Tamiflu®

Oseltamivir

Antiviral

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Tamiflu is an antiviral agent.
ATC: J05AH02

1.2 Type of Dosage Form

Capsule, hard.
75 mg capsule consisting of a grey opaque body bearing the imprint "ROCHE" and a light yellow opaque cap bearing the imprint "75 mg". Imprints are blue.

1.3 Route of Administration

Oral.

1.4 Sterile/Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: oseltamivir phosphate.
75 mg capsules, containing 98.5 mg oseltamivir phosphate equivalent to 75 mg of oseltamivir.
Excipients: Pregelatinized starch, talc, povidone K-30, croscarmellose sodium, sodium stearyl fumarate.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Treatment of influenza in adults and children one year of age or older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see section *3.1 Pharmacodynamic Properties*).

Prevention of influenza

- Post exposure prevention in adults and children one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.
- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in adults and children one years of age or older.

Tamiflu is not a substitute for influenza vaccination
The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations.

2.2 Dosage and Administration
Tamiflu capsules and Tamiflu suspension are bioequivalent formulations, 75 mg doses can be administered as either one 75 mg capsule or by administering one 30 mg dose plus one 45 mg dose of suspension. Adults, adolescents or children (> 40 kg) who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension. The safety and efficacy of Tamiflu in children less than one year of age have not been established (see section *3.3 Nonclinical Safety*).

Standard Dosage

Treatment of influenza
Treatment should begin within the first or second day of onset of symptoms of influenza.
For adults and adolescents 13 years or older the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days.

For children one year or older, Tamiflu oral suspension is available (see section *4.2 Special Instructions for Use, Handling and Disposal)*. For children with body weight above 40 kg, capsules may be prescribed at the adult dosage of 75 mg twice daily for 5 days.

Prevention of influenza
Post exposure prevention
For adults and adolescents 13 years or older, The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

Children weighing > 40 kg, who are able to swallow capsules, may also receive prevention with a 75 mg capsule once daily for 10 days as an alternative to the recommended of Tamiflu suspension.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

2.2.1 Special Dosage Instructions
Geriatric use
No dose adjustment is required, unless there is evidence of severe renal impairment.

Patient with Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults with severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 30 (mL/min)	75 mg twice daily
> 10 to ≤ 30 (mL/min)	75 mg twice daily or 30 mg suspension twice daily
≤ 10 (mL/min)	Not recommended
Dialysis patients	Not recommended

Prevention of influenza: Dose adjustment is recommended for adults with severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 30 (mL/min)	75 mg once daily
> 10 to ≤ 30 (mL/min)	75 mg every second day or 30 mg suspension once daily
≤ 10 (mL/min)	Not recommended
Dialysis patients	Not recommended

Patient with Hepatic impairment
No dose adjustment is required either for treatment or for prevention, in patients with hepatic dysfunction.

2.3 Contraindications
Tamiflu is contraindicated in patients with known hypersensitivity to oseltamivir phosphate or to any component of the product.

2.4 Warnings and Precautions
2.4.1 General
Convulsion and delirium like neuropsychiatric events have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. The contribution of Tamiflu to those events is unknown and these 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 (see section *2.6.2 Postmarketing Experience*).

Patients, especially children and adolescents, should be closely monitored for signs of abnormal behaviour.

There is no evidence for efficacy of Tamiflu in any illness caused by agents other than influenza viruses types A and B.

For dose adjustments in patients with renal impairment see section *2.2.1 Special Dosage Instructions* (see also *3.2.5 Pharmacokinetics in Special Populations*).

Paediatric population
The safety and efficacy of oseltamivir for the treatment and prevention of influenza in children of less than one year of age have not been established.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The safety and efficacy of oseltamivir in either treatment or prevention of influenza in immunocompromised patients have not been established.

Cardiac/respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section *3.1 Pharmacodynamic Properties*).

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

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adults with severe renal insufficiency. There are no data concerning the safety and efficacy of oseltamivir in children with renal impairment (see sections *2.2 Dosage and Administration* and *3.2 Pharmacokinetic Properties*).

2.4.2 Drug Abuse and Dependence
Not applicable.

2.4.3 Ability to Drive and Use Machines
No or negligible influence on the ability to drive and use machines.

2.5 Use in Special Populations
2.5.1 Females & Males of Reproductive Potential
Fertility
Fertility studies have been conducted in rats. There was no evidence of an effect on male or female fertility at any dose of oseltamivir studied (see section *3.3.3 Impairment of Fertility*).

2.5.2 Pregnancy
Risks to the Developing Embryo/Fetus and to the Mother
In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Fetal exposure in rats and rabbits was approximately 15–20% of that of the mother.

No controlled clinical trials have been conducted on the use of oseltamivir in pregnant women; however, there is evidence from postmarketing and observational studies showing benefit of the current dosing regimen in this patient population. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section *3.2.5 Pharmacokinetics in Special Population*). A large amount of data from pregnant women exposed to oseltamivir (more than 1000 exposed outcomes during the first trimester) from postmarketing reports and observational studies in conjunction with animal studies (see section *3.3 Nonclinical Safety*) indicate no direct or indirect harmful effects with respect to pregnancy, embryonal/fetal or postnatal development. Pregnant women may receive Tamiflu, after considering the available safety and benefit information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Labor and Delivery
The safe use of oseltamivir during labour and delivery has not been established.

2.5.3 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 demonstrated that oseltamivir and the active metabolite were detected in breast milk; however the levels were low, which would result in a subtherapeutic dose to the infant. Based on this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the lactating woman, administration of oseltamivir may be considered.

2.5.4 Pediatric Use
See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.5.5 Geriatric Use
See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.5.6 Renal Impairment
See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.5.7 Hepatic Impairment
See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.6 Undesirable Effects
2.6.1 Clinical Trials
Summary of Safety Profile
The overall safety profile of Tamiflu is based on data from more than 2646 adult/adolescent and 859 pediatric patients with influenza, and on data from more than 1943 adult/adolescent and 148 pediatric 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.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials are listed according to the MedDRA system organ class. The corresponding frequency category for each adverse drug reaction (Table 1) is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000).

Treatment and Prophylaxis of Influenza in Adults and Adolescents
In adult/adolescent treatment and prophylaxis studies, ADRs that occurred the most frequently (≥ 1%) at the recommended dose (75 mg b.i.d. for 5 days for treatment and 75 mg o.d. for up to 6 weeks for prophylaxis), and whose incidence is at least 1% higher on Tamiflu compared to placebo, are shown in Table 1.

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 (Table 1), despite a longer duration of dosing in the prophylaxis studies.

Table 1 Summary of Adverse Reactions in ≥ 1% of adult and adolescent patients that received oseltamivir for treatment or prophylaxis of influenza, in clinical studies (difference to placebo ≥ 1%)

System Organ Class **Adverse Drug Reaction**	**Treatment Studies** **Oseltamivir (75 mg b.i.d.) n=2646**	**Prophylaxis** **Oseltamivir (75 mg o.d.) n=1943**	**Frequency Category[a]**
Gastrointestinal disorders			
Nausea	10%	8%	Very common
Vomiting	8%	2%	Common
Nervous system disorders			
Headache	2%	17%	Very common
General disorders			
Pain	< 1%	4%	Common

[a] Frequency category is reported only for the oseltamivir group.

Treatment and Prophylaxis of Influenza in Children ≥ 1 Year of Age
A total of 1481 children (including otherwise healthy children aged 1–12 and asthmatic children aged 6–12) participated in clinical studies of oseltamivir given for the treatment of influenza. A total of 859 children received treatment with oseltamivir suspension.

The ADR that occurred in ≥ 1% of children aged 1 to 12 years receiving oseltamivir in the clinical trials for treatment of naturally acquired influenza (n=859), 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 pediatric prophylaxis study (n=49), vomiting was the most frequent ADR (8% on oseltamivir 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 pediatric treatment studies.

Treatment and Prophylaxis of Influenza in Geriatric Patients
There were no clinically relevant differences in the safety profile of the 942 elderly subjects, 65 years of age and older who received Tamiflu or placebo, compared with the younger population (aged up to 65 years).

Laboratory Abnormalities
No text.

2.6.2 Postmarketing Experience
The following adverse events have been identified during postmarketing 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 disorder: Hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, erythema multiforme, allergy, anaphylactic/anaphylactoid reactions, face edema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Hepatobiliary disorder: hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir.

Psychiatric disorder/Nervous system disorder: Convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. 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.

Gastrointestinal disorders: Gastrointestinal bleedings were observed after the use of Tamiflu. In particular, hemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with Tamiflu was interrupted.

Laboratory Abnormalities
Elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir (see above under section *2.6.2 Postmarketing Experience*).

2.7 Overdose
Reports of overdoses with Tamiflu have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported.

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Tamiflu, described in section *2.6 Undesirable Effects.*

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction
Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section *3.2 Pharmacokinetic Properties*), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Oseltamivir phosphate is extensively converted to the active compound by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in the literature. Low protein binding of oseltamivir and the active metabolite do not suggest the probability of drug displacement interactions.

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 (see section *3.2 Pharmacokinetic Properties*). There is no mechanistic basis for an interaction with oral contraceptives.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic drugs 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. Coadministration of probenecid results in approximate 2–fold increase in exposure to the active metabolite due to a decrease in active tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when coadministering with probenecid in patients with normal renal function.

However, care should be taken when prescribing oseltamivir in subjects when taking coexcreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Coadministration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak. Coadministration with paracetamol does not alter plasma levels of oseltamivir, its active metabolite, or paracetamol. No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when coadministering oseltamivir with paracetamol, acetyl-salicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), warfarin, rimantadine, or amantadine.

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3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Oseltamivir phosphate is a prodrug of oseltamivir carboxylate (OC), a potent and selective inhibitor of influenza A and B virus neuraminidase enzymes. Viral neuraminidase is primarily important for the release of recently formed virus particles from infected cells, and the further spread of infectious virus. It has also been suggested that neuraminidase can play a role in viral entry into uninfected cells.

Oseltamivir carboxylate inhibits the neuraminidases of influenza viruses of both types A and B. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published trials.

3.1.2 Clinical/Efficacy Studies

Clinical efficacy of Tamiflu has been demonstrated in human experimental infection studies and phase III studies in naturally occurring influenza.

Treatment of influenza infection

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population which included both influenza-positive and-negative subjects (ITT) primary efficacy was reduced proportional to the number of influenza-negative individuals. In the overall treatment population influenza infection was confirmed in 67% (range 46% to 74%) of the recruited patients. Of the elderly subjects, 64% were influenza-positive and of those with chronic cardiac and/or respiratory disease 62% were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents aged 13 years and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8°C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (n=2413) enrolled into treatment studies oseltamivir 75 mg twice daily for 5 days reduced the

median duration of influenza illness by approximately one day from 5.2 days (95% CI 4.9-5.5 days) in the placebo group to 4.2 days (95% CI 4.0-4.4 days) ($p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7% (135/1063) in the placebo group to 8.6% (116/1350) in the oseltamivir-treated population (p=0.0012).

Treatment of influenza in high risk populations:
The median duration of influenza illness in elderly subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In the influenza-positive elderly, 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 oseltamivir-treated population (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 population (p=0.5976).

Treatment of influenza in children: In a study of otherwise healthy children (65% influenza-positive), aged 1 to 12 years (mean age 5.3 years), who had fever (≥ 37.8° C) plus either cough or coryza, 67% of influenza-positive patients were infected with influenza A and 33% with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95% CI 0.6-2.2 days, $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5% (53/200) in the placebo group to 16% (29/183) in the oseltamivir-treated children (p=0.013).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6% were influenza-positive. In the oseltamivir-treated group the median duration of illness was not reduced significantly. By Day 6 (the last day of treatment) FEV1 had increased by 10.8% in the oseltamivir-treated group compared to 4.7% on placebo (p=0.0148) in this population.

Treatment of influenza B infection: Overall 15% of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33% in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis.

Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95% CI 0.1-1.6 days; p=0.022) and the duration of fever (≥ 37.8° C), cough and coryza by one day (95% CI 0.4-1.7 days; $p < 0.001$), compared to placebo.

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) in order to prevent one case of influenza illness varies.

Post exposure prevention: 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 seven 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% 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 1-12 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.

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).

A study in elderly residents of nursing homes, where 80% of participants received vaccine in the season of the study, 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 of the reduction in the risk of complications.

Viral resistance

Reduced sensitivity of viral neuraminidase

Treatment of influenza

The risk of emergence of influenza viruses with reduced susceptibility or resistance to oseltamivir has been examined during Roche-sponsored clinical studies. Patients who were found to carry oseltamivir-resistant virus generally did so transiently and showed no worsening of the underlying symptoms. In children a higher proportion of resistance was obseved compared to adults and adolescents. In some pediatric patients, oseltamivir-resistant virus was detected for a prolonged period compared to patients carrying oseltamivir-sensitive virus; however these patients showed no prolongation of influenza symptoms.

Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Phenotyping of Patients with Resistance Mutations (%)
Adults and adolescents	4/1245 (0.32%)
Children (1–12 years)	19/464 (4.1%)

Prophylaxis of Influenza

There has been no evidence for emergence of drug resistance associated with the use of Tamiflu 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.

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

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to the active metabolite. Plasma concentrations of the active metabolite are measurable within 30 minutes, reach near maximal levels in 2 to 3 hours post dose, and substantially exceed (> 20-fold) those of the prodrug. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are unaffected by coadministration with food (see section *2.2 Dosage and Administration*).

3.2.2 Distribution

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

The active moiety 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 seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea following oral administration of doses of oseltamivir phosphate.

The binding of the active metabolite to human plasma protein is negligible (approximately 3%). The binding of the prodrug to human plasma protein is 42%. These levels are insufficient to cause significant drug interactions.

3.2.3 Metabolism
Oseltamivir phosphate is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite are substrates for or inhibitors of cytochrome P450 isoforms (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

3.2.4 Elimination
Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to the active metabolite. The active metabolite is not further metabolized and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline with a half-life of 6 to 10 hours in most subjects.

The active drug 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 in addition to glomerular filtration occurs. Less than 20% of an oral radiolabelled dose is eliminated in faeces.

3.2.5 Pharmacokinetics in Special Populations
Pediatric Population: ***Children ≥ 1 year of age***
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 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 section *2.2 Dosage and Administration* yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

Geriatric Population
Exposure to the active metabolite at steady-state was 25–35% higher in elderly (age range 65–78) compared to young adults who were given comparable doses of Tamiflu. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients unless there is evidence of severe renal impairment (creatinine clearance below 30 mL/min) for either the treatment or prophylaxis of influenza (see section *2.2.1 Special Dosage Instructions*).

Renal impairment
Administration of 100 mg of Tamiflu twice daily for five days to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to declining renal function. For dosage information, see section *2.2.1 Special Dosage Instructions*.

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 (see section *2.2.1 Special Dosage Instructions*). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Pregnant women
A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in section *2.2 Dosage and Administration* results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC95 values) and at a

therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza.

3.3 Nonclinical Safety

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumors that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

3.3.1 Carcinogenicity

Three studies for carcinogenic potential (two-year rat and mouse studies with oseltamivir, and a six month transgenic Tg:AC mouse assay performed with the active metabolite) were negative.

3.3.2 Genotoxicity

Oseltamivir and the active metabolite were negative in the standard battery of genotoxicity assays.

3.3.3 Impairment of Fertility

A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex.

3.3.4 Reproductive Toxicity

Teratology studies have been conducted in rats and rabbits at doses up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on embryo-fetal development were observed. 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 the rats and rabbits was approximately 15 to 20% of that of the mother.

3.3.5 Other

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitization to oseltamivir was observed in a “maximization” test in guinea pigs. Approximately 50% of the animals treated with the unformulated active ingredient showed erythema after challenging the induced animals. Reversible irritancy of the rabbits’ eyes was detected.

In a two-week study in unweaned rats a single-dose of 1000 mg/kg oseltamivir phosphate to 7-day old pups resulted in deaths associated with unusually high exposure to the prodrug. These effects were seen at doses of 657 mg/kg and higher. However, at 2000 mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occurred at 500 mg/kg/day administered from 7 to 21 days post partum. In a single-dose investigatory study of this observation in 7-, 14- and 24-day old rats, a dose of 1000 mg/kg resulted in brain exposure to the prodrug that suggested, respectively, 1500-, 650-, and 2-fold the exposure found in the brain of adult (42-day old) rats.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Do not store above 25°C (under controlled air conditioning).

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Special Instructions for Use, Handling and Disposal

Emergency Home Preparation of an Oral Suspension from Tamiflu Capsules

If the commercially manufactured Tamiflu oral suspension (6 mg/mL) is not available and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home if directed by the healthcare provider.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product (e.g. chocolate syrup, cherry syrup, sugar water, dessert toppings). The mixture should be stirred and given entirely to the patient.

The mixture must be swallowed immediately after its preparation.

When only 75 mg capsules are available, and doses of 30 mg or 45 mg are needed, the home preparation of the Tamiflu suspension involves additional steps. Instructions for home preparation and syringes of appropriate volume and grading can be requested from the health care provider, such as the pharmacist.

Refer to Section *2.2 Dosage and Administration* for the proper dosing instructions.

Disposal of Unused/Expired Medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Any unused medicinal product or waste materials should be disposed of in accordance with local requirements.

Incompatibilities

Not applicable.

PACKS

Capsules 75 mg

Box, 1 blister @ 10 capsules Reg.No.: DKI2157510401A1

Medicine: keep out of reach and sight of children
Obat: jauhkan dari jangkauan dan pandangan anak-anak
On medical prescriptions only
Harus dengan resep dokter

Made by:

Delpharm Milano S.r.l.
Segrate, Italy

for:

F. Hoffmann-La Roche Ltd.
Basel, Switzerland

Imported by:
PT Menarini Indria Laboratories
Bekasi, Indonesia

Distributed by:
PT Roche Indonesia
Jakarta, Indonesia

INSTRUCTIONS FOR USE
TAMIFLU®
(oseltamivir phosphate)
capsules, for oral use

How do I mix the contents of TAMIFLU capsules with sweetened liquids, if directed by my healthcare provider or pharmacist?
You will need:

- the prescribed dose of TAMIFLU capsules
- a small bowl
- sweetened liquid, such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water)

Step 1. Open the contents of the prescribed dose of TAMIFLU capsules into a small bowl.
Step 2. Add a small amount of the sweetened liquid to the capsule contents.
Step 3. Stir the mixture and give the entire dose of TAMIFLU.

(This PI draft has been reviewed and approved for submission by Renata and Deny on 21-Jun-2023)