℞ **FLUVIR**
Oseltamivir Phosphate Capsules 75 mg
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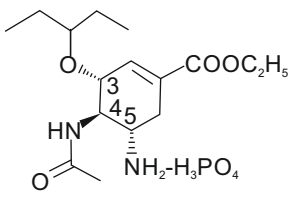
QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains Oseltamivir Phosphate equivalent to Oseltamivir 75 mg

PHARMACEUTICAL FORM
FLUVIR (Oseltamivir Capsules 75 mg)
Red / White, Size '2' hard gelatin capsules imprinted 'H' on cap and '5' on body filled with white to off white granular powder.

DRUG DESCRIPTION
Oseltamivir phosphate is a white crystalline solid with the chemical name (3R, 4R, 5S)-4-acetylamino-5-amino 3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base).
The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.
The structural formula is as follows:



CLINICAL PARTICULARS
Therapeutic indications
Treatment of influenza
In patients one year of age and 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 Pharmacodynamic properties).

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

- Post-exposure prevention in individuals 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 Oseltamivir Phosphate 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 individuals one year of age or older.

Oseltamivir Phosphate 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. Decisions regarding the use of antivirals for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses and the impact of the disease in different geographical areas and patient populations.

Posology and method of administration

- 75 mg doses can be administered as one 75 mg capsule.
- dosage of 30mg and 45mg cannot be administered using the 75mg capsules

Treatment of influenza
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
For adolescents (13 to 17 years of age) and adults: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days.
For infants older than 1 year of age and for children 2 to 12 years of age: The recommended dose of Oseltamivir Phosphate is indicated in the table below.
The following weight-adjusted dosing regimens are recommended

Body Weight	Recommended dose for 5 days
‒	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 children 6 to 12 months of age: Depending on the pathogenicity of the circulating influenza virus strain, children between 6 and 12 months of age can be treated with Oseltamivir Phosphate during a pandemic influenza outbreak, although the available data are limited. Pharmacokinetic data indicate that a dosage of 3 mg/kg twice daily in children 6 to 12 months of age provides plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in children age one or older and adults (see section Pharmacokinetic properties).
The recommended dose for treatment of children 6 to 12 months of age is 3 mg per kg body weight twice daily for 5 days for treatment.

Prevention of influenza
Post-exposure prevention
For adolescents (13 to 17 years of age) and adults: 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.

For infants older than 1 year of age and for children 2 to 12 years of age: The recommended post-exposure prevention dose of Oseltamivir Phosphate is:

Body Weight	Recommended dose for 10 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

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 6 weeks.

Special populations
Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.
Renal impairment

Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to ≤ 60 (ml/min)	30 mg twice daily
> 10 to ≤ 30 (ml/min)	30 mg once daily
≤ 10 (ml/min)	Not recommended
Heamodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg single dose

*Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prophylaxis
> 60 (ml/min)	75 mg once daily
> 30 to ≤ 60 (ml/min)	30 mg once daily
> 10 to ≤ 30 (ml/min)	30mg every second day
≤ 10 (ml/min)	Not recommended
haemodialysis patients	30 mg after every second Heamodialysis session
Peritoneal dialysis patients*	30 mg once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Geriatric Use
No dose adjustment is required, unless there is evidence of severe renal impairment.
Children
There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation.

Contraindications
Oseltamivir Phosphate is contraindicated in patients with known hypersensitivity to Oseltamivir phosphate or to any component of the product.

Special warnings and 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.

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 Pharmacodynamic properties).

Psychiatric disorders and nervous system disorders
Frequency not known: influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.
In patients with influenza who were receiving Oseltamivir Phosphate, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in accidental injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of Oseltamivir Phosphate to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Oseltamivir Phosphate. Three separate large epidemiological studies confirmed that influenza infected patients receiving Oseltamivir Phosphate are at no higher risk to develop neuropsychiatric events in comparison to influenza infected patients not receiving antivirals.

Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Oseltamivir Phosphate is not a substitute for influenza vaccination. Use of Oseltamivir Phosphate must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Oseltamivir Phosphate is administered. Oseltamivir Phosphate 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 is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation. (see sections Posology and method of administration and Pharmacokinetic properties).

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.

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 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 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), warfarin, rimantadine or amantadine.

Pregnancy and lactation
Risks to the Developing Embryo/Fetus and to the Mother
In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Foetal 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 post-marketing 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. A large amount of data from pregnant women exposed to Oseltamivir (more than 1000 exposed outcomes during the first trimester) from post-marketing reports and observational studies in conjunction with animal studies indicate no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section Nonclinical safety data). Pregnant women may receive Oseltamivir Phosphate, after considering the available safety and benefit information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

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, where there are clear potential benefits to lactating mothers.
Labor and Delivery
The safe use of oseltamivir during labor and delivery has not been established.

Effects on ability to drive and use machines
No or negligible influence on the ability to drive and use machines.

Undesirable effects
Summary of Safety Profile
The overall safety profile of Oseltamivir Phosphate is based on data from 2646 adult/adolescent and 859 paediatric patients with influenza, and on data from 1943 adult/adolescent and 148 paediatric patients receiving Oseltamivir Phosphate for the prophylaxis of influenza in clinical trials.

In adults/adolescent, the most commonly reported adverse drug reactions (ADRs) were vomiting, nausea and headache in the treatment studies. The majority of these ADRs were reported on a single occasion 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 Oseltamivir Phosphate.
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 listed in the tables below is based on the following convention: Very Common (≥ *1/10*), Common (≥ *1/100* to < *1/10*), Uncommon (≥ *1/1,000* to < *1/100*), Rare (≥ *1/10,000* to < *1/1,000*), Very rare (< *1/10,000*).

Treatment and prevention 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 Oseltamivir Phosphate compared to placebo are presented in the table below.

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 Oseltamivir Phosphate for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.

Summary of Adverse Drug 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 (SOC) Adverse Drug Reaction	Treatment studies Oseltamivir 75 mg bid (n =2646)	Prophylaxis Oseltamivir 75 mg od (n = 1943)	Frequency Category[a]
Nervous system disorders Headache	2 %	17 %	very common
Gastrointestinal disorders Nausea Vomiting	10 % 8 %	8 % 2 %	very common common
General disorders Pain	< 1 %	4 %	common

[a]Frequency category is reported only for the oseltamivir group.
Treatment and prevention 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 Oseltamivir Phosphate compared to placebo (n = 622), is vomiting (16% on oseltamivir vs. 8% on placebo). Amongst the 148 children who received the recommended dose of Oseltamivir Phosphate once daily in a post-exposure prophylaxis study in households (n = 99), and in a separate 6–week paediatric prophylaxis study (n = 49), vomiting was the most frequent ADR (8% on oseltamivir vs. 2% in the no prophylaxis group). Oseltamivir Phosphate was well tolerated in these studies and the adverse events noted were consistent with those previously observed in paediatric treatment studies.

Further post marketing surveillance data on selected serious adverse drug reactions:
Immune system disorder
Frequency not known: hypersensitivity reactions, including anaphylactic/anaphylactoid reactions.

Eye disorders
Frequency not known: visual disturbance.

Cardiac disorders
Frequency not known: cardiac arrhythmia.

Gastrointestinal disorders
Frequency not known: gastrointestinal bleedings and haemorrhagic colitis.

Hepatobiliary disorders
Frequency not known: Hepatobiliary disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Skin and subcutaneous tissue disorders
Frequency not known: severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and angioneurotic oedema.

Psychiatric disorder/Nervous system disorder
Frequency not known: Hallucinations and convulsions

Additional information on special populations:
Treatment and Prophylaxis of Influenza in Geriatric patients
There were no clinically relevant differences in the safety profile of the 942 subjects, 65 years of age and older, who received Oseltamivir Phosphate or placebo, compared with the younger population (aged up to 65 years).
The adverse event profile in adolescents and patients with chronic cardiac and/or respiratory disease was qualitatively similar to those of healthy young adults.

Overdose
Reports of overdoses with Oseltamivir Phosphate have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported.

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

PHARMACOLOGICAL PROPERTIES

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 virion surface. Viral neuraminidase enzyme activity is primarily important for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body. It has also been suggested that neuraminidase can play a role in viral entry into uninfected cells.

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.

Antiviral activity

Treatment of Influenza

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank 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 some paediatric 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

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

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza

There has been no evidence for emergence of drug resistance associated with the use of Oseltamivir Phosphate 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 rate of emergence of resistance may be higher in the youngest age groups, and in immunosupressed patients. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific (including those found in H5N1 variants).

Clinical and surveillance data: Naturally occurring mutations in influenza A/H1N1 virus associated with reduced susceptibility to oseltamivir *in vitro* have been detected in patients who, based on the reported information, have not been exposed to oseltamivir.

Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivirresistant laboratory strains of influenza viruses have been found to contain mutations in N1and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

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 influenzapositive. 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 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 ºC, 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 ≤ 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) FEV, 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: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for 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 ≤ 0.0001]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; p = 0.0042]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; p = 0.0114]).

According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; p = 0.0188]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total 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 (ITTI), 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.

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 Posology and method of administration).

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 Posology and method of administration).

Children ≥ 1 year of age

The pharmacokinetics of oseltamivir 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 enrolled in a clinical efficacy study. Younger children cleared both the pro-drug 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.

Geriatric Population

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 Posology and method of administration).

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the Oseltamivir Phosphate dosage regimen described in Section Posology and method of 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.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 Oseltamivir Phosphate in its adopted therapeutic indications.

Reproductive Toxicity

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- and 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 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 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.

Whereas very high oral single doses of oseltamivir phosphate had no effect in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These effects were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse effects were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

PHARMACEUTICAL PARTICULARS

Description: FLUVIR (Oseltamivir Capsules 75 mg)
Red / White, Size '2' hard gelatin capsules imprinted 'H' on cap and '5' on body filled with white to off white granular powder.

Container closure system: Clear Triplex-Plain Peelable Blister Pack

Pack style: 10 capsules/blister, 10 blisters per pack

Storage Condition: Store below 30°C and protect from moisture.

Special instructions for use, handling and disposal
Capsules: No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

List of excipients:
Capsule 75 mg
Capsule content: Pregelatinized Starch, Croscarmellose sodium, Povidone, Dehydrated
Alcohol, Purified water, Talc, Sodium Stearyl Fumarate, Empty hard gelatin capsule shells size'2' light yellow opaque Cap and grey opaque Body and imprinted with 'H' in blue on Cap and '5' in blue on Body.

Capsule shell: Titanium dioxide E171, Iron oxide black E172, Iron oxide yellow E172, Iron oxide red E172, Gelatin and Purified water.

Product Owner:
HETERO LABS LIMITED
7-2-A 2, Hetero Corporate, Industrial Estates,
Sanath nagar, Hyderabad - 500 018, INDIA.

2xxxxxx

Manufactured by:
HETERO LABS LIMITED
Unit-III, 22-110, IDA, Jeedimetla,
Hyderabad - 500 055, INDIA.