ml/min it is recommended that the dose be reduced to 75 mg Tamiflu every other day or 30 mg of capsules or 30 mg of suspension once daily. Tamiflu is not recommended for patients with end-stage renal failure undergoing chronic hemodialysis or continuous peritoneal dialysis or for patients with creatinine clearance ≤10 ml/min (see *Pharmacokinetics*).

Patients with hepatic impairment

No dose adjustment is necessary for treatment or prevention in patients with mild or moderate hepatic impairment (see *Pharmacokinetics*). Safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immunocompromised patients

In immunocompromised patients aged 1 year and older, prophylaxis for up to 12 weeks is recommended when the risk of infection is high due to high influenza activity. No dose adjustment is necessary in patients with normal creatinine clearance.

Elderly patients

No dose adjustment is necessary for treatment or prevention in elderly patients (see *Pharmacokinetics*).

Contraindications

Hypersensitivity to any of the components of the product.

Warnings and precautions

Neuropsychiatric disturbances such as convulsions and delirium have been observed during Tamiflu administration for the treatment of influenza, particularly in children and adolescents. In rare cases these events led to accidental injury, very rarely with fatal outcome. It is not known to what extent Tamiflu contributes directly to such events, since they have also been reported in patients with influenza who were not taking Tamiflu (see *Postmarketing experience*).

Children and adolescents in particular should be closely monitored for signs of unusual behaviour.

There is no evidence that Tamiflu is effective in illnesses caused by agents other than type A and B influenza viruses.

No information is available on the safety and efficacy of oseltamivir in patients whose poor or unstable state of health could necessitate hospital admission.

The efficacy of oseltamivir for treatment in patients with chronic cardiac and/or respiratory disease has not yet been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population.

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect individual consideration of annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is used. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is present in the community.

Dose adjustment is recommended for both treatment and prevention of influenza in patients with creatinine clearance between 10 and 30 ml/min. Tamiflu is not recommended in patients with creatinine clearance ≤10 ml/min or in patients with severe renal failure undergoing regular hemodialysis or continuous peritoneal dialysis (see *Pharmacokinetics* and *Dosage and administration*). No dosage recommendation exists for children with renal failure.

Tamiflu powder for oral suspension contains 25.713 g of sorbitol. Twice-daily administration of a 45 mg dose of oseltamivir delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

Interactions

Information from pharmacological and pharmacokinetic studies of oseltamivir suggests that clinically significant interactions are unlikely.

Oseltamivir is almost completely converted to the active metabolite (oseltamivir carboxylate) by esterases located predominantly in the liver. Drug interactions based on competition for esterases have scarcely been described in the literature. The low protein binding of oseltamivir and its active metabolite suggests that interactions based on displacement of the drug are unlikely.

In vitro studies have shown that neither oseltamivir nor its active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases (see *Pharmacokinetics*).

There is no mechanistic basis for interaction with oral contraceptives.

Cimetidine, a nonspecific inhibitor of cytochrome P450 isoforms and a competitor for renal secretion of basic or cationic substances, has no effect on plasma levels of oseltamivir or its active metabolite. Clinically important drug interactions involving a change in gastric pH (antacids) or elimination via these metabolic pathways are therefore unlikely.

Clinically important interactions involving competition for renal tubular secretion are unlikely in view of the known safety margin of most of these medicinal products, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, medicinal products with a narrow safety margin that also undergo active renal secretion (e.g. chlorpropamide, methotrexate, phenylbutazone) should be coprescribed only with caution.

Coadministration of probenecid results in an approximately 2-fold increase in systemic availability of the active metabolite due to a decrease in active tubular secretion in the kidney. Because of the wide safety margin of the active metabolite, however, no dose adjustment is necessary when Tamiflu is coadministered with probenecid.

Coadministration with amoxicillin does not alter plasma levels of either compound, indicating that competition for anionic secretion is insignificant.

Isolated cases of interaction with ganciclovir, a substance likewise subject to tubular secretion, have been reported during postmarketing surveillance.

Coadministration with paracetamol (acetaminophen) does not alter plasma levels of oseltamivir, its active metabolite or paracetamol.

Following coadministration of oseltamivir (75 mg twice daily for 4 days) and a single 900 mg dose of aspirin (acetylsalicylic acid), no relevant changes were observed in the pharmacokinetic parameters of oseltamivir, its active metabolite (oseltamivir carboxylate) or aspirin.

Following coadministration of a single 150 mg dose of oseltamivir with a single dose of an antacid containing aluminium hydroxide and magnesium hydroxide or with a single dose of an antacid containing calcium carbonate, of paracetamol, of aspirin or of cimetidine, no relevant change was seen in the pharmacokinetic parameters of oseltamivir or its active metabolite.

In phase III clinical studies Tamiflu was administered therapeutically and prophylactically together with commonly used medicines such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide [bendroflumethiazide]), antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H_2 receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators and analgesics (aspirin, ibuprofen and paracetamol). No change in adverse event profile or frequency was observed on coadministration of Tamiflu with these medicinal products.

Pregnancy and lactation

Pregnancy

As no controlled trials have been conducted on the use of oseltamivir in pregnant women, only limited data are available from postmarketing reports and retrospective observational studies. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy or embryonic/fetal or postnatal development (see *Preclinical data*). Pregnant women may receive Tamiflu after the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman have been considered. Tamiflu should therefore be used in pregnancy only if clearly necessary.

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 oseltamivir and on excretion of oseltamivir in breast milk. Limited data show that oseltamivir and the active metabolite were detectable in breast milk. Treatment with oseltamivir may be considered

where there appears to be clear benefit to breast-feeding women, bearing in mind the pathogenicity of the circulating influenza virus strain and the underlying condition of the breast-feeding woman.

Effects on ability to drive and use machines

No effects have been observed on the ability to drive or operate machinery. However, the adverse effects of influenza itself should be borne in mind.

Undesirable effects

Experience from clinical studies

Treatment studies in adults

In a total of 2107 patients (including patients receiving placebo, 75 mg Tamiflu and 150 mg Tamiflu) who participated in phase III studies on the treatment of influenza in adults, the most frequently reported adverse events were nausea and vomiting. These were transient and generally occurred after the first dose. In most cases the patients did not discontinue the study medication as a result. At the recommended dose of 75 mg twice daily, three patients left the study because of nausea and three others because of vomiting.

In adult phase III treatment studies, some adverse events occurred more often in patients taking Tamiflu than in patients taking placebo. Undesirable effects that occurred most often at the recommended dose for treatment or prevention are shown in Table 1. This summary includes healthy young adults and at-risk patients (patients at increased risk of influenza complications, e.g. elderly patients and patients with chronic cardiac or respiratory disease).

Adverse events occurring with a frequency of ≥1% and reported more often in patients taking Tamiflu than in those taking placebo, irrespective of cause, were: nausea, vomiting, abdominal pain and headache.

Table 1: Summary of undesirable effects from a total of 9 clinical studies that occurred in ≥1% of patients in the treatment of naturally acquired influenza with Tamiflu 75 mg twice daily.

Undesirable effect (MedDRA organ classes)	Treatment*		Prevention	
	Placebo	Oseltamivir 75 mg twice daily	Placebo	Oseltamivir 75 mg once daily
	n=1050	n=1057	n=1434	n=1480
Infections and infestations				
Bronchitis	52 (5.0%)	39 (3.7%)	17 (1.2%)	11 (0.7%)
Acute bronchitis	10 (1.0%)	11 (1.0%)	1 (0.0%)	0 (0.0%)
Nervous system disorders				
Dizziness	31 (3.0%)	20 (1.9%)	21 (1.5%)	24 (1.6%)
Headache	16 (1.5%)	17 (1.6%)	251 (17.5%)	298 (20.1%)
Sleep disturbances	10 (1.0%)	11 (1.0%)	14 (1.0%)	18 (1.2%)
Vertigo**	6 (0.6%)	9 (0.9%)	3 (0.2%)	4 (0.3%)
Fatigue**	7 (0.7%)	8 (0.8%)	107 (7.5%)	117 (7.9%)
Respiratory tract				
Cough**	12 (1.1%)	10 (0.9%)	86 (6.0%)	83 (5.6%)
Gastrointestinal disorders				
Nausea (without vomiting)	71 (6.8%)	113 (10.7%)	56 (3.9%)	104 (7.0%)
Vomiting	32 (3.0%)	85 (8.0%)	15 (1.0%)	31 (2.1%)
Diarrhea	84 (8.0%)	58 (5.5%)	38 (2.6%)	48 (3.2%)
Abdominal pain	21 (2.0%)	23 (2.2%)	23 (1.6%)	30 (2.0%)

* Includes all undesirable effects that occurred in the treatment studies with a frequency of >1% in patients receiving oseltamivir 75 mg twice daily.

** These events no longer qualify as among the most frequently recorded events for the treatment group but are included here for completeness as they were included in a previous version of this table which was based on a smaller dataset.

Overall, the adverse event profile in “at-risk” patients was qualitatively similar to that in healthy young adults.

Influenza prevention studies

A total of 3434 subjects (adolescents, healthy adults and elderly) participated in phase III influenza prevention studies, of whom 1480 received the recommended dose of 75 mg once daily for 6 weeks. Despite the longer duration of dosing, undesirable effects were qualitatively very similar to those seen in the treatment studies (Table 1). The following adverse events occurred in the prevention studies with Tamiflu more often than with placebo and were also more numerous than in the treatment studies: aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infection. The difference between Tamiflu and placebo in the incidence of these adverse events was, however, less than 1%. In the 942 elderly subjects who received Tamiflu or placebo there were no clinically important differences in safety profile compared with the younger population.

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children aged 1–12 years, the safety profile in the 238 subjects receiving Tamiflu was consistent with that observed in previous Tamiflu prophylaxis clinical trials.

Treatment studies in children

A total of 1032 children aged 1–12 years (including 698 otherwise healthy children aged 1–12 years and 334 asthmatic children aged 6–12 years) participated in phase III studies of oseltamivir for the treatment of influenza. A total of 515 children were treated with oseltamivir suspension.

Undesirable effects that occurred in more than 1% of children are listed in Table 2. The most frequently reported adverse event was vomiting. Other more frequently reported events in children were abdominal pain, epistaxis, earache and conjunctivitis. These events generally occurred only once, resolved despite continued dosing and did not lead to discontinuation of treatment in the majority of cases.

Table 2: Commonest undesirable effects occurring in ≥1% of children aged 1 to 12 years in phase III studies on the treatment of naturally acquired influenza.

	Treatment[a]		Treatment[b]	Prevention[b]
Undesirable effect (MedDRA organ classes)	Placebo n=517	Oseltamivir 2 mg/kg bid n=515	Oseltamivir 30–75 mg according to age[c] n=158	Oseltamivir 30–75 mg according to age[c] n=99
Infections and infestations				
Pneumonia	3.3%	1.9%	-	-
Sinusitis	2.5%	1.7%	-	-
Bronchitis	2.1%	1.6%	1.9%	-
Blood and lymphatic system				
Lymphadenopathy	1.5%	1.0%	0.6%	-
Eye disorders				
Conjunctivitis	0.4%	1.0%	-	-
Ear and inner ear disorders				
Otitis media	11.2%	8.7%	1.3%	2.0%
Ear symptoms	1.2%	1.7%	-	-
Tympanic membrane disorder	1.2%	1.0%	-	-
Respiratory tract				
Asthma	3.7%	3.5%	-	1.0%
Epistaxis	2.5%	3.1%	1.3%	1.0%
Gastrointestinal disorders				
Vomiting	9.3%	15.0%	19.6%	10.1%
Diarrhea	10.6%	9.5%	3.2%	1.0%
Abdominal pain	3.9%	4.7%	1.9%	3.0%
Nausea	4.3%	3.3%	6.3%	4.0%
Skin disorders				
Dermatitis	1.9%	1.0%	0.6%	-

a Pooled data from phase III studies on the treatment of naturally acquired influenza.

b Uncontrolled study comparing treatment (twice daily for 5 days) with prevention (once daily for 10 days).

c Uniform dose = age-based dosing (see *Properties and effects*).

Included undesirable effects were those that occurred in the treatment studies with a frequency of ≥1% in the group receiving oseltamivir 75 mg twice daily.

Observational data in children aged 6 months to 1 year

The available safety information on the treatment of influenza with Tamiflu in children aged 6 months to 1 year, obtained from observational studies, epidemiological data analyses and postmarketing reports, suggests that the safety profile in children of this age group is similar to that established for children aged one year and older. No data are available from clinical studies.

Prevention of influenza in children

The most frequent side effects in children aged 1–12 years were gastrointestinal disorders, particularly vomiting.

Postmarketing experience

Immune system

Allergy, anaphylactic or anaphylactoid reactions and facial edema have been reported rarely.

Psychiatric disorders

Convulsions and delirium (including signs of altered consciousness, confusion, unusual behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported during Tamiflu administration, particularly in children and adolescents. In rare cases such events resulted in accidental injury. It is not known whether they are directly related to Tamiflu use. Such neuropsychiatric disturbances have also been observed in patients with influenza not taking Tamiflu.

Eyes

Visual disturbances have been observed (frequency unknown).

Heart

Cardiac arrhythmias have been observed (frequency unknown).

Gastrointestinal disorders

Gastrointestinal bleeding has been observed in rare cases following Tamiflu administration. In particular, cases of hemorrhagic colitis have been reported, which subsided when the influenza abated or when Tamiflu treatment was discontinued.

Hepatobiliary system

Very rare cases of hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness.

There have been isolated reports of pancreatitis, angioedema, laryngeal edema, bronchospasm, facial edema, eosinophilia, leukopenia and hematuria.

Skin

Rare cases of hypersensitivity reactions such as skin allergies (dermatitis, drug eruption, eczema, urticaria) and very rare cases of erythema multiforme, toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported.

Overdosage

At present there has been no experience with overdose. However, acute overdose would most likely present as nausea with or without vomiting. Single doses of up to 1000 mg Tamiflu were followed in one of six healthy subjects by nausea and in one of the six subjects by vomiting that persisted for 2 days.

Properties and effects

ATC Code: J05AH02.

Mechanism of action

Oseltamivir phosphate is a prodrug. The active metabolite (oseltamivir carboxylate) is a highly active and selective inhibitor of influenza A and B virus neuraminidases, glycoprotein enzymes found on the virion surface. Viral neuraminidase enzyme activity is essential for the release of newly formed virus particles from infected cells and thus for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits neuraminidases of both type A and B influenza. Concentrations of the active metabolite required to inhibit enzyme activity by 50% *in*

vitro are in the low nanomolar range. Oseltamivir carboxylate also inhibits influenza virus infection and growth *in vitro* and influenza virus replication and pathogenicity *in vivo*.

Clinical efficacy

In studies of naturally acquired and experimental influenza, treatment with Tamiflu did not impair normal humoral antibody response to infection. Antibody response to inactivated vaccines is not expected to be affected by treatment with Tamiflu.

Studies in naturally acquired influenza

Treatment of influenza in adults

In phase III clinical studies conducted in the northern hemisphere during the influenza epidemic of winter 1997–1998, patients began treatment with Tamiflu up to 40 hours after the reported onset of symptoms. In these studies 97% of patients were infected with influenza A and 3% with influenza B. Tamiflu treatment significantly reduced the duration of clinically relevant influenza signs and symptoms by 32 hours. Disease severity in patients with confirmed influenza taking Tamiflu was also reduced by 38% compared to placebo. Moreover, Tamiflu reduced the incidence of influenza complications requiring antibiotic therapy in otherwise healthy young adults by almost 50%. These complications include bronchitis, pneumonia, sinusitis and otitis media. These phase III trials also provided clear evidence of efficacy in the secondary endpoints for antiviral activity in the form of reductions in both the duration of virus shedding and the area under the curve (AUC) of viral titres.

Data from a treatment study in elderly patients show that Tamiflu (75 mg twice daily for 5 days) leads to a clinically relevant reduction in median disease duration. These results are similar to those achieved in treatment studies in younger adults. In a separate study, patients over 13 years of age with influenza and coexisting chronic cardiac and/or respiratory disease received the same treatment with Tamiflu or placebo. No difference in the median time to alleviation of all symptoms was observed between patients treated with Tamiflu and placebo. However, the duration of febrile illness was reduced by approximately one day on treatment with Tamiflu. The proportion of patients shedding

virus on days 2 and 4 was also greatly reduced by active treatment. The safety profile of Tamiflu showed no difference between the at-risk populations and the general adult population.

Treatment of influenza in children

A double-blind, placebo-controlled treatment study was conducted in 695 children aged 1–12 years (mean age 5.3 years) who had fever (>37.8 °C) plus either cough or coryza and were recruited at a time when influenza was known to be present in the population. In this study 67% of influenza-infected patients were infected with influenza A and 33% with influenza B.

Starting Tamiflu treatment within 48 hours of symptom onset reduced the duration of illness (defined as the time to resolution of cough and nasal congestion, defervescence and return to normal health and activity) by 35.8 hours compared to placebo. Among children taking Tamiflu the proportion of patients with acute otitis media was 40% lower than on placebo. In the subgroup of children aged up to 5 years, Tamiflu reduced the risk of otitis media by 56%. Antibiotic use in the Tamiflu group was 40% lower overall than on placebo. Children taking Tamiflu returned to normal health and activity almost 2 days earlier than those receiving placebo.

A second study was conducted in 334 asthmatic children aged 6 to 12 years of whom 53.6% were influenza-positive. In the oseltamivir-treated group the median duration of illness was not reduced significantly.

Prevention of influenza

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory confirmed influenza.

The virulence of influenza epidemics is not predictable and varies within a region and from season to season; therefore the number needed to treat (NNT) to prevent one case of influenza varies.

Post-exposure prevention

In a study in contacts (12.6% vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for 7 days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12%) in the placebo group to 2/205 (1%) in the oseltamivir group (92% reduction [95% confidence interval (CI) 6–16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95% CI 9–12) and was 16 (95% CI 15–19) in the whole population (ITT) regardless of infection status in the index case.

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*. 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 to 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 prevention (64.4% reduction [95% CI 15.8–85.0; p=0.0188]). 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). The NNT for the total pediatric population was 9 (95% CI 7–24) and 8 (95%

CI 6, upper limit not estimable) in the whole population (ITT) and in pediatric contacts of infected index cases (ITTII), respectively.

* Age-based dosing: 1–2 years: 30 mg daily, 3–5 years: 45 mg daily, 6–12 years: 60 mg daily, >12 years: 75 mg daily.

Prevention during an influenza epidemic in the community

In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8%) in the placebo group to 6/520 (1.2%) in the oseltamivir group (76% reduction [95% CI 1.6–5.7; p=0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95% CI 24–50).

In a study in elderly residents of nursing homes, of whom 80% had been vaccinated in the relevant season, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4%) in the placebo group to 1/276 (0.4%) in the oseltamivir group (92% reduction [95% CI 1.5–6.6; p=0.0015]). The NNT in this study was 25 (95% CI 23–62).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Treatment of influenza in high-risk populations

The median duration of influenza illness in elderly patients (≥65 years) and in patients with chronic cardiac and/or respiratory disease receiving oseltamivir (75 mg twice daily for 5 days) was not significantly reduced. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive elderly patients, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics, from 19% (52/268) in the placebo group to 12% (29/250) in the patient group treated with oseltamivir (p=0.0156).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17% (22/133) in the placebo group and 14% (16/118) in the oseltamivir-treated group (p=0.5976).

Prophylaxis of influenza in immunocompromised patients

A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients, including 18 children aged 1 to 12 years. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibody titre. The incidence of laboratory-confirmed clinical influenza was reduced from 7/238 (2.9%) in the placebo group to 5/237 (2.1%) in the oseltamivir group (28.3% reduction [95% CI -2.3–4.1; p=0.772]).

Analysis of RT-PCR-confirmed clinical influenza shows that the incidence of 7/238 (2.9%) in the placebo group was reduced to 2/237 (0.8%) in the oseltamivir group (71.3% reduction [95% CI -0.6–5.2; p=0.176]). In study participants who were not already shedding virus at baseline, the incidence of 7/231 (3.0%) in the placebo group was reduced to 1/232 (0.4%) in the oseltamivir group (85.8% reduction [95% CI 0.1–5.7; p=0.037]).

Reduced sensitivity of viral neuraminidase

In clinical studies conducted to date in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prevention of influenza, there has been no evidence for emergence of drug resistance associated with the use of Tamiflu in immunocompromised patients.

No resistance was observed during a 12-week seasonal prophylaxis study in immunocompromised patients (n=475, ITT analysis). Four subjects developed laboratory-confirmed influenza without evidence of resistance development. Analyses of postmarketing reports from the 2009 H1N1 pandemic showed cases of resistance development in immunocompromised patients.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In all Roche-sponsored clinical trials in naturally acquired infection, regardless of treatment dose, oseltamivir-resistant virus was found in 0.32% (4/1245) of adults and adolescents by phenotyping alone and in 0.4% (5/1245) by genotyping and phenotyping (full genotyping was not performed in all studies), as well as in 4.1% (19/464) and 5.4% (25/464), respectively, of children aged between 1 and 12

years. In all these patients, oseltamivir carboxylate-resistant virus was only transiently detectable. The patients cleared the virus normally and showed no clinical deterioration.

Several different resistance mutations in the viral neuraminidase have been defined *in vitro* in Roche studies or reported in the published literature, and tend to be specific to virus subtype. The degree of reduced sensitivity varies markedly for the different mutations, ranging from 2-fold for I222V in N1 to 30,000-fold for R292K in N2. Neuraminidase resistance mutations have not been detected in influenza B. The N1 neuraminidase mutations conferring resistance or reduced sensitivity to oseltamivir carboxylate that have been identified in clinical studies and viruses (including H5N1) of patients treated with Tamiflu are H274Y and in one case N294S, while those of N2 neuraminidase are E119V, R292K and in one case each N294S and SASG245-248del. In influenza B neuraminidase there has been one report of G402S giving a 4-fold decrease in sensitivity and one report of D198N (10-fold decrease) in an immunocompromised child.

Viruses with resistant neuraminidase genotypes have varying degrees of loss of fitness compared to wild type. Infectivity, pathogenicity and transmission studies in mice and ferrets indicate that R292K mutation in N2 is very disadvantageous, whereas E119V in N2 and D198N in B deviate only slightly from wild-type virus. The effects of H274Y mutation in N1 and N294S in N2 appear intermediate.

Naturally occurring mutations in influenza A/H1N1 virus with reduced susceptibility to oseltamivir *in vitro* have been detected in patients not treated with oseltamivir. The clinical relevance of these mutations is unknown. The extent of reduction in susceptibility to oseltamivir and the incidence of such viruses can vary according to season and region.

Pharmacokinetics

Absorption

Oseltamivir is rapidly absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is rapidly converted by esterases in the liver and/or intestinal wall to the active metabolite (oseltamivir carboxylate). At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the prodrug is less than 5% relative to the active metabolite. Plasma concentrations of the active metabolite

are proportional to dose and are essentially unaffected by coadministration with food (see *Dosage and administration*).

Distribution

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

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

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

Metabolism

Oseltamivir is almost completely converted to the active metabolite (oseltamivir carboxylate) by esterases located predominantly in the liver and intestinal wall. Neither oseltamivir nor the active metabolite is a substrate – or an inhibitor – of the major cytochrome P450 isoforms. Interactions mediated by competition for these enzymes are therefore unlikely.

Elimination

Absorbed oseltamivir is mainly (>90%) eliminated by conversion to the active metabolite (oseltamivir carboxylate). The active metabolite is not further metabolized and is eliminated in the urine. After reaching its peak concentration the active metabolite declines with a half-life of 6 to 10 hours.

The active metabolite is excreted entirely (>99%) via the kidneys. Renal clearance (18.8 l/h) exceeds the glomerular filtration rate (7.5 l/h), indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20% of an oral radiolabelled dose is eliminated in feces.

Pharmacokinetics in special patient groups

Renal impairment

Treatment of influenza

Administration of 100 mg Tamiflu twice daily for 5 days to patients with various degrees of renal impairment showed that the systemic availability of the active metabolite (oseltamivir carboxylate) is inversely proportional to the decline in renal function.

No dose adjustment is necessary in patients with creatinine clearance above 30 ml/min, whereas in patients with creatinine clearance between 10 and 30 ml/min it is recommended that the dose be reduced to 75 mg Tamiflu once daily for 5 days. Tamiflu is not recommended in patients with creatinine clearance £10 ml/min or in patients with severe renal failure undergoing regular hemodialysis or continuous peritoneal dialysis (see *Dosage and administration* and *Warnings and precautions*).

Prevention 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 Tamiflu every other day or 30 mg of suspension daily. No dosage recommendation exists for patients with end-stage renal failure undergoing chronic hemodialysis or continuous peritoneal dialysis or for patients with creatinine clearance ≤10 ml/min (see *Dosage and administration, Special dosage instructions* and *Warnings and precautions*).

Hepatic impairment

Based on *in vitro* and animal studies, significant increases in exposure to oseltamivir or its active metabolite are not expected and this has been confirmed in clinical studies in patients with mild or moderate hepatic impairment. Safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Elderly patients

The systemic availability of the active metabolite (oseltamivir carboxylate) at steady state was 25–35% higher in elderly patients (age range 65–78 years) than in young adults given comparable doses of Tamiflu. Half-lives measured in the elderly patients were

similar to those seen in young adults. Based on systemic availability and tolerability, dose adjustments are not required in elderly patients (see *Dosage and administration*).

Children ≥ 1 year

The pharmacokinetics of Tamiflu have been evaluated in single-dose pharmacokinetic studies in children aged 1 to 16 years.

Multiple-dose pharmacokinetics were studied in a small number of children aged 3–12 years enrolled in a clinical trial.

The weight-adjusted clearance rate of the active metabolite, oseltamivir carboxylate, was higher in younger children than in adults, with exposure thereby lower at the same dose.

Uniform doses of 30 and 45 mg and doses of 2 mg/kg, administered to children of the appropriate categories according to the recommendations under *Dosage and administration*, gave oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg).

Oseltamivir pharmacokinetics in children over 12 years of age are similar to those in adult patients.

No data are available on children with renal failure.

Children aged 6-12 months

Limited exposure data are available for a patient subgroup aged 6–12 months. The available data indicate that in most children aged 6–12 months, exposure following a 3 mg/kg dose is similar to that achieved in older children and adults using the approved dosage.

Treatment of influenza B infection

Overall, 15% of the influenza-infected population was infected with influenza B, proportions ranging from 1 to 33% in individual studies. The median duration of illness in influenza B-infected patients did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B-infected patients were pooled across all studies for analysis. Oseltamivir reduced the time to resolution of all symptoms by 0.7 days (95% confidence interval 0.1–1.6 days; p=0.022) and the duration of fever (≥37.8

°C), cough and coryza by one day (95% confidence interval 0.4–1.7 days; p<0.001) compared to placebo.

Preclinical data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

Carcinogenicity

Three studies of carcinogenic potential (2-year rat and mouse studies with oseltamivir and a 6-month transgenic Tg:AC mouse assay performed with the active metabolite) were negative.

Mutagenicity

Oseltamivir and its active metabolites were negative in the standard genotoxicity tests.

Teratogenicity

Teratogenicity studies have been conducted in rats and rabbits at doses up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No negative effects were observed on embryofetal development.

Reproductive toxicity

A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex. In pre-/postnatal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Fetal exposure in rats and rabbits was approximately 15–20% of that of the mother.

In lactating rats, oseltamivir and the active metabolite (oseltamivir carboxylate) are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Concentrations of 0.01 mg/day for oseltamivir and 0.3 mg/day for the active metabolite would be expected on the basis of the animal data.

Toxicity in young animals

Whereas very high oral single doses of oseltamivir phosphate had no effect in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These effects were seen at doses of 700 mg/kg and higher.

Skin toxicity

In a "maximization" test in guinea pigs it was observed that oseltamivir can provoke skin reactions. Approximately 50% of the animals treated with the unformulated active substance showed erythema after exposure. Reversible ocular irritation was observed in the rabbits.

Additional information

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Capsules:

Do not store above 25°.

Powder for oral suspension

Do not store above 25 °C. Reconstituted suspension: Shelf-life: store for 17 days in a refrigerator (2–8 °C) or 10 days not above 25 °C.

Instructions for use and handling

Preparation of the ready-to-use suspension from commercially available Tamiflu powder
It is recommended that Tamiflu suspension be reconstituted by the pharmacist prior to dispensing to the patient (see *Dosage and administration*).

1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 52 ml of drinking water by filling the measuring cup to the indicated level (measuring cup included in pack).

3. Add all 52 ml of drinking water to the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and insert the adapter into the neck of the bottle.
5. Close the bottle tightly with the cap (over the bottle adapter). This will ensure that the bottle adapter fits correctly in the bottle.

The patient information and oral dispenser should be given to the patient. It is recommended that the expiry date of the reconstituted suspension (shelf-life: 17 days in a refrigerator [2–8 °C] or 10 days when stored not above 25 °C) be written on the bottle label.

Preparation of a mixture from 30 mg, 45 mg or 75 mg capsules when the patient cannot swallow the capsules and the oral suspension is not available:

In situations where commercially manufactured Tamiflu oral suspension is temporarily unavailable, adults, adolescents and children who are unable to swallow capsules may receive appropriate doses of Tamiflu by opening capsules and pouring the contents into 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 yoghurt to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient. The mixture must be swallowed immediately after preparation since the product may otherwise lose its effect. To ensure correct dosage, please follow the instructions below for preparing such a mixture:

1. Determine the number of capsules that are needed to prepare a mixture with this procedure:

Body weight	**Number of capsules needed to obtain the recommended dose for a 5-day treatment**	**Number of capsules needed to obtain the recommended dose for prevention (for 10 days)**
Less than or equal to 15 kg	One 30 mg capsule twice daily	One 30 mg capsule once daily
More than 15 kg and up to 23 kg	One 45 mg capsule twice daily	One 45 mg capsule once daily
More than 23 kg and up to 40 kg	Two 30 mg capsules twice daily	Two 30 mg capsules once daily
More than 40 kg	One 75 mg capsule twice daily	One 75 mg capsule once daily

2. Check that you are using the correct dose according to the table above. Hold the capsule(s) over a small bowl, carefully pull the capsule(s) open and pour the powder into the bowl.

3. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product (to mask the bitter taste) to the bowl and mix well.

4. Stir the mixture and give the entire contents of the bowl to the patient. The mixture must be swallowed immediately after 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.

Repeat this procedure each time the medicine has to be taken.

Preparation of a mixture from 75 mg capsules for children ≥1 year:

If neither the oral suspension nor the 30 mg or 45 mg capsules are available, an appropriately dosed mixture can be prepared for children ≥1 year from the 75 mg capsules. Please follow these instructions:

1. Hold one 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder into the bowl.
2. Add 5 ml of water to the powder using a graduated disposable syringe so that you can see how much water you have drawn up. Stir for about two minutes.
3. Draw up into the syringe the correct amount of mixture from the bowl. Consult the table below to find the correct amount of mixture, which depends on the patient's weight. It is not necessary to draw up any of the undissolved white powder, since this is an inactive substance. Push down on the plunger of the syringe, to empty its entire contents into a second bowl. Discard any unused mixture.

Body weight	**Recommended dose**	**Amount of Tamiflu mixture for one dose**
Less than or equal to 15 kg	30 mg	2 ml
More than 15 kg and up to 23 kg	45 mg	3 ml
More than 23 kg and up to 40 kg	60 mg	4 ml

4. The recommended dose is 30 mg, 45 mg or 60 mg twice daily for 5 days for treatment and once daily for 10 days for prevention.

5. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product (to mask the bitter taste) to bowl 2 and mix well.
6. Stir the mixture and give the entire contents of the second bowl to the patient. The mixture must be swallowed immediately after preparation since the product may otherwise lose its effect. 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.

Repeat this procedure each time the medicine has to be taken.

Preparation of the different dosages from 75 mg capsules is not described in the patient information since this should be done by a professional. If this is not possible, the patient must be carefully instructed.

Compounding of a magistral formula for the treatment of infants aged 6 to 12 months

The pharmacist may compound a 10 mg/ml suspension from Tamiflu 30 mg, 45 mg or 75 mg capsules by suspending the Tamiflu powder from the capsules in water containing 0.1% w/v sodium benzoate as a preservative. The preparation of a 10 mg/ml suspension that will provide one patient with enough medication for a 5-day treatment course is described below:

1. Determine the volume of suspension to be compounded and dispensed to the patient concerned, based on the patient's body weight (see table below).
2. Use the table to determine the number of capsules, amount of water and amount of sodium benzoate (0.1% w/v, based on the volume of water) needed to prepare the total volume of suspension (10 mg/ml).

Body weight (kg)	Total volume of suspension required	Number of Tamiflu capsules required (mg oseltamivir)			Volume of water required	Amount of sodium benzoate required
		75 mg	45 mg	30 mg		
Up to 7 kg	30 ml	4 capsules (300 mg)	Use capsules of different strength*	10 capsules (300 mg)	29.5 ml	29.5 mg
7 to 12 kg	45 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	44 ml	44 mg

* There is no whole number of capsules for achieving the target concentration; please therefore use either the 30 mg or 75 mg capsules

3. Procedure for compounding the suspension (10 mg/ml) from Tamiflu capsules:
   - Add the contents of the required number of Tamiflu capsules to a bottle, together with the specified amounts of water and sodium benzoate (see table above).

- Cap the bottle and shake for two minutes.
- Attach a label to the bottle stating:
  - Name of patient
  - Name of drug
  - Dosing instructions (see table below)
  - "Shake gently before use"
  - Any other required information to be in compliance with applicable pharmacy regulations
  - Expiry date appropriate to storage conditions:
    - Stable for 3 weeks (21 days) at room temperature "Do not store above 25°C".
    - Stable for 6 weeks in a refrigerator at 2°C to 8°C.

Note: This compounding procedure results in a 10 mg/ml suspension that differs from commercially available Tamiflu powder for oral suspension. The dispenser contained in the commercially available pack of Tamiflu powder for oral suspension is **not** suitable for the dosing recommendation shown in the table below.

For the correct dosage instructions, please refer to the table below:

Dosage instructions for a 10 mg/ml suspension compounded in a pharmacy from Tamiflu capsules for infants aged 6 to 12 months (3 mg/kg body weight):

Body weight	**Treatment dose (for 5 days)**
6 kg	1.8 ml twice daily
7 kg	2.1 ml twice daily
8 kg	2.4 ml twice daily
9 kg	2.7 ml twice daily
≥10 kg	3.0 ml twice daily

The compounded suspension (10 mg/ml) must be dispensed together with a graduated oral syringe.

To mask the bitter taste, the caregiver must mix the suspension with sweet liquid food (e.g. sugar water, chocolate syrup, cherry syrup or dessert toppings such as caramel sauce). For this purpose the volume of suspension drawn up according to the dosage instructions is premixed in a bowl with an equal quantity of sweetening agent, and all of this mixture administered to the patient.

Remind the parents or caregiver that any solution remaining must be disposed of once the treatment course is completed.

Disposal instructions

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Capsules 75 mg	10
Capsules 30 mg	10
Capsules 45 mg	10
Bottle containing powder for oral suspension	1

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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