

Osetamivir

OSAVIR
75 mg Capsule

Direct Acting Antiviral

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard gelatin capsule contains
Osetamivir Phosphate USP Equivalent to Osetamivir 75 mg

PHARMACEUTICAL FORM

Osetamivir Phosphate Capsules USP 75 mg

Size : 2, hard gelatin capsules with grey opaque colour body with black colour band, imprinted with "M" and light yellow opaque colour cap imprinted with "75 mg".

CLINICAL PARTICULARS THERAPEUTIC INDICATION

Treatment of influenza

Osetamivir Phosphate is indicated in adults and children including full term neonates 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.

Prevention of influenza

- Post-exposure prevention in individuals 1 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 Osetamivir 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.
- Osetamivir Phosphate is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

Osetamivir 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 osetamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations.

POSLOGY AND METHOD OF ADMINISTRATION

Posology

Osetamivir Phosphate hard capsules and Osetamivir Phosphate suspension are bioequivalent formulations. 75 mg doses can be administered as either

- one 75 mg capsule or
 - one 30 mg capsule plus one 45 mg capsule or
 - by administering one 30 mg dose plus one 45 mg dose of suspension.
- Commercially manufactured Osetamivir Phosphate powder for oral suspension (6 mg/ml) is the preferred product for pediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

Treatment: The recommended oral dose is 75 mg osetamivir twice daily for 5 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 5 days
> 40 kg	75 mg twice daily

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg osetamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 10 days
> 40 kg	75 mg once daily

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 osetamivir once daily for up to 6 weeks.

Paediatric population Children 1 to 12 years of age

Osetamivir Phosphate 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight- adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

Body Weight	Recommended dose for 5 days
10 kg to 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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Osetamivir Phosphate is:

Body Weight	Recommended dose for 10 days
10 kg to 15 kg	30 mg once daily
> 15 kg to 23 kg	45 mg once daily
> 23 kg to 40 kg	60 mg once daily
> 40 kg	75 mg once daily

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

Infants 0 – 12 months of age

Osetamivir Phosphate 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight- adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

Body Weight	Recommended dose for 5 days
> 40 kg	75 mg twice daily

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg osetamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 10 days
> 40 kg	75 mg once daily

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 osetamivir once daily for up to 6 weeks.

Paediatric population Children 1 to 12 years of age

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Body Weight	Recommended dose for 5 days
10 kg to 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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Osetamivir Phosphate is:

Body Weight	Recommended dose for 10 days
10 kg to 15 kg	30 mg once daily
> 15 kg to 23 kg	45 mg once daily
> 23 kg to 40 kg	60 mg once daily
> 40 kg	75 mg once daily

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

Infants 0 – 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults. The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	Recommended dose for 5 days
3 kg	9 mg twice daily
4 kg	12 mg twice daily
5 kg	15 mg twice daily
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
10 kg	30 mg twice daily

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age- adjusted dosing prophylaxis regimen is recommended for infants 0 - 12 months of age:

Age	Recommended dose for 10 days
0 - 12 months	3 mg/kg once daily

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age.

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 (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of osetamivir 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 prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg aGer every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of osetamivir 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.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Elderly

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

Immunocompromised patients

Treatment: The recommended oral dose is 75 mg osetamivir twice daily for 10 days for adults. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients.

Method of administration: Oral use.

Patients who are unable to swallow capsules may receive appropriate doses of Osetamivir Phosphate suspension.

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients listed in list of excipients section.

SPECIAL WARNINGS AND PRECAUTION FOR USE

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

Osetamivir Phosphate is not a substitute for influenza vaccination. Use of Osetamivir Phosphate must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Osetamivir Phosphate is administered. Osetamivir 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.

Susceptibility of circulating influenza virus strains to osetamivir has been shown to be highly variable. Therefore, prescribers should take into account the most recent information available on osetamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Osetamivir Phosphate.

Severe concomitant condition

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

Immunocompromised patients

The efficacy of osetamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established. However, the duration of treatment of influenza in immunocompromised adult patients should be 10 days, as there are no studies of a shorter course of osetamivir in this patient group.

Cardiac / respiratory disease

Efficacy of osetamivir 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.

Paediatric population

No data allowing a dose recommendation for premature children (< 36 weeks post-conceptual age) are currently available.

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation.

Neuropsychiatric events

Neuropsychiatric events have been reported during administration of Osetamivir Phosphate in patients with influenza, especially in adults and adolescents. These events are also experienced by patients with influenza without osetamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient.

INTERACTION WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacokinetic profiles of osetamivir, 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.

Probenecid

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 osetamivir.

Amoxicillin

Osetamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that osetamivir interaction with this pathway is weak.

Renal elimination

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 osetamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpromazine, methotrexate, phenylbutazone).

Additional information

No pharmacokinetic interactions between osetamivir or its major metabolite have been observed when co-administering osetamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonate), rifamidine or warfarin (in subjects stable on warfarin and without influenza).

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations including congenital heart defects. A large amount of data on osetamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor fetoneonatal toxicity by osetamivir. However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following osetamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to osetamivir and women unexposed could not be directly comparable, in particular whether or not they had influenza.

Animal studies do not indicate reproductive toxicity.

The use of Osetamivir Phosphate may be considered during pregnancy if necessary and after considering the available safety and benefit information, and the pathogenicity of the circulating influenza virus strain.

Breastfeeding

In lactating rats, osetamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking osetamivir and on excretion of osetamivir in breast milk. Limited data demonstrated that osetamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of osetamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility

Based on preclinical data, there is no evidence that Osetamivir Phosphate has an effect on male or female fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Osetamivir Phosphate has no influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The overall safety profile of Osetamivir Phosphate is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Osetamivir Phosphate or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Osetamivir Phosphate or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 199 immunocompromised adult patients received Osetamivir Phosphate for the treatment of influenza and 475 immunocompromised patients (including 18 children, of these 10 Osetamivir Phosphate and 8 placebo) received Osetamivir Phosphate or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Osetamivir Phosphate.

The following serious adverse reactions have been rarely reported since osetamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.

Tabulated list of adverse reactions

The ARs listed in the tables below fall in to the following categories: 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), and very rare (< 1/10,000). ARs are ordered to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:

In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of Osetamivir 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.

Table 1 Adverse reactions in studies investigating Osetamivir Phosphate for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	Common	Uncommon	Rare
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory		
		tract infections, Sinusitis		

Blood and lymphatic system disorders			Hypersensitivity reaction	Thrombocytopenia
Immune system disorders				Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsion	Visual disturbances
Eye disorders				
Cardiac disorders			Cardiac arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting, Abdominal pain (incl. upper abdominal pain), Dyspepsia		Gastrointestinal bleeding, Haemorrhagic colitis
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepatitis, Hepatic failure, Hepatitis
Skin and subcutaneous tissue disorders			Eczema, Dermatitis, Rash, Urticaria	Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
General disorders and administration site condition		Pain Dizziness (incl vertigo), Fatigue, Pyrexia, Pain in limb		

Treatment and prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of osetamivir given for the treatment of influenza. Of those, 851 children received treatment with osetamivir suspension. A total of 158 children received the recommended dose of Osetamivir Phosphate once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from pediatric clinical trials.

Table 2 Adverse reactions in studies investigating Osetamivir Phosphate for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very Common	Common	Uncommon	Rare
Infections and infestations		Otitis media		
Nervous system disorders		Headache		
Eye disorders		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders

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 Osetamivir Phosphate, there have been marketing reports of confusions 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 self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and Gen had an abrupt onset and rapid resolution. The contribution of Osetamivir Phosphate to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Osetamivir Phosphate.

Hepato-biliary disorders

Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza - like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)

In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of osetamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrhea and diaper rash being the most frequently reported adverse events. Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks. Safety information available on osetamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and 1 marketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,360) in the oseltamivir treated population (p = 0.0012).

Treatment of influenza in high-risk populations: The median duration of influenza illness in older 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 influenza-positive older people, 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 pregnant women: No controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, however, there is evidence from post-marketing and retrospective observational studies showing benefit of the current dosing regimen in this patient population in terms of lower morbidity/mortality. 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.

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 (as defined as the simultaneous return to normal health and activity and alleviation of fever, cough and/or 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 % (28/183) 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 (wheezes – only) was reduced significantly. By day 6 (the last day of treatment) FEV1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo (p = 0.0148) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Oseltamivir Phosphate in one or more subsets of the paediatric population in influenza. The indication in Infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended dosology is based upon pharmacokinetic modelling data.

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.

Treatment of influenza in immunocompromised adults: randomized, double -blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza- infected adult immunocompromised patients, included 151 patients evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant (SOT) patients, haematopoietic stem cell transplant (HSCT) patients, HIV positive patients with a CD4+ cell count <500 cells/mm³, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset, with standard dose (75 patients) or double dose (78 patients) of oseltamivir, for a duration of 10 days. The median time to resolution of symptoms (TTRES) was similar between the standard dose group (103 hours [90% CI 75.4-110.0]) and double dose group (104 hours [90% CI 65.8-131.0]). The proportion of patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%).

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 153 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 6–12) and was 16 (95 % CI 15–19) in the whole population (TTT 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 % (27/138) 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 illness (23/69) in the group not receiving prevention to 11 % (8/64) 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 15–88.0; p = 0.0188]). Among children who had received viral attack, 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 (TTT) and in paediatric index cases (ITT), respectively.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Prevention during an influenza pandemic has not been studied in controlled clinical studies in children 0 – 12 months of age.

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 (CI 1.6 – 5.7; p = 0.0056) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).

A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily 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).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomized study was conducted for influenza A and B viruses isolated from 15 patients with haematopoietic stem cell transplantation (13 placebo, 193 oseltamivir), 87 patients with haemopoietic stem cell transplantation (43 placebo, 44 oseltamivir), no patient with other immunosuppressant conditions), including 18 children, 18 adults and 12 young adults. The incidence of influenza in the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI 2.3 – 4.1 %; p = 0.772). Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir resistance
Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank resistance to oseltamivir has been studied in developing countries. In a study in children, the incidence of influenza (88 patients) resistant virus during treatment was more frequent in children than adults, ranging from less than 1 % in adults to 18 % in infants aged below 1 year. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a longer period compared to subjects with susceptible virus. However, treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms.

An overall higher incidence of oseltamivir resistance was observed in adult immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.9% (10/67) in standard dose group and 2.8% (2/71) in double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult patients. The majority of patients that developed resistance were transplant recipients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most of the patients with oseltamivir-resistant virus were infected with influenza type A and had prolonged viral shedding.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	0.88% (21/2377)	1.12% (27/2391)
Children (1-12 years)	3.89% (66/1698)	4.24% (72/1698)
Infants (<1 year)	18.31% (13/71)	18.31% (13/71)

* Full genotyping was not performed in all subjects. Prophylaxis of Influenza
There has been no evidence of emergence of drug resistance associated with the use of Oseltamivir Phosphate in clinical studies conducted to date in the post-exposure (7 days), post-exposure in household groups (10 days) and seasonal (42 days) prevention of influenza in immunocompetent patients. There was no resistance observed during a 12-week prophylaxis study in immunocompromised patients.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from 15 patients with haematopoietic stem cell transplantation (13 placebo, 193 oseltamivir), 87 patients with haemopoietic stem cell transplantation (43 placebo, 44 oseltamivir), no patient with other immunosuppressant conditions), including 18 children, 18 adults and 12 young adults. The incidence of influenza in the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HA1 antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI 2.3 – 4.1 %; p = 0.772). Specific studies have not been conducted to assess the reduction in the risk of complications.

PHARMACOKINETIC PROPERTIES
General information
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 %).

Biotransformation
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*.

Other special populations
Paediatric population
Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Oseltamivir Phosphate have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 0-12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious with a safety profile comparable to that seen in older children and adults using the approved dose. The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile. No clinical studies of prophylaxis in infants aged <1 have been performed.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. 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 and adolescents 12 years of age or older are similar to those in adults.

Elderly
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml/min).

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
Two studies have now 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.

Pregnant women
Controlled population pharmacokinetic analysis indicates that the Oseltamivir Phosphate dosage regimen described in 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 (IC50 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.

Immunocompromised Patients
Population pharmacokinetic analysis indicates that treatment of adult immunocompromised patients with oseltamivir results in an increased exposure (of up to 50%) to the active metabolite when compared to adult non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in adults due to their immunocompromised status. However, for adult immunocompromised patients with renal impairment, treatment should be adjusted. Posology and method of administration.

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.

Toxicology studies have been conducted in rats and rabbits at doses of up to 1,500 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 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day; the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. 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 "maximization" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritation of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post-partum).

Pharmaceutical particulars List of excipients
Capsule core
Oseltamivir Phosphate Capsules USP 75 mg
Pregelatinized starch, Povidone K-30, Carboxymethylcellulose sodium, Talc, Sodium stearyl fumarate

Capsule shell
Oseltamivir Phosphate Capsules USP 75 mg
Gelatin, Iron oxide red (E172), Iron oxide yellow (E172), Iron oxide black (E172), Titanium dioxide (E171)

Printing ink
Oseltamivir Phosphate Capsules USP 75 mg
Shellac (E904), Ethanol anhydrous (E150), 2-Propanol, Butanol, Propylene glycol (E1520), Ammonia solution, concentrated (E527), Iron oxide black (E172), Potassium hydroxide (E525)

Incompatibilities
Not applicable.
Special precautions for storage
Store below 30°C. Keep out of the sight and reach of children.

Nature and contents of container PVC/PE/PVDC-Alu Blister Pack Pack-size 10 capsules.
Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

Excipients/active substance
When Oseltamivir Phosphate powder for oral suspension is not available
Commercially manufactured Oseltamivir Phosphate for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that commercially manufactured Oseltamivir Phosphate powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Oseltamivir Phosphate capsules or tablets can prepare the suspension from capsules at home.

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Oseltamivir Phosphate capsules under "Making liquid Oseltamivir Phosphate at home".
Syringes of appropriate volume and grading should be provided for administering the pharmacy preparation. The pharmacy preparation should be used for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding
Pharmacy compounded 6 mg/ml suspension prepared from capsules
Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules

This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis.
Third, follow the procedure below for compounding the 6 mg/ml suspension from Oseltamivir Phosphate 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.
First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment (according to the dosing table above) or the oral syringe for each patient.
When only 75 mg capsules are available, and doses of 30 mg or 45 mg are needed, the preparation of Oseltamivir Phosphate suspension involves additional steps. Detailed instructions can be found in the package leaflet of Oseltamivir Phosphate capsules under : Making liquid Oseltamivir Phosphate at home.

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered		Total volume to compound per patient weight (ml) Measurement loss considered	
	75 mg	45 mg	30 mg	
10 kg to 15 kg	50 ml		60 ml or 75 ml*	
> 15 kg to 23 kg	75 ml		90 ml or 100 ml*	
> 23 kg to 40 kg	100 ml		125 ml	
> 40 kg	125 ml		137.5 ml (or 150 ml)*	

* Depending on the capsule strength used.
* Second, determine the number of capsules and the amount of vehicle (water containing 0.05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below.

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

Total volume of compounded suspension to be prepared	Required number of Oseltamivir Phosphate capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
90 ml	Please use alternative capsule strength	12 capsules (540 mg)	18 capsules (540 mg)	89 ml
100 ml	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98.5 ml
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.
(Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Oseltamivir Phosphate capsules, which are insoluble.)
[1] In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
[2] Open the stated amount of Oseltamivir Phosphate capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
[3] With a suitable stirring device, stir for 2 minutes.
[4] Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
[5] Close the bottle using a child-resistant cap.
[6] Put an ancillary label on the bottle indicating : Shake Gently Before Use.
(Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Oseltamivir Phosphate capsules, which are insoluble.)
[7] Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
[8] Place an appropriate expiration date label according to storage condition.
Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Oseltamivir Phosphate capsules for infants and children 1 year of age or older

Body weight (kg)	Dose (mg)	Volume per dose (6 mg/ml)	Treatment dose (for 5 days)	Prophylaxis dose (for 10 days)
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7.5 ml	7.5 ml twice daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12.5 ml	12.5 ml twice daily	12.5 ml once daily

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.
The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Infants less than 1 year of age
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.
The pharmacist may compound a 6 mg/ml suspension from Oseltamivir Phosphate 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.
First, calculate the total volume needed to be compounded and dispensed for each patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight compounded 6 mg/ml suspension prepared based upon the patient's weight

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
≤ 7 kg	up to 40 ml	50 ml
> 7 kg to 10 kg	50 ml	60 ml or 75 ml*

* Depending on the capsule strength used.
* Second, determine the number of capsules and the amount of vehicle (water containing 0.05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight

Total volume of compounded suspension to be prepared	Required number of Oseltamivir Phosphate capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
50 ml	4 capsules (300mg)	Please use alternative capsule strength*	10 capsules (300mg)	49.5 ml
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450mg)	15 capsules (450 mg)	74 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.
[1] In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
[2] Open the stated amount of Oseltamivir Phosphate capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.

[3] With a suitable stirring device, stir for 2 minutes.
(Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Oseltamivir Phosphate capsules, which are insoluble.)
[4] Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
[5] Close the bottle using a child-resistant cap.
[6] Put an ancillary label on the bottle indicating : Shake Gently Before Use.
(Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Oseltamivir Phosphate capsules, which are insoluble.)
[7] Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.

[8] Place an appropriate expiration date label according to storage condition.
Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.
Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Oseltamivir Phosphate capsules for infants less than 1 year of age

Body Weight (nearest 0.5 kg)	Dose (mg)	Volume per dose (6 mg/ml)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)	Dispenser size to use (grading 0.1 ml)
3 kg	9 mg	1.5 ml	1.5 ml twice daily	1.5 ml once daily	2.0 ml or 3.0 ml
3.5 kg	10.5 mg	1.8 ml	1.8 ml twice daily	1.8 ml once daily	2.0 ml or 3.0 ml
4 kg	12 mg	2.0 ml	2.0 ml twice daily	2.0 ml once daily	3.0 ml
4.5 kg	13.5 mg	2.3 ml	2.3 ml twice daily	2.3 ml once daily	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml once daily	3.0 ml
5.5 kg	16.5 mg	2.8 ml	2.8 ml twice daily	2.8 ml once daily	3.0 ml
6 kg	18 mg	3.0 ml	3.0 ml twice daily	3.0 ml once daily	3.0 ml (or 5.0 ml)
6.5 kg	19.5 mg	3.3 ml	3.3 ml twice daily	3.3 ml once daily	5.0 ml
7 kg	21 mg	3.5 ml	3.5ml twice daily	3.5 ml once daily	5.0 ml
7.5 kg	22.5 mg	3.8 ml	3.8 ml twice daily	3.8 ml once daily	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml once daily	5.0 ml
8.5 kg	25.5 mg	4.3 ml	4.3 ml twice daily	4.3 ml once daily	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml once daily	5.0 ml
9.5 kg	28.5 mg	4.8 ml	4.8 ml twice daily	4.8 ml once daily	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml once daily	5.0 ml

Dispense the pharmacy compounded suspension with graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.
The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask