SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUZAVIR 75 mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Active substance:

Oseltamivir phosphate……98.5 mg (equivalent to 75 mg of oseltamivir)

Excipients:

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Hard capsule

A hard gelatin capsule with a light yellow cap printed with "75mg" in black ink and a light grey body printed with "DEVA" in black ink, filled with white or off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLUZAVIR is indicated for the treatment of influenza and avian influenza in infants over 2 weeks of age, children and adults (see Sections 4.4 and 5.3). It is indicated in newborns over 2 weeks of age if treatment is initiated within the first two days following the onset of symptoms.

FLUZAVIR is indicated for the prophylaxis of influenza in children over 1 year of age (see Section 5.2).

4.2 Posology and method of administration

Dosage/frequency and duration of administration:

Standard dose for treatment

Treatment should be initiated on the first or second day of influenza symptoms.

Adults and adolescents (aged 13–17 years):

The recommended dose for adults and adolescents aged ≥13 years weighing over 40 kg is 75 mg capsules twice daily for 5 days, or one 30 mg capsule and one 45 mg capsule twice daily for 5 days. Adults and adolescents aged ≥13 years who cannot swallow capsules may take 75 mg oseltamivir suspension twice daily for 5 days.

Children:
Recommended therapeutic oral FLUZAVIR doses for infants and children aged 1 year or older:

Body weight	Recommended treatment dose for 5 days
10–15 kg	30 mg twice daily
> 15–23 kg	45 mg twice daily
> 23–40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

As an alternative to the recommended oseltamivir suspension doses, children weighing >40 kg who have no difficulty swallowing capsules may be treated with 75 mg capsules twice daily or one 30 mg capsule and one 45 mg capsule twice daily.

Treatment should be started on the first or second day of influenza symptoms.

Recommended oral FLUZAVIR doses for infants under 1 year of age:
The recommended treatment dose for infants aged 0-12 months is 3 mg/kg twice daily. This dosage recommendation is based on pharmacokinetic and safety data. According to these data, the recommended dose provides clinically effective and safe plasma drug concentrations of the prodrug and active metabolite in the majority of 0-12 month-old infant patients, comparable to those seen in older children and adults (see Section 5.2).

The following dosage regimens based on body weight are recommended for the treatment of infants aged 0–12 months.

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

* This table is not intended to cover all possible weights for infants aged 0-12 months. A dose of 3 mg/kg should be used to determine the dose for infant patients under 1 year of age.

Treatment should be initiated immediately within the first 2 days of influenza symptoms appearing.

Dosage recommendations are not for premature infants (e.g., those with a postmenstrual age of less than 36 weeks). There is insufficient data for these patients, who may require different doses due to their underdeveloped physiological functions.

Doses to be prepared by the pharmacist are described in Section 6.6.

Standard dose for prophylaxis

Adults and adolescents (aged 13–17 years):
Following close contact with infected individuals, the recommended oral dose of FLUZAVIR for influenza prophylaxis is 75 mg capsules once daily or one 30 mg capsule and one 45 mg capsule once daily for 10 days. Treatment should be started within two days of close contact with infected individuals. The recommended dose for prophylaxis during an influenza outbreak in the community is 75 mg daily. The safety and efficacy of FLUZAVIR have been demonstrated over a six-week period. Protection continues as long as the medication is taken.

Infants and children aged 0-12 years or older:
As an alternative to the recommended oseltamivir suspension doses, children weighing >40 kg who have no difficulty swallowing capsules may take one 75 mg capsule or one 30 mg capsule and one 45 mg capsule once daily for 10 days as post-exposure prophylaxis.

Recommended post-exposure prophylactic oral FLUZAVIR doses for infants and children aged 1 year or older:

Body weight	**Recommended post-exposure prophylaxis dose for 10 days**
10–15 kg	30 mg once daily
> 15–23 kg	45 mg once daily
> 23–40 kg	60 mg once daily
> 40 kg	75 mg once daily

Prevention during influenza epidemics in the community:
There are no studies available on the prophylactic use of this product in infants under 12 months of age during influenza epidemics.

For information on preparation at the time of use (extemporaneous formulation), see Section 6.6.

Method of administration:
Administer orally with a small amount of water.

FLUZAVIR may be taken alone or with food (see Section 5.2). Taking FLUZAVIR with food may improve tolerance in some patients.

In patients unable to take capsules orally, FLUZAVIR suspension may be administered at appropriate doses.

Additional information on specific populations:
Renal impairment:
When used for influenza treatment: In moderate or severe renal impairment, dose adjustment is recommended for adults and adolescents (aged 13-17 years). The recommended doses are shown in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (mL/min)	75 mg twice daily
> 30 - 60 (mL/min)	30 mg twice daily (suspension or capsule)
> 10 - 30 (mL/min)	30 mg once daily (suspension or capsule)
≤ 10 (mL/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsule) single dose

*Based on results from studies in continuous ambulatory peritoneal dialysis (CAPD) patients, oseltamivir carboxylate clearance is expected to be higher when the automated peritoneal dialysis mode (APDM) is used. If deemed necessary by the nephrologist, the treatment mode may be changed from APDM to CAPD.

When used for influenza prophylaxis: In moderate or severe renal impairment, dose adjustment is recommended for adults and adolescents (aged 13-17 years). The recommended doses are shown in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (mL/min)	75 mg once daily
> 30 - 60 (mL/min)	30 mg once daily (suspension or capsule)
> 10 - 30 (mL/min)	30 mg daily thereafter (suspension or capsule)
≤ 10 (mL/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every 2nd haemodialysis session
Peritoneal dialysis patients*	30 mg once weekly (suspension or capsule)

*Based on results from studies in continuous ambulatory peritoneal dialysis (CAPD) patients, oseltamivir carboxylate clearance is expected to be higher when the automated peritoneal dialysis mode (APDM) is used. If deemed necessary by the nephrologist, the treatment mode may be changed from APDM to CAPD.

There are insufficient clinical data to recommend any dosage in infants and children (aged 12 years and under) with renal impairment.

Hepatic impairment:

For influenza treatment or prophylaxis, no dose adjustment is necessary in patients with hepatic dysfunction (see Section 5.2). No studies have been conducted in paediatric patients with hepatic impairment.

Paediatric population:
The safety and efficacy of FLUZAVIR have not been established in children under 1 year of age (see Section 5.2).

FLUZAVIR can only be used for the treatment of influenza in children younger than 1 year of age, provided that it is used temporarily, during an epidemic, on the recommendation of or under the supervision of a doctor. Otherwise, FLUZAVIR should not be used in children under 1 year of age (see Section 5.3).

Geriatric population:
For influenza treatment or prophylaxis, no dose adjustment is necessary in elderly patients unless there is evidence of moderate or severe renal impairment (see Section 5.2).

Patients with immunodeficiency:
Treatment: The recommended oral dose for adults is 75 mg of oseltamivir twice daily for 10 days (see Sections 4.4, 4.8 and 5.1). Treatment should be initiated as early as possible within the first two days after the onset of influenza symptoms.

Seasonal prophylaxis: Seasonal prophylaxis for up to 12 weeks has been evaluated in patients with immunodeficiency (see Sections 4.4, 4.8 and 5.1).

4.3. Contraindications
It is contraindicated in individuals with known hypersensitivity to oseltamivir phosphate or any of the excipients contained in the medicinal product (listed in Section 6.1).

4.4. Special warnings and precautions for use
There is no evidence that FLUZAVIR is effective against diseases caused by agents other than influenza A and B viruses.

FLUZAVIR is not a substitute for the influenza vaccine.
The use of FLUZAVIR does not affect the assessment of individuals' annual influenza vaccination. Protection against influenza lasts only as long as FLUZAVIR is administered. FLUZAVIR can be used for the treatment and prevention of influenza when reliable epidemiological data indicate that the influenza virus is circulating in the community. The susceptibility of circulating virus strains to oseltamivir has been shown to be highly variable (see Section 5.1). Therefore, physicians should consider the most up-to-date information on the susceptibility of circulating viruses to oseltamivir when deciding on the use of FLUZAVIR.

Neuropsychiatric events
Neuropsychiatric events, such as convulsions and delirium, have been reported in patients receiving oseltamivir for influenza treatment, particularly in children and adolescents. Neuropsychiatric events have also been reported in influenza patients not receiving oseltamivir.

Patients should be closely monitored for signs of abnormal behaviour, and a benefit-risk assessment should be performed for each patient before continuing treatment (see Section 4.8).

Concomitant serious conditions
There is no information on the safety and efficacy of oseltamivir in patients with unstable medical conditions that are sufficiently serious or potentially life-threatening to require hospitalisation.

Patients with immunodeficiency
The safety and efficacy of oseltamivir treatment or prophylaxis in patients with immunodeficiency have not been conclusively established. However, the duration of influenza treatment in adult patients with immunodeficiency should be 10 days, as there are no studies on a shorter course of oseltamivir in this patient group (see Section 5.1).

Severe Skin/Hypersensitivity Reactions
Serious skin reactions such as anaphylaxis and toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in post-marketing experience with oseltamivir. If an allergic reaction occurs or is suspected, discontinue oseltamivir and initiate appropriate treatment. The use of oseltamivir is contraindicated in patients with known severe hypersensitivity to oseltamivir.

Risk of Bacterial Infection
There is no evidence that oseltamivir is effective in any disease caused by pathogens other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms, may coexist during the course of influenza, or may arise as a complication. Oseltamivir has not been proven to prevent such complications. Awareness of the potential for secondary bacterial infection and appropriate treatment of such infections is required.

Heart failure / respiratory disease
The efficacy of oseltamivir in the treatment of cases with chronic heart failure 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).

Paediatric population
There is currently no data available to provide dosage recommendations for preterm infants (postmenstrual age <36 weeks).

Severe renal impairment
In adolescents (aged 13–17 years) and adults with severe renal impairment, dose adjustment is recommended during the treatment and prophylaxis of influenza. Clinical data are insufficient to recommend any dosage in infants and children (aged 1 year or older) with renal impairment (see Sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction
The pharmacokinetic properties of oseltamivir, including its low plasma protein binding and metabolism independent of the cytochrome P450 and glucuronidase systems, indicate that it is unlikely to cause drug interactions via these mechanisms (see Section 5.2).

Renal elimination
Clinically significant drug interactions involving competition for renal tubular secretion are unlikely, based on the known safety margin of these drugs, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion), and the excretion capacity of these pathways. However, caution should be exercised when prescribing oseltamivir to patients taking drugs that are eliminated by the same pathway and have a narrow therapeutic range (e.g., chlorpropamide, methotrexate, phenylbutazone).

Influenza Virus Vaccine (Live/Attenuated):
Antiviral Agents (Influenza A and B) may reduce the therapeutic effect of the Influenza Virus Vaccine (Live/Attenuated). Avoid anti-influenza antivirals for a period starting 48 hours before and ending 2 weeks after administration of the live influenza virus vaccine.

Probenecid
No dose adjustment is necessary in patients with normal renal function when used concomitantly with probenecid. Concomitant use with probenecid, a potent inhibitor of anionic tubular secretion in the kidney, results in an approximately twofold increase in active metabolite concentration.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that interaction between oseltamivir and this pathway is weak.

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite and paracetamol, acetylsalicylic acid, cimetidine or antacids (magnesium and aluminium hydroxides and calcium carbonates), warfarin or rimantadine have been observed.

Additional information for specific populations
No interaction studies have been conducted in special populations.

Paediatric population:
No interaction studies have been conducted in the paediatric population.

4.6 Fertility, pregnancy and lactation
General advice
Pregnancy category: C

Women of childbearing potential/Contraception
There is no recommendation regarding the use of the drug in women of childbearing potential and those using contraception.

Pregnancy
Influenza is associated with adverse pregnancy and foetal outcomes, including congenital malformations such as congenital heart defects. A large amount of data from post-marketing reports and observational studies indicate that no malformations or foetal or neonatal toxicity associated with oseltamivir occurred in pregnant women exposed to oseltamivir (more than 1,000 exposed during the first trimester).

However, one observational study reported inconclusive results for major congenital heart defects diagnosed within 12 months after birth, although the overall risk of malformations did not increase. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 babies out of 397 pregnancies), compared to 1.01% in pregnancies not exposed to oseltamivir in the general population (estimated risk ratio 1.75, 95% CI 0.51-5.98). As the study was limited, the clinical significance of this finding is unclear. Furthermore, this study was too small to reliably assess individual types of major malformations, and women exposed to oseltamivir and those not exposed could not be fully compared, particularly with regard to whether or not they had influenza.

Animal studies have not shown reproductive toxicity (see Section 5.3).

FLUZAVIR should not be used during pregnancy unless necessary. If necessary during pregnancy, FLUZAVIR may be used after evaluating the available safety and benefit information (for benefit information in pregnant women, see Section 5.1) and the pathogenicity of the circulating influenza virus strain.

Lactation
Studies in lactating rats have shown that oseltamivir and its active metabolite are excreted in milk. There is very limited data on the excretion of oseltamivir in human milk. Limited data indicate that oseltamivir and its active metabolite are detected in breast milk, but the levels detected in milk are very low and therefore it is expected that less than a therapeutic dose would be passed to the infant. Considering the pathogenicity of the circulating influenza virus strain

and the underlying condition of the breastfeeding mother, oseltamivir may be considered in situations where there are clear potential benefits for breastfeeding mothers.

Reproductive ability/Fertility
Preclinical data indicate that oseltamivir has no effect on female or male fertility (see Section 5.3).

4.7 Effects on the ability to drive and use machines
FLUZAVIR has no effect on the ability to drive and use machines.

4.8 Undesirable effects
Summary of safety profile
The safety profile of oseltamivir is based on data from clinical studies involving 6,049 adults or adolescents and 1,473 paediatric patients who received oseltamivir or placebo for the treatment of influenza, and 3,990 adults or adolescents and 253 paediatric patients who received oseltamivir or placebo for the prophylaxis of influenza. Additionally, 199 adult patients with immunodeficiency received oseltamivir for influenza treatment, while 475 patients with immunodeficiency (including 18 paediatric patients, 10 receiving oseltamivir and 8 receiving placebo) received oseltamivir or placebo for influenza prophylaxis.

The most commonly reported adverse effects in adults or adolescents were vomiting and nausea in treatment studies and nausea in prophylaxis studies. The majority of these adverse effects were reported on the first or second day of treatment following the first dose and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse effect is vomiting. In most patients, these side effects did not require discontinuation of oseltamivir treatment.

Since oseltamivir was introduced to the market, the following serious adverse reactions have been reported rarely: anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic dysfunction and jaundice), angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal haemorrhage, and neuropsychiatric disorders (for neuropsychiatric disorders, see Section 4.4).

Tabulated list of adverse reactions
Adverse drug reactions are listed below according to the frequency defined as follows:
Very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Adverse effects have been added to the appropriate categories in the tables based on pooled analyses from clinical trials.

Treatment and prevention of influenza in adults and adolescents:

The most common adverse drug reactions or effects derived from post-marketing experience following use at the recommended dose (75 mg twice daily for five days for influenza treatment and 75 mg once daily for up to six weeks for influenza prophylaxis) in studies investigating the treatment and prevention of influenza in adults and adolescents are shown in Table 1 below.

The safety profile reported in individuals using oseltamivir at the recommended dose for influenza prophylaxis (75 mg once daily for up to 6 weeks) is qualitatively similar to that seen in influenza treatment studies, despite the longer dosing duration.

Table 1: Most common adverse reactions observed in studies or post-marketing experience with oseltamivir for influenza treatment or prophylaxis in adults and adolescents

System Organ Class	Adverse Effects by Frequency of Occurrence			
	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 diseases			Hypersensitivity reaction	Anaphylactic reactions, anaphylactoid reactions
Psychiatric disorders				Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucinations, nightmares, self-harm
Nervous system disorders	Headache	Insomnia	Variability in level of	

			consciousness, convulsions	
Eye diseases				Visual impairment
Cardiac diseases			Cardiac arrhythmia	
Respiratory, chest disorders and mediastinal diseases		Cough, sore throat, rhinorrhoea		
Gastrointestinal diseases	Nausea	Vomiting, abdominal pain (including upper abdominal pain), dyspepsia		Gastrointestinal bleeding, haemorrhagic colitis
Hepatobiliary diseases			Liver enzyme elevation	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 disorders related to the application site		Pain, dizziness (including vertigo), fatigue, pyrexia, pain in the arms and legs		

Influenza treatment and prophylaxis in children:

A total of 1,473 children (otherwise healthy children aged 1–12 years and asthmatic children aged 6–12 years) participated in clinical trials of oseltamivir for influenza treatment. Of these children, 851 received oseltamivir suspension treatment. In a post-exposure prophylaxis study in household groups (n=99), another 6-week paediatric prophylaxis study (n=49), and a 12-week paediatric seasonal prophylaxis study in immunocompromised individuals (n=10), a total

of 158 children received oseltamivir once daily at the recommended dose. Table 2 shows the most frequently reported adverse effects in paediatric clinical studies.

Table 2: Most common adverse drug reactions (age/weight-based dosing, 30-75 mg once daily) in studies investigating oseltamivir for influenza treatment and prophylaxis in children

System Organ Class	Adverse Effects by Frequency of Occurrence		
	Very common	**Common**	**Uncommon**
Infections and infestations		Otitis media	
Nervous system diseases		Headache	
Eye diseases		Conjunctivitis (including redness, discharge, and pain in the eye)	
Ear and inner ear diseases		Ear pain	Tympanic membrane disorders
Respiratory, chest disorders and mediastinal diseases	Cough, nasal congestion	Rhinorrhoea	
Gastrointestinal diseases	Vomiting	Abdominal pain (including upper abdominal pain), dyspepsia, nausea	
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)

The following serious adverse effects are described below.

Psychiatric disorders/Nervous system disorders
Influenza may be associated with various neurological and behavioural symptoms, including hallucinations, delirium, and abnormal behaviour, which in some cases may be fatal. These events may occur in cases of encephalitis or encephalopathy, but may also occur without severe illness.

During post-marketing oseltamivir treatment, convulsions and delirium (involving symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported in a few cases, resulting in accidental injury or death. These events have been reported particularly in paediatric and adolescent patients and have often been described as sudden onset and rapidly resolving. The contribution of oseltamivir to these types of events is unknown. Such neuropsychiatric events have also been reported in influenza patients not receiving oseltamivir.

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

Additional information for specific populations:
Geriatric population and patients with chronic heart and/or respiratory failure: The population included in influenza treatment studies consists of other healthy adults/adolescents and "at-risk" patients (patients at high risk of developing influenza-related complications, e.g., elderly people and those with chronic heart or respiratory failure). In general, the safety profile in patients "at risk" is similar to that in other healthy adults or adolescents.

Paediatric population (children under one year of age):
In two studies examining the pharmacokinetic, pharmacodynamic, and safety profile of oseltamivir treatment in 135 children under one year of age with influenza infection, the safety profile was found to be similar across age groups, with vomiting, diarrhoea, and rash being the most commonly reported adverse events. There is insufficient data for infants with a post-conception age of less than 36 weeks.

Based on prospective and retrospective observational studies (covering more than 2,400 children in this age group), an epidemiological database study, and post-marketing reports, the available safety data on the use of oseltamivir for influenza treatment in children under one year of age suggest that the safety profile in children under one year of age is similar to the established safety profile in children aged one year and older.

Patients with immunodeficiency:
In a double-blind study for influenza treatment, a total of 199 adult patients with immunodeficiency (evaluable for safety) were randomised to receive oseltamivir for 10 days: 98 patients received the standard dose (75 mg twice daily) and 101 patients received the double

dose (150 mg twice daily). The safety profile of oseltamivir observed in this study is consistent with that observed in previous clinical studies of oseltamivir for influenza treatment in patients without immunodeficiency (other healthy patients or "at-risk" patients [e.g., those with respiratory and/or cardiac comorbidities]). The percentage of patients reporting adverse events was lower in the standard dose group compared to the double dose group (49% versus 59.4%, respectively) (see Section 5.1).

The safety profile observed in 238 patients in a 12-week prophylaxis study involving 475 immunocompromised patients, including 18 paediatric patients aged 1–12 years, is consistent with that observed in previous clinical studies of oseltamivir prophylaxis.

Children with a history of asthma:
In general, the adverse effect profile observed in children with a history of bronchial asthma is qualitatively similar to that observed in healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose
Cases of overdose with oseltamivir have been reported in clinical trials and during the post-marketing period. In the majority of these cases, no adverse events were reported.

The adverse events reported following overdose are similar to the undesirable effects seen at the recommended therapeutic doses of oseltamivir and described in Section 4.8.

There is no known specific antidote.
Paediatric population
Overdose has been reported more frequently in children than in adults and adolescents. Care should be taken when preparing oseltamivir oral suspension and when administering FLUZAVIR products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors
ATC code: J05AH02

Mechanism of action
Oseltamivir phosphate is a prodrug 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 newly formed viral particles from infected cells and the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits the neuraminidase enzymes of influenza A and B viruses in *vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication in vitro. Orally administered oseltamivir inhibits influenza A and B virus replication and pathogenicity in vivo in animal models of influenza infection, and this effect is similar to that achieved in humans with 75 mg twice daily.

The antiviral efficacy of oseltamivir has been supported by experimental challenge studies in healthy volunteers for influenza A and B.

The neuraminidase enzyme IC50 values of oseltamivir are between 0.1 nM and 1.3 nM for clinically isolated influenza A and 2.6 nM for influenza B. Higher IC50 values (average 8.5 nM) for influenza B have been observed in published studies.

Clinical studies:
Treatment of influenza infection
The indication is based on clinical studies of naturally occurring influenza, with influenza A infection being predominant.

Oseltamivir is only effective against diseases caused by the influenza virus. Therefore, statistical analysis is presented only for subjects infected with influenza. In the mixed treatment study population (ITT), which included both influenza-positive and influenza-negative subjects, primary efficacy decreased proportionally with the number of influenza-negative individuals. Influenza infection was confirmed in 67% (range 46% to 74%) of patients enrolled in the total treatment population. 64% of elderly patients were influenza-positive, and 62% of those with chronic cardiac and/or respiratory disease were influenza-positive. In all phase III treatment studies, patients were enrolled only during periods when influenza was circulating in the local community.

Adults and adolescents aged 13 years and older:
Patients were selected from those reporting symptom onset within 36 hours, with a temperature ≥ 37.8 °C and at least one respiratory symptom (cough, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweating, fatigue, tiredness, or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2413) participating in the treatment studies, 75 mg oseltamivir administered twice daily for five days reduced the median duration of influenza illness by 1 day to 4.2 days (95% CI (confidence interval) 4.0–4.4 days; $p \leq 0.0001$); in the placebo group, this figure was 5.2 days (95% CI 4.9–5.5 days).

The proportion of subjects developing lower respiratory tract complications (particularly bronchitis) treated with antibiotics was 12.7% (135/1063) in the placebo group and decreased to 8.6% (116/1350) in the oseltamivir-treated population (p = 0.0012).

Treatment of influenza in high-risk populations:
In elderly patients (≥ 65 years) and cases with chronic cardiac and/or respiratory disease who received 75 mg oseltamivir twice daily for five days, the median duration of influenza illness was not significantly reduced. The total duration of fever was reduced by one day in the oseltamivir group. In influenza-positive elderly patients, the incidence of lower respiratory tract complications (especially bronchitis) decreased from 19% (52/268) in the placebo group treated with antibiotics to 12% (29/250) in the population treated with oseltamivir (p = 0.0156).
In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (especially bronchitis) treated with antibiotics was 17% (22/133) in the placebo group, it was 14% (16/118) in the oseltamivir-treated population (p = 0.5976).

Treatment of influenza during pregnancy:
There are no controlled clinical studies on the use of oseltamivir in pregnant women, but data from post-marketing and retrospective observational studies indicate that the current dosage regimen is appropriate for this patient population in terms of morbidity/mortality. Although pharmacokinetic studies indicate low exposure to the active metabolite, dose adjustment is not recommended for pregnant women receiving influenza treatment or prophylaxis.

Treatment of influenza in children:
In a study of otherwise healthy children aged 1 to 12 years (mean age 5.3 years) with fever (≥37.8 °C) and cough or rhinitis (65% influenza-positive), 67% of influenza-positive patients were infected with influenza A and 33% with influenza B. Oseltamivir treatment started within 48 hours of symptom onset significantly reduced the duration of illness (return to normal health and activity, resolution of fever, cough, and runny nose) by approximately 1.5 days compared to placebo (95% CI 0.6–2.2 days; p <0.0001). Oseltamivir reduced the incidence of acute otitis media from 26.5% (53/200) in the placebo group to 16% (29/183) in children treated with oseltamivir (p = 0.013).
The second study was completed in 334 asthmatic children aged 6 to 12 years, 53.6% of whom were influenza-positive. The average duration of illness did not decrease significantly in the group treated with oseltamivir. From day 6 onwards (the last day of treatment), ZEV (forced expiratory volume in 1 second) increased from 4.7% in the placebo group to 10.8% in the oseltamivir-treated group (p = 0.0148).

The indication for infants under 1 year of age is based on extrapolation of efficacy data from older children, and the recommended posology is based on pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection:
Overall, with rates ranging from 1% to 33% across studies, 15% of the influenza-positive population was infected with influenza B. The mean duration of illness in influenza B-infected cases did not differ significantly between treatment groups. Data from 504 influenza B-infected cases from all studies were pooled for analysis. Compared to placebo, oseltamivir reduced the time to resolution of all symptoms by 0.7 days (95% CI 0.1–1.6 days; p = 0.022), reduced the duration of cough and fever (≥ 37.8 °C), and nasal congestion by one day (95% CI 0.4–1.7 days; p < 0.001).

Treatment of influenza in adults with immunodeficiency:
A randomised, double-blind study to assess the safety of oseltamivir in immunocompromised adults affected by influenza and to characterise its effects on the development of resistant influenza virus (primary analysis) included 151 patients who could be evaluated for the efficacy of oseltamivir (secondary analysis, unpowered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV-positive patients with CD4+ cell counts <500 $^{cells/mm^3}$, patients receiving systemic immunosuppressive therapy, and those with haematological malignancies. These patients were randomised to receive oseltamivir at a standard dose (73 patients) or double dose (78 patients) for 10 days within 96 hours of symptom onset.

The median time to resolution of symptoms (TTRS) was similar between the standard dose group (103 hours [90% CI 75.4-110]) and the double dose group (104 hours [90% CI 65.8-131]). The proportion of patients with secondary infections was similar in the standard dose group and the double dose group (5.1% versus 8.2%).

Prevention of influenza:
The efficacy of oseltamivir in preventing naturally occurring influenza has been demonstrated in a household exposure prophylaxis study and two seasonal prophylaxis studies. The primary efficacy parameter for all these studies is the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is unpredictable and varies by region and season. Therefore, the number of people who need to be treated for prophylaxis for one case of influenza also varies.

Post-exposure prophylaxis:
In a study of individuals exposed to an index influenza case (12.6% of whom were vaccinated against influenza), treatment with 75 mg of oseltamivir once daily was initiated within 2 days of symptom onset in the index case and continued for 7 days. Influenza was confirmed in 163 of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza in individuals exposed to confirmed influenza cases; it was 24/200 (12%) in the placebo group and 2/205 (1%) in the oseltamivir group (92% reduction [95% CI 6–16; p ≤ 0.0001]). The number needed to treat among individuals exposed to genuine influenza cases was 10 (95% CI

9–12) and 16 (95% CI 15–19) in the entire population (ITT), regardless of the infection status of the index case.

The efficacy of oseltamivir in the prophylaxis of naturally occurring influenza disease has been demonstrated in a post-exposure prophylaxis study in households including adults, adolescents, and children aged 1–12 years, both as index cases and household contacts. The primary efficacy parameter in this study was the incidence of laboratory-confirmed clinical influenza in households. Oseltamivir prophylaxis lasted 10 days. In the total population, the incidence of laboratory-confirmed clinical influenza in households decreased; being 20% (27/136) in those not receiving prophylaxis treatment and 7% (10/135) in those receiving prophylaxis treatment (a 62.7% reduction [95% CI 26.0–81.2; p = 0.0042]). In index cases infected with influenza in households, the incidence of influenza decreased from 26% (23/89) in those not receiving prophylactic treatment to 11% (9/84) in those receiving prophylactic treatment (58.5% decrease [95% CI 15.6–79.6; p = 0.0114]). According to the subgroup analysis of children aged 1 to 12 years, the incidence of laboratory-confirmed clinical influenza was significantly reduced in children; from 19% (21/111) in those not receiving prophylactic treatment to 7% (7/104) in those receiving prophylactic treatment (64.4% reduction [95% CI 15.8–85.0; p = 0.0188]). The incidence of laboratory-confirmed clinical influenza decreased in children who were not initially spreading the virus; it was 21% (15/70) in those not receiving prophylactic treatment and 4% (2/47) in those receiving prophylactic treatment (80.1% decrease [95% CI 22.0–94.9; p = 0.0206]).For the total paediatric population, the number needed to treat (NNT) was 9 (95% CI 7–24) in the entire population (ITT) and 8 (95% CI 6, upper limit not defined) in paediatric individuals exposed to infected index cases (ITTII).

Prophylaxis during an influenza epidemic in the community:
During an influenza outbreak, a pooled analysis of two studies in otherwise healthy unvaccinated adults showed that 75 mg oseltamivir administered once daily for 6 weeks significantly reduced the incidence of clinical influenza illness; compared with 25/519 (4.8%) in the placebo group and 6/520 (1.2%) in the oseltamivir group (76% reduction [95% CI 1.6–5.7; p = 0.0006]).
The number needed to treat in this study was 28 (95% CI 24–50). In a study of elderly people in nursing homes, 80% of participants were vaccinated during the study period and received 75 mg of oseltamivir once daily for 6 weeks; the incidence of clinical influenza illness was significantly reduced. This was 12/272 (4.4%) in the placebo group and 1/276 (0.4%) in the oseltamivir group (92% reduction [95% CI 1.5–6.6; p = 0.0015]). The number needed to treat in this study was 25 (95% CI 23–62).

Influenza prophylaxis in immunocompromised patients:
In 475 cases of immunodeficiency (including 18 children aged 1–12 years; 388 solid organ transplant cases [195 placebo; 193 oseltamivir], 87 haematopoietic stem cell transplant cases [43 placebo; 44 oseltamivir], no cases with other immunosuppressive conditions), a double-blind, placebo-controlled, randomised trial was conducted for seasonal influenza prophylaxis.

The primary endpoint of this study was the incidence of laboratory-confirmed clinical influenza cases with a fourfold increase in viral culture and/or haemagglutination inhibition (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% to 4.1%; p = 0.772).

No specific studies have been conducted to assess the reduction in the risk of complications.

Oseltamivir resistance
Clinical studies: Clinical studies with oseltamivir have examined the risk of decreased susceptibility or resistance development of influenza virus to oseltamivir. Patients who developed oseltamivir-resistant virus during treatment were generally more common in children than in adults; less than 1% in adults and 18% in infants under 1 year of age. Compared to patients carrying oseltamivir-sensitive viruses, oseltamivir-resistant viruses were detected for a longer period in paediatric patients. However, the side effects associated with oseltamivir treatment did not affect the treatment response and did not cause a prolongation of influenza symptoms.

Compared to data from studies conducted in adults without other illnesses who were treated with oseltamivir, a generally higher incidence of oseltamivir resistance was observed in adult patients with immunodeficiency who were treated with standard or double doses of oseltamivir for 10 days [standard dose group (10/67) and double dose group 2.8% (2/71)]. The majority of patients who developed resistance were transplant patients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most patients with oseltamivir-resistant virus were infected with influenza type A and had experienced prolonged viral infection.

Incidence of Oseltamivir Resistance in Clinical Trials

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

* Full genotyping was not performed in all studies.

Influenza Prophylaxis
To date, no evidence of drug resistance associated with oseltamivir use has been found in clinical studies conducted in immunocompetent patients for influenza prophylaxis after exposure to the disease (7 days), after exposure in household groups (10 days), and seasonally (42 days). No resistance was observed in a 12-week prophylaxis study in immunocompromised patients.

Clinical and observational data: Natural mutations associated with reduced susceptibility to oseltamivir in *vitro* have been detected in influenza A and B viruses obtained from patients not receiving oseltamivir. Resistant strains selected during oseltamivir treatment were obtained from both immunocompetent individuals and immunocompromised individuals. Immunocompromised patients and young children are at higher risk of developing oseltamivir-resistant viruses during treatment.
Oseltamivir-resistant viruses isolated from patients treated with oseltamivir and oseltamivir-resistant laboratory strains of influenza virus contain mutations in the N1 and N2 neuraminidases. Resistance mutations tend to be specific to the viral subtype. Since 2007, the H275Y mutation associated with resistance has become widespread in seasonal H1N1 strains. The rate of decrease in oseltamivir susceptibility and the prevalence of these viruses vary seasonally and geographically. In 2008, H275Y was present in over 99% of H1N1 influenza isolates in Europe.
In 2009, H1N1 influenza ("swine flu") is almost uniformly susceptible to oseltamivir, with the exception of rarely reported cases of resistance in therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General properties

Absorption:

Oseltamivir is rapidly absorbed from the gastrointestinal tract following oral administration of oseltamivir phosphate (prodrug) and is extensively converted to its active metabolite (oseltamivir carboxylate) by hepatic esterases. At least 75% of the oral dose reaches the systemic circulation as the active metabolite. Exposure to the prodrug is less than 5% of that to the active metabolite. Plasma concentrations of the prodrug and active metabolite are dose-proportional and are not affected by co-administration with food.

Distribution:

The mean steady-state volume of distribution of oseltamivir carboxylate in humans is approximately 23 litres, which is equivalent to extracellular body fluid. Since neuraminidase activity occurs extracellularly, oseltamivir carboxylate distributes to all sites where the influenza virus is present.

The binding of oseltamivir carboxylate to human plasma protein is negligible (approximately 3%).

Biotransformation:

Oseltamivir is largely converted to oseltamivir carboxylate by esterases, mainly located in the liver. *In vitro* studies have shown that oseltamivir and its active metabolite are not substrates or inhibitors of the major cytochrome P450 isoforms. *In vivo*, no phase 2 conjugates of either compound are found.

Elimination:

Absorbed oseltamivir is primarily eliminated (>90%) as oseltamivir carboxylate. The active metabolite is excreted in the urine without further metabolism. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most cases. The active metabolite is completely eliminated via the renal route. Renal clearance (18.8 L/hour) exceeds the glomerular filtration rate (7.5 L/hour), indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20% of the labelled oral dose is excreted in the faeces.

Linearity/non-linearity:
Plasma concentrations of the active metabolite are proportional to the dose and remain unchanged when the drug is taken with food (see Section 4.2).

Additional information on specific populations
Renal impairment:
Administration of 100 mg oseltamivir twice daily for 5 days to patients with varying degrees of renal impairment demonstrated an inverse relationship between active metabolite concentration and renal dysfunction (see Section 4.2).

Hepatic impairment:
In vitro studies concluded that neither a significant increase in oseltamivir exposure nor a significant decrease in active metabolite exposure is expected in patients with hepatic impairment (see Section 4.2).

Geriatric population:
When young adults given oseltamivir at comparable doses were compared with elderly patients (aged 65-78 years), steady-state active metabolite concentrations were found to be 25-35% higher in elderly patients. The half-lives of the drug in elderly patients were approximately the same as in young adults. In terms of drug exposure and tolerance, no dose adjustment is necessary in elderly patients unless there is evidence of moderate or severe renal impairment (, i.e., creatinine clearance not below 60 mL/min) (see Section 4.2).

Paediatric population:
Infants and children aged 1 year and older
The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in children aged 1 to 16 years. Multiple-dose pharmacokinetics have been studied in a clinical efficacy study involving a small number of children. For the administered dose (mg/kg), it was observed that younger children eliminated the prodrug and active metabolite more rapidly than adults, resulting in lower exposure. Comparable oseltamivir carboxylate concentrations were observed in children given a 2 mg/kg dose and adults given a single 75 mg (approximately 1 mg/kg) capsule. The pharmacokinetics of oseltamivir in children aged 12 years and older and adolescents are similar to those observed in adults.

Prevention of influenza in newborns and infants under 1 year of age during a pandemic

In simulations, the exposure provided by a dose of 3 mg/kg once daily in newborns under 1 year of age was found to be within the same range or higher than the exposure seen with a dose of 75 mg once daily in adults. Exposure does not exceed the limits in infants under 1 year of age (3 mg/kg twice daily) during treatment and is expected to show a comparable safety profile (see Section 4.8). No clinical studies on prophylaxis have been conducted in infants under 1 year of age.

Newborns and infants under 1 year of age

The pharmacokinetics, pharmacodynamics, and safety of oseltamivir were evaluated in two uncontrolled open-label studies in infants under 1 year of age (n=135). The body weight-adjusted active metabolite clearance rate is reduced in those under 1 year of age. Exposure to metabolites showed greater variability in the smallest neonates. Current data indicate that exposure achieved with a 3 mg/kg dose in 0-12 month-old neonates is similar to the clinically effective exposure seen in children and adults (see Sections 4.1 and 4.2). Reported adverse events are consistent with the safety profile obtained in older children.

There are no data available on influenza prophylaxis following exposure in infants under 1 year of age. There are no studies on prophylaxis during influenza epidemics in children under 12 years of age.

Pregnant women

Population pharmacokinetic studies indicate that exposure to the active metabolite is lower in pregnant women than in non-pregnant women at the current oseltamivir dose regimen (approximately 30% lower on average across all trimesters). However, the expected lower exposure remains above the inhibitory concentration (IC95) and at therapeutic levels for influenza virus. In addition, observational studies have found evidence that the current dosage regimen is beneficial in this patient population. Therefore, no dose adjustment is recommended in pregnant women for influenza treatment or prophylaxis (see Section 4.6).

Patients with Immunodeficiency

Population pharmacokinetic analysis indicates that treatment with oseltamivir in adult patients with immunodeficiency (as described under Section 4.2. Posology and method of administration) results in increased exposure to the active metabolite (up to 50%) compared to patients without immunodeficiency who have similar creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustment is necessary in adults with immunodeficiency. However, for adult patients with immunodeficiency accompanied by renal impairment, doses should be adjusted as summarised in Section 4.2. Dosage and administration.

5.3 Preclinical safety data

Preclinical data, based on commonly used safety pharmacology, repeated-dose toxicity, and genotoxicity studies, do not indicate any hazard to humans. According to the findings of conventional rodent carcinogenicity studies, there is a dose-dependent increase in the incidence of certain tumours that are characteristic of the rodent species used. These findings do not

alter the benefit-risk balance of oseltamivir in the accepted therapeutic indications when exposure limits are considered in relation to expected exposure in humans.

Teratology studies were conducted in rats and rabbits at maximum doses of 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A fertility study conducted in rats at a maximum dose of 1500 mg/kg/day revealed no adverse effects in either sex. In prenatal and postnatal rat studies, delayed births were recorded at a dose of 1500 mg/kg/day: The safety margin between human exposure and the no-effect dose in rats (500 mg/kg/day) is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in rats and rabbits is approximately 15 to 20% of maternal exposure.

Oseltamivir and the active metabolite have been excreted into milk in lactating rats. Limited data are available on whether oseltamivir or the active metabolite are excreted into human milk. Extrapolation of animal data suggests estimates of 0.01 mg/day and 0.3 mg/day, respectively, for the relevant compounds.

In a "maximisation" study conducted in guinea pigs, a potential for skin sensitisation to oseltamivir was identified. Erythema was observed in approximately 50% of animals treated with the unformulated active substance following challenge in induced animals. Reversible irritation was observed in the eyes of rabbits.

Very high oral single doses of oseltamivir phosphate, up to the highest dose tested (1310 mg/kg), produced no adverse reactions in adult rats, but these doses resulted in toxicity, including death, in 7-day-old juvenile rats. These reactions were observed at doses of 657 mg/kg and higher.

No adverse reactions were observed at a dose of 500 mg/kg (administered at 500 mg/kg/day between days 7 and 21 post-birth), including following chronic treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-gelatinised starch
Croscarmellose sodium
Povidone
Talc
Sodium stearyl fumarate
Hard gelatin capsule contents:
Titanium dioxide
Yellow iron oxide
Deionised water
Gelatin (bovine gelatin)
Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Must be stored at room temperature below 25°C.

A suspension prepared from the capsule with water containing 0.05% sodium benzoate by weight/volume should be used within 10 days if stored at room temperature below 25°C, or within 17 days if stored at 2°C–8°C. The suspension prepared from the capsule using sugar water, chocolate syrup, cherry syrup, or caramel should be used immediately.

6.5 Nature and contents of container
Transparent PVC/PE/PVDC blister and aluminium foil are used as the primary packaging materials for our product. The blisters are packaged in cardboard boxes. Each box contains blister packs with 10 capsules, accompanied by a package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Formulation prepared at the time of use
Adults, adolescents, or children who cannot swallow capsules may use FLUZAVIR suspension (6 mg/mL) prepared by a pharmacist from FLUZAVIR capsules.

The pharmacy-prepared preparation should be preferred over the home-prepared preparation. Detailed information on home preparation can be found under the heading "Home preparation of FLUZAVIR solution".

An appropriate volume and graduated syringe should be used to administer the suspension prepared at the pharmacy to the patient and for preparation at home. In both cases, the syringe should preferably have volume markings.

Preparation at the pharmacy
6 mg/mL suspension prepared from capsules at the pharmacy
➢ *Adults, adolescents, infants, and children aged 1 year or older who cannot swallow capsules*
This procedure describes the preparation of a 6 mg/mL concentration solution to provide a sufficient dose for a patient's 5-day treatment or 10-day prophylaxis.

The pharmacist may prepare a 6 mg/mL preparation using FLUZAVIR 30 mg, 45 mg, or 75 mg capsules and water containing 0.05% w/v sodium benzoate as a preservative.

First, the total volume to be prepared and administered to the patient for their 5-day treatment or 10-day prophylaxis is calculated. The required total volume should be calculated according to the recommendations in the table below, based on the patient's weight. To ensure the correct volume is drawn up for up to 10 doses (2 doses drawn up daily for a 5-day treatment), the column indicating measurement loss should be taken into account.

Volume of Suspension (6 mg/mL) to be Prepared by the Pharmacist Based on the Patient's Weight

Body Weight (kg)	Total Volume (mL) to be Prepared Based on Patient Weight, Without Considering Measurement Losses	Total Volume (mL) to be Prepared According to Patient Weight, Taking Measurement Losses into Account
10 to 15 kg	50 mL	60 mL or 75 mL*
> 15 to 23 kg	75 mL	90 mL or 100 mL*
> 23 to 40 kg	100 mL	125 mL
> 40 kg	125 mL	137.5 mL (or 150 mL)*

* Depends on the capsule dosage used.

Secondly, the number of capsules and the amount of carrier solution (water containing 0.05% w/v sodium benzoate as a preservative) required to create the total volume of the 6 mg/mL suspension to be prepared at the pharmacy, as calculated according to the table above, must be determined by the pharmacist.

Number of Capsules and Amount of Carrier Solution Required to Form the Total Volume of the Suspension (6 mg/mL) to be Prepared at the Pharmacy

Total Volume of Suspension to be Prepared	Number of FLUZAVIR capsules required (mg oseltamivir)			Required Carrier Solution Volume
	75 mg	45 mg	30 mg	
60 mL	Use alternative capsule dosage*	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	Use alternative capsule dosage*	12 capsules (540 mg)	18 capsules (540 mg)	89 mL
100 mL	8 capsules (600 mg)	Use alternative capsule dosage*	20 capsules (600 mg)	98.5 mL
125 mL	10 capsules (750 mg)	Use alternative capsule dosage*	25 capsules (750 mg)	123.5 mL

137.5 mL	11 capsules (825 mg)	Use the alternative capsule dose*	Use alternative capsule dosage*	136 mL

*The exact number of capsules required to achieve the target concentration cannot be calculated; therefore, the alternative capsule dose should be used.

Thirdly, to prepare a suspension (6 mg/mL) using FLUZAVIR capsules, the following procedure should be followed:
1. The specified amount of carrier solution (water containing 0.05% sodium benzoate as a preservative) is added to the beaker.
2. The specified number of FLUZAVIR capsules are opened and their contents are poured into the preservative-containing water solution in the beaker.
3. Mix for 2 minutes using a suitable mixing device. (Note: The active ingredient, oseltamivir phosphate, is completely soluble in water. The suspension is formed due to some insoluble excipients in the FLUZAVIR capsules.) Transfer the suspension to an amber glass or polyethylene terephthalate (PET) bottle. A funnel may be used during transfer to prevent spillage.
4. The bottle is sealed with a child-resistant cap.
5. A label stating "Shake gently before use" is affixed to the bottle. (Note: The suspension should be shaken before use to prevent air pockets.)
6. Parents or carers should be warned that any remaining solution must be discarded after the entire dose has been administered to the patient. This warning should be explained on a label affixed to the bottle by the pharmacy.
7. The expiry date specified according to the storage conditions described below should be explained on the label affixed to the bottle by the pharmacy (see Section 6.3).

The pharmacy must affix a label to the bottle containing the patient's name, the name of the medicine, and other necessary information. Refer to the table below for appropriate dosing instructions.

Dosage Schedule for 6 mg/ml Suspension Prepared at the Pharmacy Using FLUZAVIR Capsules for Infants, One-Year-Old Children, or Children Over One Year of Age

Body Weight (kg)	**Dose (mg)**	**Per Dose Volume 6 mg/mL**	**Therapeutic Dose (5 days)**	**Prophylactic Dose (10 days)**
10 kg to 15 kg	30 mg	5 mL	Twice daily, 5 mL	5 mL once daily
> 15 to 23 kg	45 mg	7.5 mL	Twice daily 7.5 mL	Once daily 7.5 mL
> 23 to 40 kg	60 mg	10 mL	Twice daily 10 mL	Once daily 10 mL
> 40 kg	75 mg	12.5 mL	Twice daily 12.5	Once daily 12.5

			mL	mL

The suspension prepared at the pharmacy is administered to the patient using a graduated oral syringe to measure small amounts. If possible, the graduations corresponding to the appropriate dose for each patient should be marked.

The suspension at the appropriate dose should be administered by the caregiver, mixed with an equal amount of sweetened water, chocolate syrup, cherry syrup, caramel or other sweet food to mask the bitter taste of the medicine.

➢ *Infants Under 1 Year of Age*
This procedure describes the preparation of a solution at a concentration of 6 mg/mL to provide a sufficient dose for a patient's 5-day treatment or 10-day prophylaxis.

The pharmacist can prepare the suspension (6 mg/mL) using FLUZAVIR 30 mg, 45 mg or 75 mg capsules and water containing sodium benzoate at a ratio of 0.05 a/h as a preservative.

First, the total volume to be prepared and administered to each patient is calculated. The required total volume should be calculated according to the recommendations given in the table below, based on the patient's weight. To ensure the correct volume is drawn up for up to 10 doses (2 doses drawn up daily for a 5-day course of treatment), the column indicating measurement loss should be taken into account.

Volume of Suspension (10 mg/mL) to be Prepared Based on Patient Weight

Body Weight (kg)	**Total volume to be prepared according to patient weight (mL) when measurement losses are not taken into account.**	**Total Volume to be Prepared (mL) Based on Patient Weight, Taking Measurement Losses into Account)**
≤ 7 kg	Up to 40 mL	50 mL
> 7 and < 10 kg	50 mL	60 mL or 75 mL*

*Depends on the capsule dose used.

Secondly, the number of capsules and the amount of carrier solution (water containing 0.05% w/v sodium benzoate as a preservative) required to create the total volume of the 6 mg/mL suspension to be prepared at the pharmacy, as calculated according to the table above, must be determined by the pharmacist.

Number of Capsules and Amount of Carrier Solution Required to Form the Total Volume of the Suspension (6 mg/mL) to be Prepared at the Pharmacy

Total Volume of Suspension	**Number of FLUZAVIR capsules required (mg oseltamivir)**	**Required Carrier**

to be Prepared	75 mg	45 mg	30 mg	Solution Volume
50 mL	4 capsules (300 mg)	Use the alternative capsule form*	10 capsules (300 mg)	49.5 mL
60 mL	Use the alternative capsule form*	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

*The exact number of capsules required to achieve the target concentration cannot be calculated; therefore, an alternative capsule dose should be used.

Thirdly, to prepare a suspension (6 mg/mL) using FLUZAVIR capsules, the following procedure should be followed:
1. The specified amount of carrier solution (water containing 0.05% sodium benzoate as a preservative) is added to the beaker.
2. The specified number of FLUZAVIR capsules are opened and their contents are poured into the preservative-containing water solution in the beaker.
3. Mix for 2 minutes using a suitable mixing device. (Note: The active ingredient, oseltamivir phosphate, is completely soluble in water. The suspension is formed due to some insoluble excipients in the FLUZAVIR capsules.) Transfer the suspension to an amber glass or polyethylene terephthalate (PET) bottle. A funnel may be used during transfer to prevent spillage.
4. The bottle is sealed with a child-resistant cap.
5. A label stating "Shake gently before use" is affixed to the bottle. (Note: The suspension should be shaken before use to prevent air bubbles.)
6. Parents or carers should be warned that any remaining solution must be discarded after the entire dose has been administered to the patient. This warning should be explained on a label affixed to the bottle by the pharmacy.
7. The expiry date, as specified according to the storage conditions described below, should be explained on a label affixed to the bottle by the pharmacy (see Section 6.3).

A label containing the patient's name, the name of the medicine, and other necessary information should be affixed to the bottle by the pharmacy. Refer to the table below for appropriate dosing instructions.

Dosage Schedule for Suspension Prepared at the Pharmacy Using FLUZAVIR Capsules (6 mg/mL) for Infants Under 1 Year of Age

Body Weight (rounded to	Dose (mg)	Volume per dose (6	Treatment Dose	Prophylactic dose	Syringe size to be used

the nearest 0.5 kg)		mg/mL)	(5 days)	(10 days)	(0.1 mL graduated)
3 kg	9 mg	1.5 mL	Twice daily, 1.5 mL	1.5 mL once daily	2 mL or 3 mL
3.5 kg	10.5 mg	1.8 mL	Twice daily 1.8 mL	1.8 mL once daily	2 mL or 3 mL
4 kg	12 mg	2 mL	Twice daily 2 mL	Once daily 2 mL	3 mL
4.5 kg	13.5 mg	2.3 mL	Twice daily 2.3 mL	Once daily 2.3 mL	3 mL
5 kg	15 mg	2.5 mL	Twice daily 2.5 mL	Once daily 2.5 mL	3 mL
5.5 kg	16.5 mg	2.8 mL	Twice daily 2.8 mL	Once daily 2.8 mL	3 mL
6 kg	18 mg	3 mL	Twice daily 3 mL	Once daily 3 mL	3 mL (or 5 mL)
6.5 kg	19.5 mg	3.3 mL	Twice daily 3.3 mL	3.3 mL once daily	5 mL
7 kg	21 mg	3.5 mL	Twice daily 3.5 mL	3.5 mL once daily	5 mL
7.5 kg	22.5 mg	3.8 mL	Twice daily 3.8 mL	Once daily, 3.8 mL	5 mL
8 kg	24 mg	4 mL	Twice daily 4 mL	4 mL once daily	5 mL
8.5 kg	25.5 mg	4.3 mL	Twice daily 4.3 mL	Once daily 4.3 mL	5 mL
9 kg	27 mg	4.5 mL	Twice daily 4.5 mL	4.5 mL once daily	5 mL
9.5 kg	28.5 mg	4.8 mL	Twice daily 4.8 mL	Once daily 4.8 mL	5 mL
10 kg	30 mg	5 mL	Twice daily 5 mL	5 mL once daily	5 mL

The suspension prepared at the pharmacy is administered to the patient using a graduated oral syringe to measure small amounts. If possible, the graduations corresponding to the appropriate dose for each patient should be marked.

The suspension in the appropriate dose should be administered by the caregiver, mixed with an equal amount of sweetened water, cherry syrup, chocolate syrup, caramel or other sweet food to mask the bitter taste of the medicine.

Preparation at Home

When commercially available FLUZAVIR oral suspension is not available, a suspension prepared from FLUZAVIR capsules at a pharmacy may be used (detailed instructions are provided on the previous pages). If it is not possible to prepare the suspension at the pharmacy, it can also be prepared at home.

If the capsule form containing the required dose is available, the capsule is opened and its contents are mixed with no more than one teaspoon of sweet food. The bitter taste of the medicine can be masked by mixing it with sweet foods. This mixture prepared with sweet food should be thoroughly mixed and given to the patient in its entirety. The mixture should be swallowed immediately after preparation.

When only 75 mg capsules are available and 30 mg or 45 mg doses are required, preparing the mixture involves a few additional steps. Detailed instructions are provided in the FLUZAVIR capsule package leaflet.

7. MARKETING AUTHORISATION HOLDER

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