Flumivir®

Oseltamivir

FORMS AND PRESENTATION

Flumivir®: Capsules: Box of 10.

COMPOSITION:

Flumivir®: Each capsule contains Oseltamivir Phosphate eq. to Oseltamivir: 75 mg.

Excipients: Starch, croscarmellose sodium, povidone, talc, sodium stearyl fumarate, gelatin, sunset yellow, titanuim dioxide, allura red, brilliant blue.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AH02.

Oseltamivir phosphate is a pro-drug of the active metabolite. 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 important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for 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 phosphate 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 phosphate was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for Oseltamivir phosphate 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.

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 Oseltamivir phosphate 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- 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 phosphate 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 phosphate and the active metabolite are excreted in the milk. It is not known whether Oseltamivir phosphate or the active metabolite is 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 phosphate 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 given 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 singledose 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.

Pharmacokinetic Properties

Absorption: Oseltamivir phosphate 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 phosphate is extensively converted to Oseltamivir carboxylate by esterases located predominantly in the liver. In vitro studies demonstrated that neither Oseltamivir phosphate 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 phosphate 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 hrs 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.

Hepatic impairment: In vitro studies have concluded that exposure to Oseltamivir phosphate is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment.

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 phosphate. 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 (Clcr below 30 ml/min).

Children: The pharmacokinetics of Oseltamivir phosphate 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 phosphate in children over 12 years of age are similar to those in adults.

INDICATIONS.

Treatment of influenza: In patients 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.

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 Flumivir® 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.

Flumivir® 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.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

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

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

No information is available regarding the safety and efficacy of Oseltamivir phosphate 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 phosphate in either treatment or prevention of influenza in immunocompromised patients have not been established.

Efficacy of Oseltamivir phosphate 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.

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.

Ability to drive and use machine: Oseltamivir phosphate has no influence on the ability to drive and use machines.

PREGNANCY AND LACTATION

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

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

DRUG INTERACTIONS

Pharmacokinetic properties of Oseltamivir phosphate, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems, 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 phosphate. Oseltamivir phosphate has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that Oseltamivir phosphate 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

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Oseltamivir phosphate in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g., chlorpropamide, methotrexate, phenylbutazone).
No pharmacokinetic interactions between Oseltamivir phosphate or its major metabolite have been observed when co-administering Oseltamivir phosphate with paracetamol, acetyl-salicylic acid, cimetidine or with antacids (magnesium and aluminium hydroxides and calcium carbonates).

ADVERSE 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 casuality) 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 paients 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 phosphate compared to subjects receiving placebo (in addition to the events listed in the table below) were: aches and pains, rhinorrhoea, dyspesia and upper respiratory tract infection. There were no phosphate or placebo compared with the younger population.
Most frequent Adverse Events in Studies in Naturally Acquired Influenza. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness under treatment with Oseltamivir 75 mg twice daily.

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%	-	-
	Cough	1,1%	0,9%	6,0%	5,6%
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%
	Vertigo	0,6%	0,9%	0,2%	0,3%

1 Subjects who experienced nausea alone; exclude subjects who experienced nausea in association with vomiting.
2 The difference between the placebo and Oseltamivir phosphate groups was statistcally 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 II studies of Oseltamivir phosphate given for the treatment of influenza. Adverse events occuring in greater than 1% of children receiving Oseltamivir phosphate are listed in the table below. The most frequently reported adverse event was vomiting. Other events reported more frequently by Oseltamivir phosphate treated children included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally ocurred 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 Occuring on Treatment in > 1% of Paediatric Patients).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness under treatment with Oseltamivir 2 mg/kg bid.

	Treatment[1]		Treatment[2]	Prevention[2]
Adverse Event	Placebo N = 517	Oseltamivir 2 mg/kg bid N = 515	Oseltamivir 30 to 75 mg[3] N = 158	Oseltamivir 30 to 75 mg[3] 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%)	-	-

[1] Pooled data from Phase III trials of Oseltamivir phosphate treatment of naturally acquired influenza.
[2] Uncontrolled study comparing treatment (twice-daily dosing for 5 days) with prevention (once-daily dosing for 10 days).
[3] 30 to 75 mg = age-based dosing.
Adverse events included are: all events reported in the treatment studies with a frequency ≥ 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 postexposure prevention study in households, both as index cases (n=134) and as contacts (n=222).
Gastrointestinal events, particulary 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 phosphate: dermatitis, rash, eczema, 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. These cases include fatal fulminant hepatitis/hepatic failure.
Convulsions and psychiatric events such as depressed level of consciousness, abnormal behaviour, hallucinations and delirium have been reported during Oseltamivir phosphate administration. In rare cases, the delirium resulted in accidental injury. The symptoms were mainly reported in children adolescents. Convulsions and psychiatric symptoms have also been reported in patients with influenza not taking Oseltamivir phosphate.
In rare cases gastro-intestinal bleedings and hemorrhagic colitis were observed after the use of Oseltamivir phosphate.

DOSAGE AND ADMINISTRATION

Flumivir® is not recommended for use in children less than one year of age due to insufficient data on safety and efficacy.

Treatment of influenza:

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
Adolescents 13-17 years and adults: The recommended oral dose is 75 mg Flumivir® twice daily for 5 days.
Children 2-12 years: Children weighing > 40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for 5 days.
Elderly: No dose adjustment is required, unless there is evidence of severe renal impairment.
Renal impairment: Dose adjustment is recommended for adults with severe renal impairment.
Recommended doses are detailed in the table below.

CI_{cr}	Recommended dose for treatment
> 30 (ml/min)	75 mg twice daily
> 10 to ≤ 30 (ml/min)	75 mg once daily, or 30 mg capsules twice daily
≤ 10 (ml/min)	Not recommended
dialysis patients	Not recommended

Prevention of influenza: Post-exposure prevention:
Adolescents 13-17 years and adults: The recommended dose for prevention of ifluenza following close contact with an infected individual is Flumivir® 75 mg once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.
Children 2-12 years: Children weighing > 40 kg and who are able to swallow capsules may receive prevention with a 75 mg capsule once daily for 10 days.
Elderly: No dose adjustment is required, unless there is evidence of severe ranal impairment.
Renal impairment: Dose adjustment is recommended for adults with severe renal impairment as detailed in the table below.

CI_{cr}	Recommended dose for prevention
> 30 (ml/min)	75 mg once daily
> 10 to ≤ 30 (ml/min)	75 mg every second day, or 30 mg capsules once daily
≤ 10 (ml/min)	Not recommended
dialysis patients	Not recommended

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.
Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is Flumivir® 75 mg once daily for up to 6 weeks.

OVERDOSAGE

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 CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: February 2014.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medicament: keep out of reach of children.

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