# TAMIFLU®

Oseltamivir

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**Antiviral**

## PHARMACEUTICAL FORM

**Powder for oral suspension.**

The powder is a granulate or clumped granulate with a white to light yellow colour

## QUALITATIVE AND QUANTITATIVE COMPOSITION

*Active ingredient:* osetalmivir phosphate.

Powder for oral suspension, containing 39.4 mg oseltamivir phosphate per 1 g filling mixture.

The reconstituted suspension contains 12 mg oseltamivir per ml.

## PHARMACOLOGICAL PROPERTIES & EFFECTS

### Pharmacodynamic Properties

Oseltamivir is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuramidase enzymes, which are glycoproteins found on the virion surface. Viral neuramides enzyme activity is essential 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 neuramides 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.

Neuramides 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 median of 8.5 nM, have been observed in published trials.

**Reduced sensitivity of viral neuramides :** In clinical studies in naturally acquired infection, 0.34 % (4/1177) of adults and adolescents and 4.5 % (17/374) of children aged one to 12 years were found to transiently carry influenza A virus with decreased neuramides susceptibility to oseltamivir carboxylate. Neuramides from influenza B with reduced sensitivity has not been observed either in cell culture or in clinical studies.

Cross resistance between zanamivir-resistant influenza mutants and oseltamivir-resistan influenza mutants has been observed in vitro. Insufficient information is available to fully characterise the risk of emergence of oseltamivir resistance and cross-resistance in clinical use.

**Treatment of infuenza 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 infuenza 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 patient 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 treatment) FEV 1 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 (≥ 37,8oC), cough and coryza by one day (95 % CI 0.4 – 1.7 days; p < 0.0001), compared to placebo.

**Prevention of influenza**
The efficacy of oseltamivir in preventing naturally occuring influenza illness has been demonstrated in a post-exposure prophylaxis study in households and two seasonal prophylaxis 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 occuring 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 < 0.0001). The 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.

*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 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 study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/274 (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.

**Pharmacokinetic properties**

***Absorption***
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of aseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic asterases 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 concentration 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 esterase located predominantly in the liver. In-vitro studies demonstrated, that neither oseltamivir, nor the active metabolite is a substance 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 1/h) exceeds glomerular filtration rate (7.5 1/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 Posology and method of administration.

***Hepatic impairment***
In vitro studies have conclude 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 *Posology and method of administration*).

***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/mn) (See *Posology and method of administration*).

***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.

***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 carcinogenecty 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 (500mg/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 2000mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occured 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.

**CLINICAL PARTICULAR**

**Therapeutic Indication**

***Treatment of influenza*** in adults and children one year 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 predominat infection was influenza A (see *Pharmacodynamic properties*).

***Prevention of influenza***

• Post exposure prevention in adults and adolescents 13 years of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

• The appropriote use of Tamiflu for prevention of influenza should be determined on a case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of mismatch between the circulating and vaccine virus starins, and a pandemic situation) seasonal prevention could be considered in adults and adolescents 13 years of age or older.

Tamiflu is not a subsitute 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.

**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 able to swallow capsules may receive appropriate doses of Tamiflu capsules.

***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 of one to 12 years of age : The recommended dose of Tamiflu oral suspension is indicated in the table below. The following weight adjusted dosing regimens are recommended for children one year or older :

| 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 |

For dosing an oral dispenser with 30 mg, 45 mg, and 60 mg graduations is provided in the box. For accurate dosing the oral dispenser supplied should be used exclusively.

The safety and efficacy of Tamiflu in children less than one year of age have not been established (Please see also *Preclinical Safety Data*).

***Prevention of influenza***
Post exposure prevention in 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 at least 7 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

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.

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

**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 recomended for adults with severe renal impairment.

Recomended doses are detailed in the table below.

| Creatinine clearance | Recommended dose for treatment |
|---|---|
| > 30 (ml/min) | 75 mg twicw 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 treatment |
|---|---|
| > 30 (ml/min) | 75 mg twicw 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 requiered, unless there is evidence of severe renal impairment.

**Contraindications**
Hypersensitivity to oseltamivir phosphate or to any of the excipients.

## 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 treatment of children off less than one year of age have not been established (Please see also *Preclinical Safety Data*).
The safety and efficacy of aseltamivir for the prevention of influenza in children 12 years or younger have not been established.

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

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

Efficacy of aseltamivir in either in treatment of subject with chronic cardiac disease and/or espiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see *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 *Posology and method of administration and Pharmacokinetic properties*)

This medicinal product contains 26 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

## Interactions with other Medical 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 *Pharmacokinetic properties*), 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 aseltamivir.
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).

## 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 *Preclinical Safety Data*). 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.

## Effects on ability to drive and use machines

Tamiflu has known influence on the ability to drive and use machines.

## Undesirable Effects

Treatment of influenza in adults an 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 single occasion on either the the first or second treatment day and resolved spontaneously within 1-2 days. All event 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 qualitativeely similar to that of healthy yaoung 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 respiratory tract infection. There were no clinically relevant difference in the safety profile of the elderly subjects, who received oseltamivir pr placebo, compared with the younger population.

**Most Frequent in Studies in Naturally Acquired Influenza**

| System Organ Class | Adverse Events | Treatment | | Prevention | |
|---|---|---|---|---|---|
| | | Placebo (N=1050) | Oseltamivir 75 mg twice daily (N=1057) | Placebo | Oseltamivir 75 mg twice daily (N=1480) |
| Gastrointestinal Disorder | 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 | Dizzines | 3.0 % | 1.9 % | 1.5 % | 1.6 % |
| | Fatigue | 0.7 % | 0.8 % | 7.5 % | 7.9 % |
| Neurological Disorder | 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 occuring 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, apistaxis, ear disorder and conjunctivitis. These events generally occured once, resolved despite continued dosing and did not cause discontinuation of treatment in the vast majority of cases.

**Adverse Events occurring in grater than 1 % of children enrolled in Phase III studies of oseltamivir tretment of naturally acquired influenza.**

| System Organ Class | Adverse Event | Treatment | |
|---|---|---|---|
| | | Placebo (N=517) | Oseltamivir 2mg/kg (N=515) |
| Gastrointestinal Disorders | Vomiting | 9.3 % | 15.0 % |
| | Diarrhea | 10.6 % | 9.5 % |
| | Abdominal pain | 3.9 % | 4.7 % |
| | Nausea | 4.3 % | 3.3 % |
| Infections and Infestation | Otitis Media | 11.2 % | 8.7 % |
| | Pneumaonia | 3.3 % | 1.9 % |
| | Sinusitis | 2.5 % | 1.7 % |
| | Bronchitis | 2.1 % | 1.6 % |
| Respiratory Disorder | Asthma (incl. Aggravated) | 3.7 % | 3.5 % |
| | Epistaxis | 2.5 % | 3.1 % |
| Disorder of the Ear and Labyrinth | Ear disorder | 1.2 % | 1.7 % |
| | Tympanic membrane disorder | 1.2 % | 1.0 % |
| Skin and Subcutaneous Disorder | Dermatitis | 1.9 % | 1.0 % |
| Disorders of the Blood and Lymphatic System | Lymphanodenophaty | 1.5 % | 1.0 % |
| Vision disorder | Conjunctivitis | 0.4 % | 1.0 % |

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

*Observed during clinical practice*: The following adverse reactions have been reported during poatmarketing use of oseltamivir: dermatitis, rash, eczema, urticaria, hypersensitivity reactions,

including anaphylactic/anaphylactoid reactions, as well as very rare reports of severe skin reactions, including Steven-Jhonson Syndrome and erythema multiforme. Additionally, there are very rare reports of hepatic function disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness.

## 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.

## Storage condition

Do not store above 25$^{o}$C

After reconstitution, store the suspension at 2$^{o}$C-8$^{o}$C (in refrigerator)
Shelf-life 2 years

## Nature and contents of container

Carton containing a 100 ml amber glass bottle (with child-resistant plastic screw cap) with 30 g of powder for oral suspension, a plastic adapter, a plastic oral dispenser and a plastic measuring cup). After reconstitution with 52 ml of water, the usable volume of oral suspension allows for the retrieval of total of doses of 75 mg oseltamivir.

## Instructions for use and handling and disposal

It is recommended that Tamiflu oral suspension should be reconstituted by the pharmacist prior to its dispensing to the patient.

## Preparation of Oral Suspension

1. Tap the closed bottle gently several times to loosen the powder
2. Measure 52 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box)
3. Add all 52 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push the bottle adapter into the neck of the bottle.
5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.

Tamiflu powder for suspension will appear as an opaque and white to light yellow suspension after reconstitution.

## PACKS

Capsules 75 mg

Box, I botol @ 30 g Reg. No :

Medicine : keep out of reach of children

On medical prescriptions only

Harus dengan resep dokter

Made in Switzerland by

F.Hoffman-La Roche Ltd, Basel
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