

SUMMARY OF PRODUCT CHARACTERISTICS

Tamiflu® ▼

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 75 mg capsule, hard.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 98.5 mg oseltamivir phosphate, corresponding to 75 mg of oseltamivir. For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

The hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “75 mg”. Imprints are blue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 5.1).

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 year 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.

4.2 Posology and method of 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 5.3).

Treatment of influenza

Treatment should be initiated as soon as possible within the first two days 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. 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 dose 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.

Special populations

Hepatic impairment

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

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 once 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

Elderly

No dose adjustment is required, unless there is evidence of severe renal impairment.

4.3 Contraindications

Hypersensitivity to oseltamivir phosphate or to any of the excipients.

4.4 Special warnings and special precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses.

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 (see Section 5.3).

The safety and efficacy of oseltamivir for the prevention of influenza in children 12 years or younger have not been established.

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.

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

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 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation 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 4.2 and 5.2).

4.5 Interaction 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 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir. Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway suggesting that oseltamivir interaction with this pathway is weak.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

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

4.6 Pregnancy and lactation

There are no adequate data from the use of oseltamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see Section 5.3). Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk. Oseltamivir should be used during lactation only if the potential benefit for the mother justifies the potential risk for the nursing infant.

4.7 Effects on ability to drive and use machines

Tamiflu has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Treatment of influenza in adults and adolescents: A total of 2107 patients participated in phase III studies in the treatment of influenza. The most frequently reported undesirable effects were nausea, vomiting and abdominal pain. The majority of these events were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. All events that were reported commonly, (i.e. at an incidence of at least 1 %, irrespective of causality) in subjects receiving oseltamivir 75 mg twice daily, are included in the table below.

Treatment of influenza in elderly: In general, the safety profile in the elderly patients was similar to adults aged up to 65 years: the incidence of nausea was lower in oseltamivir treated elderly persons (6.7 %) than in those taking placebo (7.8 %) whereas the incidence of vomiting was higher in those who received oseltamivir (4.7 %) than among placebo recipients (3.1 %).

The adverse event profile in adolescents and in the patients with chronic cardiac and/or respiratory disease was qualitatively similar to that of healthy young adults.

Prevention of influenza In prevention studies, where the dosage of oseltamivir was 75 mg once daily for up to 6 weeks,, adverse events reported more commonly in subjects receiving oseltamivir compared to subjects receiving placebo (in addition to the events listed in the table below) were: Aches and pains, rhinorrhoea, dyspepsia and upper respiratory tract infection. There were no clinically relevant differences in the safety profile of the elderly subjects, who received oseltamivir or placebo, compared with the younger population.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

System Organ Class	Adverse Event	Treatment		Prevention	
		Placebo (N=1050)	Oseltamivir 75 mg twice daily (N=1057)	Placebo (N=1434)	Oseltamivir 75 mg once daily (N=1480)
Gastrointestinal Disorders	Vomiting ²	3.0 %	8.0 %	1.0 %	2.1 %
	Nausea ^{1,2}	5.7 %	7.9 %	3.9 %	7.0 %
	Diarrhoea	8.0 %	5.5 %	2.6 %	3.2 %
	Abdominal Pain	2.0 %	2.2 %	1.6 %	2.0 %

Infections and Infestations	Bronchitis	5.0 %	3.7 %	1.2 %	0.7 %
	Bronchitis acute	1.0 %	1.0 %	-	-
General Disorders	Dizziness	3.0 %	1.9 %	1.5 %	1.6 %
	Fatigue	0.7 %	0.8 %	7.5 %	7.9 %
Neurological Disorders	Headache	1.5 %	1.6 %	17.5 %	20.1 %
	Insomnia	1.0 %	1.0 %	1.0 %	1.2 %

¹ Subjects who experienced nausea alone; excludes subjects who experienced nausea in association with vomiting.

² The difference between the placebo and oseltamivir groups was statistically significant.

Treatment of influenza in children: A total of 1032 children aged 1 to 12 years (including 695 otherwise healthy children aged 1 to 12 years and 334 asthmatic children aged 6 to 12 years) participated in phase III studies of oseltamivir given for the treatment of influenza. A total of 515 children received treatment with oseltamivir suspension. Adverse events occurring in greater than 1 % of children receiving oseltamivir are listed in the table below. The most frequently reported adverse event was vomiting. Other events reported more frequently by oseltamivir treated children included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once, resolved despite continued dosing and did not cause discontinuation of treatment in the vast majority of cases.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Children

[Adverse Events Occurring On Treatment in >1% of Paediatric Patients]

Adverse Event	Treatment ^a		Treatment ^b	Prevention ^b
	Placebo N=517	Oseltamivir 2 mg/kg bid N=515	Oseltamivir 30 to 75 mg ^c N=158	Oseltamivir 30 to 75 mg ^c N=99
Vomiting	48 (9.3%)	77 (15.0%)	31 (19.6%)	10 (10.1%)
Diarrhoea	55 (10.6%)	49 (9.5%)	5 (3.2%)	1 (1.0%)
Otitis media	58 (11.2%)	45 (8.7%)	2 (1.3%)	2 (2.0%)
Abdominal pain	20 (3.9%)	24 (4.7%)	3 (1.9%)	3 (3.0%)
Asthma (including aggravated)	19 (3.7%)	18 (3.5%)	-	1 (1.0%)
Nausea	22 (4.3%)	17 (3.3%)	10 (6.3%)	4 (4.0%)
Epistaxis	13 (2.5%)	16 (3.1%)	2 (1.3%)	1 (1.0%)
Pneumonia	17 (3.3%)	10 (1.9%)	-	-
Ear disorder	6 (1.2%)	9 (1.7%)	-	-
Sinusitis	13 (2.5%)	9 (1.7%)	-	-
Bronchitis	11 (2.1%)	8 (1.6%)	3 (1.9%)	-
Conjunctivitis	2 (0.4%)	5 (1.0%)	-	-
Dermatitis	10 (1.9%)	5 (1.0%)	1 (0.6%)	-
Lymphadenopathy	8 (1.5%)	5 (1.0%)	1 (0.6%)	-
Tympanic membrane disorder	6 (1.2%)	5 (1.0%)	-	-

^a Pooled data from Phase III trials of Tamiflu treatment of naturally acquired influenza.

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

^c 30 to 75 mg = age-based dosing (see Section 5.1).

Adverse events included are: all events reported in the treatment studies with a frequency $\geq 1\%$ in the oseltamivir 2 mg/kg bid group.

In general, the adverse event profile in the children with asthma was qualitatively similar to that of otherwise healthy children.

Prevention of influenza in children

Paediatric patients aged 1 to 12 years participated in a post exposure prevention study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events, particularly vomiting were the most frequently reported. The adverse events were consistent with those previously observed (see table above).

Observed during clinical practice: The following adverse reactions have been reported during postmarketing use of oseltamivir: dermatitis, rash, eczema, urticaria, angioneurotic oedema, hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, as well as very rare reports of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Additionally, there are very rare reports of hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness.

4.9 Overdose

There is no experience with overdose. However, the anticipated manifestations of acute overdose would be nausea, with or without accompanying vomiting, and dizziness. Patients should discontinue the treatment in the event of overdose. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral
ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the viral surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. 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.

Reduced sensitivity of viral neuraminidase:

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.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In all clinical studies in naturally acquired infection 0.32% (4/1245) of adults and adolescents and 4.1% (19/464, range 0-19% in individual studies) of children aged 1-12 were found to transiently carry influenza virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. The emergence of resistance may be higher in young children and in children who had immunosuppression or who were under-exposed to oseltamivir. Patients carrying resistant virus

cleared it normally and showed no clinical deterioration. Rare cases of oseltamivir-resistant virus strains in patients who were not confirmed to have been exposed to oseltamivir have been reported. All resistant genotypes are disadvantaged compared to the corresponding wild-type isolate and are likely to be less contagious in man. Thus far, there is no evidence for resistance in influenza B *in vitro* or in clinical trials.

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 $\geq 37.8^{\circ}\text{C}$, 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 ($\geq 37.8^{\circ}\text{C}$) 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 ($\geq 37.8^\circ\text{C}$), 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 (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 paediatric population was 9 (95 % CI 7-24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTH) 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.

5.2 Pharmacokinetic properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution

The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular oseltamivir carboxylate distributes to all sites of influenza virus spread.

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

Metabolism

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In-vitro* studies demonstrated, that neither oseltamivir, nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination

Absorbed oseltamivir is primarily (>90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds 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 faeces.

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see Section.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see Section 4.2).

Elderly

Exposure to the active metabolite at steady state was 25 to 35 % higher in elderly (age 65 to 78 years) compared to adults less than 65 years of age, given comparable doses of oseltamivir. 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) (see Section 4.2).

Children

The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged one to 16 years. Multiple dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the prodrug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults, receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

5.3 Preclinical safety data

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 tumours 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.

Teratology studies have been conducted in rats and rabbits at doses of up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal 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- / post-natal 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. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk, but 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 sensitisation to oseltamivir was observed in a "maximisation" 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 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 pro-drug. 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 pro-drug that suggested, respectively, 1500-, 650-, and 2-fold the exposure found in the brain of adult (42-day old) rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch (derived from maize starch), talc, povidone, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172) and titanium dioxide (E171). The printing ink contains shellac, titanium dioxide (E171) and FD and C Blue 2 (indigo carmine, E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

One box contains 10 capsules in a triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2002

10. DATE OF REVISION OF THE TEXT

22 February 2006

LEGAL STATUS

POM