WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

1. NAME OF THE MEDICINAL PRODUCT

[IN019 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 59.10 mg oseltamivir phosphate equivalent to 45 mg oseltamivir.
For a full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Capsules.
White to off-white powder, filled in size "4" hard gelatin capsules with a grey, opaque colour body with a black-coloured band, imprinted with "M" and having a grey opaque colour cap imprinted with "45 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza

[IN019 trade name] 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 [IN019 trade name] 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.
- [IN019 trade name] is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

[IN019 trade name] is not a substitute for influenza vaccination

The use of antivirals for the treatment and prevention of influenza should be determined based on official recommendations. Decisions regarding the use of [IN019 trade name] 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 (see section 5.1).

4.2 Posology and method of administration

Posology

Adults, adolescents or infants and children (1 year of age or older) who cannot swallow capsules may receive oseltamivir suspension.

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 oseltamivir powder 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. If commercially manufactured oseltamivir powder for oral suspension is not available, the pharmacist may

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

compound a suspension (6 mg/ml) from [IN019 trade name] capsules or patients can prepare the suspension from the capsules at home (see section 6.6).

Adults, and adolescents 13 years and over

Treatment:

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

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

Body weight	Recommended dose for 5 days	Recommended dose for 10 days* Immunocompromised patients
> 40 kg	75 mg twice daily	75 mg twice daily

***** The recommended treatment duration in immunocompromised adults and adolescents is 10 days. See *Special Populations, Immunocompromised Patients* for more information.

Post-exposure prevention:

Therapy should begin as soon as possible within two days of exposure to an infected individual.

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

Body weight	Recommended dose for 10 days	Recommended dose for 10 days Immunocompromised patients
> 40 kg	75 mg once daily	75 mg once daily

Prevention during an influenza epidemic in the community:

The recommended dose for prevention of influenza during a community outbreak is oseltamivir 75 mg once daily for up to 6 weeks (or up to 12 weeks in immunocompromised patients, see sections 4.4, 4.8 and 5.1).

Paediatric population

Children 1 to 12 years of age

Oseltamivir 30 mg, 45 mg and 75 mg capsules and oral suspension can be given to infants and children 1 year of age or older

Treatment:

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

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

Body weight	Recommended dose for 5 days	Recommended dose for 10 days* Immunocompromised patients
10 kg to 15 kg	30 mg twice daily	30 mg twice daily
> 15 kg to 23 kg	45 mg twice daily	45 mg twice daily
> 23 kg to 40 kg	60 mg twice daily	60 mg twice daily
> 40 kg	75 mg twice daily	75 mg twice daily

*****The recommended treatment duration in immunocompromised children (≥1 year old) is 10 days. See Special Populations, Immunocompromised Patients for more information.

Post-exposure prevention:

The recommended post-exposure prevention dose of oseltamivir is:

Body weight	Recommended dose for 5 days	Recommended dose for 10 days* Immunocompromised patients
10 kg to 15 kg	30 mg once daily	30 mg once daily
> 15 kg to 23 kg	45 mg once daily	45 mg once daily
> 23 kg to 40 kg	60 mg once daily	60 mg once daily
> 40 kg	75 mg once daily	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:

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

The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based on 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 (see section 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

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

** The recommended duration in immunocompromised infants (0-12 months old) is 10 days. See *Special Populations, Immunocompromised Patients* for more information.

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 5 days	Recommended dose for 10 days Immunocompromised patients
0 – 12 months	3 mg/kg once daily	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.

For instructions on preparing the extemporaneous formulation, see section 6.6.

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 disorders.

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 (no data available)
Haemodialysis patients	30 mg after each treatment
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 treatment
> 60 mL/min	75 mg once daily
> 30 to 60 mL/min	30 mg once daily
> 10 to 30 mL/min	30 mg every second day
≤ 10 mL/min	Not recommended (no data available)
Haemodialysis patients	30 mg after every second treatment
Peritoneal dialysis patients*	30 mg single dose 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.

Elderly

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

Immunocompromised patients

Treatment:

For treatment of influenza, the recommended duration for immunocompromised patients is 10 days (see sections 4.4, 4.8 and 5.1). No dose adjustment is necessary. 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 (see sections 4.4, 4.8 and 5.1).

Method of administration

For oral administration.

Patients who are unable to swallow capsules may receive appropriate doses of oseltamivir suspension (see section 6-6).

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6-1.

4.4 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 (see section 5.1).

Oseltamivir is not a substitute for influenza vaccination. Use of oseltamivir must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as oseltamivir is administered. Oseltamivir 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 oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use oseltamivir.

Severe concomitant conditions:

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.

Immunocompromised patients:

The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease:

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Premature infants:

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 (see sections 4.2 and 5.2).

Neuropsychiatric events:

Neuropsychiatric events have been reported during administration of oseltamivir in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

The pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

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 oseltamivir.

Amoxicillin

Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir 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 oseltamivir to patients taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information

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

4.6 Fertility, pregnancy and breastfeeding

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 oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative or foetal/neonatal toxicity by oseltamivir.

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 oseltamivir 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 and was too small to reliably assess individual types of major malformations. Finally, women exposed to oseltamivir and women unexposed could not be made fully comparable, specifically as to whether or not they had influenza.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of oseltamivir may be considered during pregnancy if necessary and after considering the available safety and benefit information (for data on benefit in pregnant women please refer to section 5.1 “treatment of influenza in pregnant women”), and the pathogenicity of the circulating influenza virus strain.

Breastfeeding:

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very little 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. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding

woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility:

Based on preclinical data, there is no evidence that oseltamivir influences male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oseltamivir does not affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile:

The overall safety profile of oseltamivir is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with oseltamivir or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving oseltamivir or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 245 immunocompromised patients (including 7 adolescents and 39 children) received oseltamivir for the treatment of influenza and 475 immunocompromised patients (including 18 children) received oseltamivir 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 oseltamivir.

The following serious adverse reactions have been rarely reported since oseltamivir 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
- Neuropsychiatric disorders (see section 4.4)

Tabulated list of adverse reactions:

The ARs listed in the tables below fall into the following categories: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

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

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.

Table 1: Adverse reactions in studies investigating oseltamivir 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				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsions	
Eye disorders				Visual disturbance
Cardiac disorders			Cardiac arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting, Abdominal pain (including 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

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	Common	Uncommon	Rare
General disorders and administration site conditions		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 oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of oseltamivir 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 paediatric clinical trials.

Table 2: Adverse reactions in studies investigating oseltamivir 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		
		Abdominal pain (including 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 oseltamivir there have been post-marketing 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 self-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 to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

Hepato-biliary disorders

Hepato-biliary system disorders, including hepatitis and elevated liver enzymes have occurred 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 oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrhoea and diaper rash being the most frequently reported adverse events (see section 5.2). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on oseltamivir 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 post-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.

Elderly patients and patients with chronic cardiac and/or respiratory disease

The population included in the influenza treatment studies is 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.

Immunocompromised patients

The treatment of influenza in immunocompromised patients was evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of oseltamivir (see section 5.1). The safety profile of oseltamivir observed in these studies was consistent with that observed in previous clinical trials where oseltamivir was administered for treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or “at risk” patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent adverse reaction reported in immunocompromised children was vomiting (28%).

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in oseltamivir prophylaxis clinical studies.

Children with pre-existing bronchial asthma

In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

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

Adverse events reported following overdose were similar in nature and distribution to those with therapeutic doses of oseltamivir, described in section 4.8.

There is no known specific antidote, and treatment is supportive.

Paediatric population

Overdose has been reported more frequently for children than for adults and adolescents. Caution should be exercised when preparing oseltamivir oral suspension and when giving oseltamivir products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors

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 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 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 studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

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 proportionally 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 older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older:

Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, Oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) 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 (see section 5.2, Pharmacokinetics, Special Population).

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_1 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 in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

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 patients:

A 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 immunocompromised patients, included 151 adult patients, 7 adolescents and 9 children 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/mm^3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were

randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatment regimens were: standard dose (75 mg or weight adjusted dose for children) twice daily (73 adult patients, 4 adolescent patients and 4 children) or double dose (150 mg or weight-adjusted dose for children) twice daily (78 adult patients, 3 adolescent patients and 5 children) of oseltamivir.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95% CI 63.9-140.0]). The TTRS for children was variable and the interpretation is limited by the small sample size. The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).

A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤ 12 years of age, n=30) receiving standard (75 mg or weight adjusted twice daily) vs. triple dose (225 mg or weight adjusted twice daily) oseltamivir for an adaptive dosing period of 5 to 20 days dependant on duration of viral shedding (mean treatment duration: 9 days). No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis).

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 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) 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; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95% CI 9 – 12) and was 16 (95% CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

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

According to subgroup analysis in children at 1 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 (ITTII), 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. See Section 5.2 for exposure simulation details.

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 older people in 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).

Prophylaxis of influenza in immunocompromised patients:

A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with hematopoietic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was 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 examined during Roche-sponsored clinical studies. Developing oseltamivir-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 prolonged period compared with 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 and adolescent immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.5% (10/69) in the standard dose group and 2.7% (2/74) in the double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult and adolescent patients. Most adult 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.

The incidence of oseltamivir resistance observed in immunocompromised children (≤ 12 years of age) treated with oseltamivir across the two studies and evaluated for resistance was 20.7% (6/29). Of the six immunocompromised children found with treatment-emergent resistance to oseltamivir, 3 patients received standard dose and 3 patients received high dose (double or triple dose). The majority had acute lymphoid leukemia and were ≤ 5 years of age.

Table: Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Patients with resistance mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	0.88% (21/2382)	1.13% (27/2396)
Children (1-12 years)	4.11% (71/1726)	4.52% (78/1727)
Infants (< 1 year)	18.31% (13/71)	18.31% (13/71)

* 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 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 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 patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. 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.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [IN019 trade name]. A bioequivalence study was conducted with a product containing 75 mg oseltamivir [IN020 tradename], that is essentially the same as [IN019 trade name] in qualitative terms and with respect to the ratio of active and other ingredients.

The absorption characteristics of [IN020 trade name] (containing 75 mg oseltamivir) have been determined after administration of one tablet in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
Maximum concentration (C_{max})	97 ± 39 (90) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	187 ± 40 (182) ng.h/mL
Time to attain maximum concentration (t_{max})**	0.67 (0.17 – 3.5) h

*geometric mean, **median (range)

Pharmacokinetics of oseltamivir

General	
	Following oral administration, oseltamivir phosphate (OP) is rapidly absorbed and converted to the active metabolite oseltamivir carboxylate (OC). OC is detectable in plasma within 30 minutes of dosing with a T_{max} of 3-4 hours.
Absorption	
Absolute bioavailability	Approximately 80%
Oral Bioavailability	>75% as active metabolite
Food effect	None
Distribution	

Volume of distribution (mean)	OC: 23 - 26 L
Plasma protein binding *in vitro*	OP: 42% OC: Approximately 3%
Tissue distribution	OC distributes to the extracellular body fluid compartment and present in the lung, sinuses and nasal mucosa.
Metabolism	
	Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver
Elimination	
Means systemic clearance (Cl/F)	
Renal clearance	18.8 L/h
% of dose excreted in urine	> 80%
% of dose excreted in faeces	< 20%
Pharmacokinetic linearity	
	OP and OC: Linear over the dose range
Drug interactions *(in vitro)*	
Transporters	Secreted into urine by the proximal tubular anionic transporters
Metabolising enzymes	Not metabolised by CYP450 enzymes or glucuronyl transferases Not an inhibitor or inducer of CYP450 enzymes in vitro No phase 2 conjugates of OP or OC have been identified in vivo.
Special populations	
Renal impairment	Exposure to OC is inversely proportional to declining renal function
Hepatic impairment	Exposure expected not to be affected.
Elderly patients	Increased exposure to OC by 25 – 35%.
Paediatric patients	The pharmacokinetics in children and adolescents 12 years of age or older are similar to those in adults. 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. The rate of clearance of OC, corrected for body weight, decreases with ages below one year.

CrCl: creatinine clearance

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of oseltamivir in its adopted therapeutic indications.

Teratology 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 "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:

Pregelatinised starch
Povidone
Croscarmellose sodium
Talc
Sodium stearyl fumarate

Capsule shell:

Gelatin
Iron oxide black (E172)
Titanium dioxide (E171)

Printing ink:

Shellac (E904)
Iron oxide black(E172)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

6.5 Nature and contents of container

Clear, transparent PVC/PE/PVDC-Alu blister card of 10 capsules.
Pack sizes: 1, 3 or 10 blister cards packed in a carton.

6.6 Instructions for use and handling and disposal

Information for the user

For people who find it hard to take capsules, including very young children, a liquid medicine called an oral suspension is preferred, if available.

If you need the oral suspension, but it is not available, your pharmacy can prepare it for you. The pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make an oseltamivir suspension from capsules at home according to the instructions given below.

Making oseltamivir suspension at home

- **If you have the right capsule** for the dose needed (45 mg dose), you will need to open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. See **Part A** of the instructions below.
- **If you need smaller doses,** making oseltamivir suspension from capsules involves extra steps. This is suitable for younger, lighter children and babies, who usually need a smaller dose. See **Part B** of the instructions below.

PART A: If you have the right capsule for the dose

Children 1 to 12 years old who need to take 45 mg dose of oseltamivir.

You need:

- **One capsule of [IN019 trade name]** (containing 45 mg oseltamivir)
- **Sharp scissors** (preferred, if available)
- **One small bowl**
- **Teaspoon (5-ml spoon)**
- **Sweet food** to hide the bitter taste of oseltamivir powder, e.g., sweet porridge or you can make sugar water by mixing three-quarters (¾) of a teaspoonful of sugar with a teaspoon of water.

Step 1: Check the dose is correct

To find the correct amount to use, find the patient's weight on the left of the table.

Body weight	Dose of oseltamivir	Number of capsules
15 kg to 23 kg	45 mg	One 45 mg capsule

- Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.
- You should use only 45 mg capsules for 45 mg doses. Do not try to make a 45 mg dose by using the contents of 30 mg capsules.

Step 2: Pour all the powder in the bowl

- Wash your hands thoroughly
- Hold a 45 mg capsule upright over a bowl and carefully snip off the rounded tip with scissors.
    - If you do not have scissors, you can hold the capsule on both ends, and gently twist and pull to open the capsule.
- Pour all the powder into the bowl.
- Be careful with the powder because it may irritate your skin and eyes.

Step 3: Sweeten the suspension and give it to the patient

- Add a small amount of sweet food - no more than one teaspoon - to the powder in the bowl. This is to hide the bitter taste of the oseltamivir powder.
- Stir the mixture well.
- **Give the whole contents** of the bowl to the patient straightaway.
- **If there is any mixture left** in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all. This is to make sure that the patient gets the full dose.

Repeat these three steps every time you need to give the medicine.

PART B: If you need to give a smaller dose

Infants aged under 1 year (weighing up to 10 kg) and **children weighing less than 23 kg** who need to take smaller doses of oseltamivir:

You need:

- **One capsule of [IN019 trade name]** (containing 45 mg oseltamivir)

- **Sharp scissors** (preferred, if available)
- **Two small bowls**
- **One large oral dose dispenser** to measure out water: a 5-ml or 10-ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5-ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of oseltamivir powder, e.g., sweet porridge or you can make sugar water by mixing three-quarters (¾) of a teaspoonful of sugar with a teaspoon of water.

Step 1: Pour all the powder into the bowl

- Wash your hands thoroughly
- Hold a 45 mg capsule upright over one of the bowls and carefully snip off the rounded tip with scissors.
    - If you do not have scissors, you can hold the capsule on both ends, and gently twist and pull to open the capsule.
- Pour **all** the powder into the bowl, **whatever dose you are making**
- Be careful with the powder because it may irritate your skin or eyes.

Step 2: Add water to dilute the medicine

- Use the larger dispenser to draw up 7.5 ml water.
- Add the water to the powder in the bowl.
- Stir the mixture with the teaspoon for about 2 minutes.

Don’t worry if the powder does not dissolve completely. The undissolved powder is just inactive ingredients.

Step 3: Measure out the correct amount for your child’s age and weight

- Look up the child’s weight on the left side of the table.
- Then look under ‘How much mixture to draw up’ which shows how much of the liquid mixture you need to draw up.

Infants less than 1 year (including full-term newborn babies) (oseltamivir dose 3 mg/kg)

Weight (nearest)	Oseltamivir dose	How much mixture to draw up
3.0 kg	9.0 mg	1.5 mL
3.5 kg	10.5 mg	1.8 mL
4.0 kg	12.0 mg	2.0 mL
4.5 kg	13.5 mg	2.3 mL
5.0 kg	15.0 mg	2.5 mL
5.5 kg	16.5 mg	2.8 mL
6.0 kg	18.0 mg	3.0 mL
6.5 kg	19.5 mg	3.3 mL
7.0 kg	21.0 mg	3.5 mL
7.5 kg	22.5 mg	3.8 mL
8.0 kg	24.0 mg	4.0 mL
8.5 kg	25.5 mg	4.3 mL
9.0 kg	27.0 mg	4.5 mL
9.5 kg	28.5 mg	4.8 mL
10.0 kg	30.0 mg	5.0 mL

Children over 1 year, weighing less than 23 kg

Weight (nearest)	Oseltamivir dose	How much mixture to draw up
10-15 kg	30 mg	5 mL
15-23 kg	45 mg	10 mL

Step 4: Draw up the liquid mixture

- Make sure you have the right size of dispenser
- Draw up the correct amount of liquid mixture from the first bowl. Make sure there are no bubbles in the mixture when you measure the amount drawn up.
- Gently squirt the correct dose from the dispenser into the second bowl

Step 5: Sweeten and give to the child

- Add a small amount of sweet food—no more than one teaspoon—to the second bowl. This is to hide the bitter taste of the oseltamivir.
- Mix the sweet food and oseltamivir liquid well.
- Give the whole contents of the second bowl (oseltamivir in the sweet food) to the child straightaway.
- If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. If the child cannot drink form the bowl, use a spoon or use a bottle to feed the child the remaining liquid. This is to make sure that the child gets the full dose.
- Give the child something to drink after taking the medicine.

Throw away any liquid left in the first bowl.

Repeat these five steps every time you need to give the medicine.

Disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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For the PK section 5-2

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European Medicines Agency: Tamiflu SmPC (Last updated April 23, 2020)

UK EMC: Tamiflu 30 mg, 45 mg, 75 mg Hard Capsules SmPC (Last updated April 28, 2020)

UK EMC: Tamiflu 30 mg, 45 mg, 75 mg Hard Capsules PIL (Last updated April 20, 2020)

IN014part3 OSV 30 mg

IN014part4 OSV 30 mg

IN015part3 OSV 45 mg

IN015part4 OSV 45 mg

IN016part3 OSV 75 mg

IN016part4 OSV 75 mg

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/