SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUZAVIR 12mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each bottle (30 g) contains 1.182 g of oseltamivir phosphate equivalent to 900 mg oseltamivir as the active ingredient, and each 1 ml suspension contains 15.76 mg of oseltamivir phosphate equivalent to 12 mg oseltamivir as the active substance.

Excipient(s):

Sorbitol 25.713 g (amount in one bottle)
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
A white or off-white powder for oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- When no more than 2 days have passed since the onset of symptoms in children older than 2 weeks and adults (symptom duration may be longer in those at increased risk for influenza infection)
- It is used for influenza prophylaxis in children aged 1 year and over.

The effectiveness of the drug has not been demonstrated when more than 48 hours have elapsed after the onset of symptoms.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

Standard dose for treatment
Treatment should be started on the first or second day of influenza symptoms.

Adults and adolescents (13-17 years old):

The recommended dose for adults and adolescents aged ≥13 years is 75 mg capsules or one 30 mg capsule + one 45 mg capsule for 5 days twice daily. Adults and adolescents aged ≥13 years who cannot swallow capsules may receive 75 mg of oseltamivir suspension twice daily for 5 days.

Infants and children aged 1 year and older:
Recommended oral therapeutic doses of FLUZAVIR for infants and children aged 1 year and older:

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

As an alternative to the recommended doses of FLUZAVIR suspension, FLUZAVIR 30 mg and 45 mg hard gelatin capsules are available.

As an alternative to the recommended doses of FLUZAVIR suspension, children weighing >40 kg who do not have difficulty swallowing capsules may be treated with either 75 mg capsules or one 30 mg capsule + one 45 mg capsule twice daily.

Recommended therapeutic oral doses of FLUZAVIR for infants aged 0-12 months:
The recommended treatment dose for infants aged 0-12 months is 2 mg/kg to 3 mg/kg twice daily. This dose recommendation is based on limited pharmacokinetic data. Based on these data, the majority of infants aged 0 to 12 months treated at the recommended dose achieved clinically effective and safe plasma concentrations of the prodrug and active metabolites comparable to those seen in older children and adults (see Section 5.2).

Below are the recommended dosing regimens based on body weight for treating infants 0-12 months of age.

Age	**Recommended treatment dose for 5 days**
Babies older than 3 months and younger than 12 months	3 mg/kg twice daily
Babies older than 1 months and younger than 3 months	2.5 mg/kg twice daily
* Babies younger than 1 month	2 mg/kg twice daily

* There are no data on the use of FLUZAVIR in infants younger than 1 month of age.

Administration of FLUZAVIR to infants younger than 1 year of age should be decided after the potential benefit of drug treatment against possible risks that may occur in the infant has been carefully evaluated by the doctor.

Age-related dosage recommendations are not for premature infants (i.e., postmenstrual age less than 37 weeks). Current data are insufficient for these patients, who may require different doses because their physiologic functions are not fully developed.

Standard dose for prophylaxis after exposure
- Adults and adolescents (13-17 years old):
Following close contact with infected persons, the recommended oral dose of FLUZAVIR for prophylaxis of influenza is 75 mg capsules or one 30 mg capsule + 45 mg capsules once daily for 10 days. Treatment should be started within two days after close contact with infected persons. Protection continues as long as the drug is continued. Adults and adolescents aged ≥13 years who cannot swallow capsules may take 75 mg FLUZAVIR suspension once daily for 10 days.
- Infants and children aged 1 year or older:
As an alternative to the recommended doses of FLUZAVIR suspension, FLUZAVIR 75 mg, 30 mg and 45 mg capsules are available.

Below are the recommended dosing regimens based on body weight for treating infants under 1 year of age.

Age	**Recommended prophylaxis dose for 10 days**
Babies older than 3 months and younger than 12 months	3 mg/kg twice daily
Babies older than 1 months and younger than 3 months	2.5 mg/kg twice daily
* Babies younger than 1 month	2 mg/kg twice daily

* There are no data on the use of FLUZAVIR in infants younger than 1 month of age.

Administration of FLUZAVIR to babies younger than 1 year of age should be decided after the potential benefit of drug treatment against possible risks that may occur in the baby has been carefully evaluated by the doctor.

Age-related dosage recommendations are not for premature infants (i.e., postmenstrual age less than 37 weeks). Current data are insufficient for these patients, who may require different doses because their physiologic functions are not fully developed.

Protection during a community influenza epidemic:
Protection during a community influenza epidemic has not been studied in children younger than 12 years. The recommended dose for prevention during a community influenza pandemic in adults and adolescents is oseltamivir 75 mg once daily for up to 6 weeks.

Method of administration:
For oral use.

FLUZAVIR can be taken alone or with food (see Section 5.2). When taken with food, FLUZAVIR may increase tolerance in some patients.

There is a dosing syringe in the box for oral suspension. For correct dosing, the dose should be given using the dosing syringe.

It is recommended that FLUZAVIR suspension is prepared by a pharmacist before administration to the patient (see Section 6.6).

Additional information for special populations:
Renal impairment:
When used for the treatment of influenza:
Dose adjustment is not necessary for patients with creatinine clearance above 60 ml/min; 75 mg twice daily can be continued.
Adults and adolescents (13-17 years of age) with moderate or severe renal impairment may require dose adjustment.

Creatinine clearance	**Recommended treatment dose**
> 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)
Patients on hemodialysis	30 mg after each hemodialysis session
Patients on peritoneal dialysis*	30 mg (suspension or capsule) single dose

*Based on results from studies in continuous ambulatory peritoneal dialysis (CAPD) patients, the clearance of oseltamivir carboxylate is expected to be higher when the automatic peritoneal dialysis mode (OPM) is used. The treatment mode can be changed from OPM to CAPD if deemed necessary by the nephrologist.

When used for prophylaxis of influenza:
Dose adjustment is not necessary for patients with creatinine clearance above 60 ml/min; 75 mg once daily can be continued.
Adults and adolescents (13-17 years of age) with moderate or severe renal impairment may require dose adjustment.

Creatinine clearance	**Recommended prophylaxis dose**
> 60 (mL/min)	75 mg twice daily
> 30 - 60 (mL/ min)	30 mg twice daily (suspension or capsule)

> 10 - 30 (mL/ min)	30 mg twice daily (suspension or capsule) for the following days
≤ 10 (mL/ min.)	Not recommended (no data available)
Patients on hemodialysis	30 mg after every second hemodialysis session
Patients on peritoneal dialysis*	30 mg once a week (suspension or capsule)

*Based on results from studies in continuous ambulatory peritoneal dialysis (CAPD) patients, the clearance of oseltamivir carboxylate is expected to be higher when the automatic peritoneal dialysis mode (OPM) is used. The treatment mode can be changed from OPM to CAPD if deemed necessary by the nephrologist.

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

Hepatic impairment:
No dose adjustment is needed for the treatment or prophylaxis of influenza in patients with hepatic impairment (see Section 5.2). The safety and pharmacokinetic properties have not been studied in patients with severe hepatic impairment.
No studies have been conducted in pediatric patients with hepatic impairment.

Pediatric patients:
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 the treatment or prophylaxis of influenza, no dose adjustment is needed in elderly patients unless there is evidence of moderate or severe renal impairment (see Section 5.2).

Patients with immunosuppressed:
Longer seasonal prophylaxis, up to 12 weeks, has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

4.3. Contraindications
It is contraindicated in people with known hypersensitivity to oseltamivir phosphate or any of the ingredients of the drug (listed in section 6.1).

4.4. Special warnings and precautions for use

There is no evidence that FLUZAVIR is effective in diseases caused by agents other than influenza A and B viruses (see Section 5.1).

FLUZAVIR may not be used as a substitute for influenza vaccine. The use of FLUZAVIR does not affect the evaluation of an individual's annual influenza vaccination. Protection against influenza lasts only as long as FLUZAVIR is administered. FLUZAVIR can be used in the treatment and prevention of influenza if reliable epidemiological data show that influenza virus is circulating.

Neuropsychiatric events

Neuropsychiatric events such as convulsions and delirium have been reported in patients treated for influenza with FLUZAVIR, particularly in children and adolescents. In rare cases, these events have led to accidental injuries. The contribution of FLUZAVIR to these events is not known. Neuropsychiatric events have also been reported in influenza patients not taking FLUZAVIR (see Section 4.8). In three separate large-scale epidemiological studies, it has been proven that the risk of neuropsychiatric events is not higher in influenza patients taking FLUZAVIR compared to influenza patients not receiving antiviral treatment.

Patients should be carefully monitored for signs of abnormal behavior, and the benefits and risks of continued treatment should be evaluated for each patient (see Section 4.8).

Serious accompanying conditions

There is no information on the safety and efficacy of oseltamivir in patients with unstable medical conditions that are sufficiently serious or at possible risk of requiring hospitalisation.

Patients with immunodeficiency

The safety and efficacy of oseltamivir treatment or prophylaxis in immunocompromised patients has not been conclusively established (see Section 5.1).

Heart failure/respiratory disease

The efficacy of oseltamivir in the treatment of patients 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).

Pediatric patients

No data are currently available to provide a dose recommendation for premature infants (postmenstrual age* <37 weeks).

*Time between the first day of the last normal menstrual cycle and the day of assessment, gestational age plus postnatal age.

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

Sorbitol: A 30 g bottle of FLUZAVIR oral suspension powder contains 25.713 g sorbitol. Doses administered twice daily, each containing 75 mg oseltamivir, contain a total of 2.6 g sorbitol. This amount is above the maximum recommended daily limit of sorbitol for people with hereditary fructose intolerance. Patients with rare inherited fructose intolerance should not use this medicine.

4.5 Interactions with other medicinal products and other forms of interaction
According to the information obtained from pharmacological and pharmacokinetic studies, clinically significant drug interactions with oseltamivir phosphate are unlikely.

Oseltamivir phosphate is largely converted to its active metabolite by esterases, mostly in the liver. Drug interactions, including competition for esterases, have not been widely reported in the literature. The low binding of oseltamivir and its active metabolite to plasma proteins indicates that drug interactions should not be a problem.

In vitro studies have shown that oseltamivir phosphate or its active metabolite is not a good substrate for microsomal P450 cytochrome enzymes and glucuronyl transferases (see section 5.2). There is no evidence of interaction with oral contraceptives.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin of these drugs, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion), and the elimination capacities of these pathways.

Probenecid
Due to decreased anionic tubular secretion in the kidney, the concentration of active metabolite increases approximately 2-fold as a result of concomitant use with probenecid. However, due to the wide safety margin of the active metabolite, dose adjustment is not necessary in patients with normal renal function during concomitant use with probenecid.

Amoxicillin
Concomitant use with amoxicillin does not alter plasma levels of either compound, due to the weakness of competition for anionic secretion pathways.

Additional information
No pharmacokinetic interactions are seen between oseltamivir or its major metabolite when co-administered with paracetamol, acetyl salicylic acid, cimetidine or antacids (magnesium and aluminum hydroxides and calcium carbonates), warfarin or rimantadine.

In phase III treatment and prophylaxis clinical trials, oseltamivir, ACE-inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide), antibiotics (penicillin, cephalosporin, azithromycin, erythromycin, doxycycline), H2-receptor blockers (ranitidine, cimetidine), beta blockers (propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators and analgesics (aspirin, ibuprofen and paracetamol). No change in the adverse event profile or frequency was observed as a result of co-administration of oseltamivir with these compounds.

Caution should be exercised when prescribing oseltamivir to patients taking drugs with a narrow therapeutic range (e.g. chlorpropamide, methotrexate, phenylbutazone) that are excreted by the same route.

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

Pediatric population:
No interaction studies have been conducted in pediatric population.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)
There is no recommendation for the use of this medicine in women of childbearing potential and women using birth control (contraception).

Pregnancy
Although no controlled studies have been conducted in pregnant women taking oseltamivir, limited data are available from post-marketing and retrospective observational follow-up reports. These data, together with animal studies, do not demonstrate direct or indirect harmful effects in relation to pregnancy/embryonal/fetal development/birth or postnatal development

(see section 5.3). FLUZAVIR may be used in pregnant women, taking into account available safety data, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

FLUZAVIR should not be used in pregnant women unless the potential benefit to the patient is greater than the potential risk to the foetus.

Lactation
Animal studies show that oseltamivir is 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. However, the levels detected in milk are very low and therefore less than the therapeutic dose will be passed to the infant. The pathogenicity of the circulating influenza virus strain, the benefit of breastfeeding for the child and the benefit of FLUZAVIR treatment for the breastfeeding mother should be taken into account when deciding whether to stop breastfeeding or to stop FLUZAVIR treatment.

Reproductive ability/Fertility
In non-clinical studies, reproductive performance, fertility and sperm evaluation parameters were not affected when FLUZAVIR was administered. Non-clinical data based on reproductive toxicity studies do not suggest a potential risk to humans.

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

4.8 Undesirable effects
Summary of the safety profile
The safety profile of oseltamivir is based on data from clinical studies with 6049 adult or adolescent and 1473 pediatric patients who received oseltamivir or placebo for the treatment of influenza, and with 3990 adult or adolescent and 253 pediatric patients who received placebo or oseltamivir/not treated for prophylaxis of influenza.

The most common adverse reactions reported in adults or adolescents were vomiting and nausea in treatment studies and nausea in prevention studies. The majority of these adverse events were reported on the first or second day of treatment upon use of the first dose, and resolved spontaneously within 1-2 days. The most common adverse reaction reported in children was vomiting. In the majority of patients, these side effects did not require discontinuation of oseltamivir therapy.

The following serious adverse reactions have been reported rarely during the postmarketing experience with oseltamivir: Anaphylactic and anaphylactoid reactions, hepatic disorders

(fulminant hepatitis, hepatic dysfunction and jaundice), angioneurotic edema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders (for neuropsychiatric disorders, see Section 4.4).

Table of adverse reactions list
Adverse drug reactions are listed according to the frequencies defined below:
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). Adverse effects have been added to the appropriate categories in the tables according to pooled analyses from clinical trials. Adverse effects are listed in order of decreasing severity in each frequency group.

In the treatment and prevention of influenza in adults and adolescents:
Table 1 below shows the most common adverse drug reactions or effects from post-marketing experience after use at the recommended dose (75 mg twice daily for five days for influenza treatment and 75 mg once daily for up to 6 weeks for influenza prophylaxis) in studies investigating the treatment and prevention of influenza in adults and adolescents.

The safety profile reported in people taking 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: Adverse reactions observed in studies investigating oseltamivir for the treatment or prophylaxis of influenza in adults and adolescents or in the postmarketing period

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 disorders			Hypersensitivity reaction	Anaphylactic reactions, anaphylactoid reactions

Psychiatric disorders				Agitation, abnormal behavior, anxiety, confusion, delusion, delirium, hallucination, nightmares, self-mutilation
Nervous system disorders	Headache	Insomnia	Altered consciousness, convulsions	
Eye disorders				Visual disturbances
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, hemorrhagic colitis
Hepatobilier disorders			Elevated hepatic enzymes	Fulminant hepatitis, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders			Eczema, dermatitis, rash, urticaria	Angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

General disorders and administration site conditions		Pain, dizziness (including vertigo), fatigue, pyrexia, pain in arms and legs		

Treatment and prevention of influenza in children:

A total of 1473 children (healthy children 1-12 years old and asthmatic children 6-12 years old) were included in clinical studies with oseltamivir for the treatment of influenza. 851 of these children received oseltamivir suspension therapy. In a post-exposure prophylaxis study in household groups (n=99), another 6-week pediatric prophylaxis study (n=49), and a 12-week pediatric seasonal prophylaxis study in immunocompromised groups (n=10), a total of 158 children received oseltamivir once a day in line with the recommended dose. The table below shows the most frequently reported adverse effects in paediatric clinical trials.

Table 2: Adverse drug reactions seen in studies investigating the use of oseltamivir in the treatment and prevention of influenza in children (dosage based on age/weight, 30-75 mg once daily)

System Organ Class	**Adverse Effects by Frequency of Occurrence**			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media		
Nervous system disorders		Headache		
Eye disorders		Conjunctivitis (including eye redness, crusting, and eye pain)		
Ear and labyrinth disorders		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal	Cough, nasal congestion	Rhinorrhea		

disorders					
Gastrointestinal disorders	Vomiting	Abdominal pain (including upper abdominal pain), dyspepsia, nausea			
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)		

Selected serious adverse reactions are described below.

Psychiatric disorders/Nervous system disorders
Influenza can be associated with a variety of neurological and behavioral symptoms, including events such as hallucinations, delirium, and abnormal behavior, and may be fatal in some cases. These events may occur in the case of encephalitis or encephalopathy, but may be present without a severe disease.

Convulsions and delirium (including symptoms such as altered consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares) have been reported post-marketing during treatment with oseltamivir, in a few cases resulting in accidental injury or death. These events have been reported especially in pediatric and adolescent patients and as events that often start suddenly and resolve rapidly. The contribution of oseltamivir to these events is unknown. Such neuropsychiatric events have also been reported in influenza patients who did not receive oseltamivir.

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

Other special populations:
Geriatric population: There were no clinically relevant differences in safety in the elderly patient population receiving oseltamivir or placebo compared with patients aged <65 years.

Patients with chronic heart and/or respiratory failure: The adverse reaction profile in adults and patients with cardiac and/or respiratory diseases is qualitatively similar to the profile in healthy young adults.

Pediatric population (children younger than one year of age):
In two studies examining the pharmacokinetic, pharmacodynamic and safety profile of oseltamivir treatment in 124 children less than one year of age with influenza infection, the safety profile was similar across age cohorts, with vomiting, diarrhoea and diaper rash being the most commonly reported adverse events. There are insufficient data for infants less than 36 weeks of post-conceptual age.

Available safety data from prospective and retrospective observational studies (including more than 2,400 children in this age class), epidemiological database research, and post-marketing reports on oseltamivir for the treatment of influenza in children less than one year of age suggest that the safety profile in children under one year of age is similar to the proven safety profile in children aged 1 year and above.

Patients with immunodeficiency: In a 12-week prophylaxis study in 475 immunosuppressed patients, including 18 children aged 1 year to 12 years and older than 12 years, the safety profile of 238 patients receiving oseltamivir is consistent with the safety profile previously observed in the oseltamivir prophylaxis clinical trial.

Children with pre-existing asthma: Overall, the adverse reaction profile in children with pre-existing bronchial asthma is qualitatively similar to that 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 officials are asked to report any suspected side effects via the national reporting system.

4.9 Overdose and treatment
Overdose experiences with oseltamivir have been reported in clinical studies and post-marketing. Majority of these cases did not report any adverse effects.

Adverse drug effects reported after overdose are similar in structure and distribution to the undesirable effects seen at recommended therapeutic doses of oseltamivir and described in section 4.8.

Pediatric population
Overdose has been reported more frequently in children than in adults and adolescents. Caution should be exercised when preparing FLUZAVIR oral suspension and administering FLUZAVIR 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 prodrug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of newly formed virus particles from infected cells and further spread of infectious virus throughout 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*. Oral administered oseltamivir inhibits influenza A and B virus replication and pathogenicity in vivo in animal models of influenza infection with antiviral effect similar to that achieved in humans with 75 mg twice daily.

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

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

Clinical trials:
Treatment of influenza infection
The indication is based on clinical trials of naturally occurring influenza, predominantly influenza A infection.

Oseltamivir is effective only against diseases caused by influenza virus. Therefore, statistical analysis is presented only for subjects infected with influenza. In a pooled intent-to-treat population (ITT), which included both influenza-positive and influenza-negative subjects, primary efficacy decreased proportionally to the number of influenza-negative subjects. In the total treatment population, influenza infection was confirmed in 67% (ranging from 46% to 74%) of the subjects. 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 included only during the period when influenza spread in the local community.

Adults and adolescents aged 13 and over:
Patients were chosen among those who were reported to have onset of symptoms within 36 hours, patients with a fever ≥ 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) included in the studies, 75 mg oseltamivir administered twice daily for five days reduced the median duration of influenza disease by 1 day to 4.2 days (95% CI (confidence interval) 4.0 to 4.4 days; $p \leq 0.0001$), which was 5.2 days (95% CI 4.9 vs 5.5 days) in the placebo group.

The ratio of subjects who developed lower respiratory complications (especially bronchitis) treated with antibiotics decreased from 12.7% (135/1063) in the placebo group to 8.6% (116/1350) in the oseltamivir-treated population ($p = 0.0012$).

Treatment of influenza in high-risk populations:
The median duration of influenza disease was not significantly reduced in elderly patients (≥ 65 years) and patients with chronic cardiac and/or respiratory disease who received oseltamivir 75 mg twice daily for five days. Total duration of fever decreased by one day in the oseltamivir group. In the influenza-positive elderly, the incidence of lower respiratory tract complications (especially bronchitis) decreased from 19% (52/268) in the antibiotic-treated 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 (especially 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 pregnancy: There are no controlled clinical studies on the use of oseltamivir in pregnant women; however, data from post-marketing and observational studies indicate that the current dosing regimen for this patient population is appropriate in terms of morbidity/mortality. Although pharmacokinetic studies show low exposure to the active metabolite, dose adjustment is not recommended in pregnant women for the treatment or prophylaxis of influenza.

Treatment of influenza in children:
In a study of healthy children (65% influenza-positive) aged 1 to 12 years (mean age 5.3 years) with fever (≥ 37.8 °C) and cough or cold, 67% of influenza-positive patients had influenza A and 33% were infected with influenza B. Oseltamivir treatment was initiated within 48 hours of onset of symptoms and significantly reduced recovery time (return to normal health and activity, relief of fever, cough, and cold) by approximately 1.5 days compared to placebo (95% CI 0.6 to 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 oseltamivir-treated children (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 mean duration of disease was not significantly reduced in the oseltamivir-treated group. From day 6 (last day of treatment), FEV_1 (forced expiratory volume) increased from 4.7% in the placebo group to 10.8% in the oseltamivir-treated group (p = 0.0148).

Treatment of influenza B infection:
Overall, 15% of the influenza-positive population is infected with influenza B, with rates ranging from 1 to 33% across studies. The median duration of illness in subjects infected with influenza B did not differ significantly between treatment groups. Data from 504 influenza B-infected cases from all studies were collected for analysis. Oseltamivir reduced the duration of relief of all symptoms by 0.7 days (95% CI 0.1 to 1.6 days; p = 0.022), cough, fever (≥ 37.8 °C) and cold by one day (95% CI 0.4 - 1.7 days; p <0.001).

Prevention of influenza:
The efficacy of oseltamivir in the prevention of naturally occurring influenza disease has been demonstrated in a study of household post-exposure prevention and in two seasonal prophylaxis studies. The primary efficacy parameter for all these studies was the incidence of laboratory-confirmed influenza. The virulence of the influenza epidemic is unpredictable and varies by region and season. Therefore, the number of people number of people needed-to-treat (NTT) for prevention of a case of influenza disease also varies.

Post-exposure prevention:
In a study of subjects in contact with an index case of influenza (12.6% vaccinated against influenza), oseltamivir 75 mg once daily was initiated within 2 days of the onset of symptoms in the index influenza case and continued for 7 days. Influenza was confirmed in 163 of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza in people in contact with confirmed cases of influenza, with rates of 24/200 (12%) in the placebo group versus 2/205 (1%) in the oseltamivir group (92% decrease [95% CI 6 to 16; p ≤ 0.0001]). The number of people needed to treat (NTT) among those in contact with actual cases of influenza

was 10 (95% CI 9 - 12), and 16 (95% CI 15 - 19) in the entire population (ITT) regardless of infection status of the index case.

The efficacy of oseltamivir in naturally occurring influenza prophylaxis has been demonstrated both as index cases and family contacts in a study of household post-exposure prophylaxis that included adults, adolescents and children aged 1 to 12 years. The primary efficacy parameter in this study was the incidence of laboratory-confirmed household clinical influenza. Oseltamivir prophylaxis lasted 10 days. In the overall population, the incidence of laboratory-confirmed household clinical influenza decreased, with 20% (27/136) in those not receiving prophylaxis versus 7% (10/135) in those receiving prophylaxis (62.7% decrease [95% CI 26.0 to 81.2; p = 0.0042]). In household influenza-infected index cases, the incidence of influenza decreased from 26% (23/89) in those not receiving prophylaxis treatment to 11% (9/84) in those receiving prophylaxis treatment (58.5% decrease [95% CI 15.6 - 79.6%); p = 0.0114]). Based on the subgroup analysis of children aged 1 to 12 years, the incidence of laboratory-confirmed clinical influenza in children was significantly reduced, with 19% (21/111) in those who did not receive prophylaxis treatment versus 7% (7/104) in those who received prophylaxis treatment (64.4% decrease [95% CI 15.8 - 85.0; p=0.0188]). The incidence of laboratory-confirmed clinical influenza decreased in children who did not transmit the virus in the beginning, with 21% (15/70) in those who did not receive prophylaxis versus 4% (2/47) in those who received prophylaxis (80.1% decrease [95% CI 22.0 - 94.9; p=0.0206]). The number needed to treat (NNT) for the total pediatric population was 9 (95% CI 7 - 24) and 8 (95% CI 6, upper limit is not known) in the entire population (ITT) and in pediatric people who contacted infected index cases (ITTII), respectively.

Prevention during the community influenza epidemic:
In a pooled analysis of two studies in healthy unvaccinated adults during the influenza epidemic, oseltamivir 75 mg once daily for 6 weeks significantly reduced the incidence of clinical influenza disease, with rates of 25/519 (4.8%) in the placebo group versus 6/520 (1.2%) in the oseltamivir group (76% decrease [95% CI 1.6 to 5.7; p = 0.0006]).
The number of people needed to treat in this study was 28 (95% CI 24 - 50). In a study with the elderly in nursing homes, 80% of the subjects were vaccinated during the study period and received oseltamivir 75 mg once daily for 6 weeks; the incidence of clinical influenza disease was significantly reduced. It was 12/272 (4.4%) in the placebo group versus 1/276 (0.4%) in the oseltamivir group (92% decrease [95% CI 1.5 - 6.6; p = 0.0015]). The number of patients needed to treat in this study was 25 (95% CI 23 - 62).

Prophylaxis of influenza in patients with immunodeficiency:
475 cases with immunodeficiency including 18 children aged 1 to 12 years (388 with solid organ transplants [195 placebo; 193 oseltamivir], 87 with hematopoietic stem cell transplants

[43 placebo; 44 oseltamivir], none with other immunosuppressive conditions) were included in a double-blind, placebo-controlled randomized trial for seasonal prophylaxis of influenza. The primary endpoint of this study was the incidence of laboratory-confirmed clinical influenza with a four-fold elevation in viral culture and/or HAI (hemagglutination inhibition) 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% vs. 4.1%; p = 0.772).

No specific studies have been conducted to assess the reduction in the risk of complications.
Oseltamivir resistance
Clinical trials: In clinical studies supported by Roche, the risk of decreased susceptibility of the influenza virus to oseltamivir or the risk of developing resistance was examined.
All patients with oseltamivir-resistant virus cleared the virus normally and did not experience any clinical deterioration. In some paediatric patients, oseltamivir-resistant virus was detected for a longer period of time compared with patients with oseltamivir-sensitive virus. However, influenza symptoms were not prolonged in these patients.

There is no evidence of drug resistance associated with the use of oseltamivir in clinical studies conducted to date in patients who are not immunosuppressed for influenza protection 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 immunosuppressed patients.

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

* Whole-genome genotyping was not performed in all studies.

Natural mutations associated with reduced susceptibility to oseltamivir have been detected *in vitro* in influenza A and B viruses from patients not using oseltamivir. The resistant strains selected during oseltamivir therapy were obtained from both immunocompetent individuals and immunodeficient individuals. Immunodeficient 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 viral subtype specific. Since 2007, the H275Y mutation associated with resistance has become common in seasonal H1N1 strains. The rate of

decrease in susceptibility to oseltamivir and the prevalence of these viruses vary seasonally and geographically. In 2008, H275Y was found in more than 99% of H1N1 influenza isolates found in Europe. The 2009 H1N1 influenza ("swine flu") shows an almost even distribution of susceptibility to oseltamivir, except for rare cases of resistance reported 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 largely converted to its active metabolite (oseltamivir carboxylate) mainly by hepatic esterases. At least 75% of the oral dose reaches the systemic circulation as the active metabolite. Exposure to prodrug is less than 5% of the active metabolite. Plasma concentrations of prodrug and active metabolite are proportional to the dose and not affected by taking the drug with food.

Distribution:

The mean volume of distribution of oseltamivir carboxylate at steady state is approximately 23 liters in humans, equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate is distributed to all areas where influenza virus spreads.

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

Biotransformation:

Oseltamivir is extensively 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 major cytochrome P450 isoforms. There is no phase 2 conjugate of either compound *in vivo*.

Elimination:

Absorbed oseltamivir is eliminated primarily (>90%) as converted to oseltamivir carboxylate. The active metabolite is excreted in the urine without being further metabolized. Peak plasma concentrations of oseltamivir carboxylate decrease in most cases with a half-life of 6 to 10 hours. The active metabolite is completely excreted renally. Renal clearance (18.8 L/h) exceeds the glomerular filtration rate (7.5 L/h) , indicating that tubular secretion as well as glomerular filtration occurs. Less than 20% of the radiolabeled oral dose is excreted in the feces.

Linearity / non-linearity:
The pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate are linear. The increases in plasma concentrations of oseltamivir and oseltamivir carboxylate are proportional to dose increases following single dose administration in the range of 20 to 1000 mg and dose increases following repeated administration twice daily for 5 days in the range of 75 mg to 450 mg.

Additional information for special populations
Renal impairment:
Treatment with 100 mg of oseltamivir twice daily for 5 days in patients with varying degrees of renal impairment have shown that the active metabolite concentration is inversely related to 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 exposure to its active metabolite is expected in patients with hepatic impairment (see Section 4.2).

Geriatric population:
Elderly patients (65 to 78 years of age) had 25-35% higher steady-state active metabolite concentrations in elderly patients compared to younger adults receiving comparable doses of oseltamivir. The half-life of the drug in elderly patients was approximately the same as in young adults. No dose adjustment is needed relating to drug exposure and tolerance in elderly patients unless there is evidence of moderate or severe renal impairment (creatinine clearance is not below 60 mL/min) (see Section 4.2).

Pediatric patients:
Infants aged 1 year and above and children
The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in babies, children and adolescents 1-16 years of age. Multiple-dose pharmacokinetics were studied in a clinical efficacy study in a small number of children. For the dose administered (mg/kg), young children appeared to eliminate the prodrug and active metabolite faster than adults, resulting in lower exposure. Comparison of children receiving 2 mg/kg dose and adults receiving 75 mg (approximately 1 mg/kg) single capsule showed comparable oseltamivir carboxylate concentrations. The pharmacokinetics of oseltamivir in children aged 12 years and above and adolescents were similar to those observed in adults.

Prevention of influenza in newborns and infants younger than 1 year of age during the pandemic
The exposure provided by 3 mg/kg once-daily dose in newborns less than 1 year of age in simulations was in the same range or greater than the exposure observed in adults with 75 mg

once-daily dose. Exposure does not exceed treatment limits in infants less than 1 year of age (3 mg/kg twice daily) and is expected to show a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis have been conducted in infants less than 1 year of age.

Newborns and infants under 1 year old

The pharmacokinetics, pharmacodynamics and safety of FLUZAVIR were evaluated in 2 uncontrolled open-label studies in infants less than 1 year old (n=135). The rate of body weight-adjusted clearance of active metabolites decreases below 1 year of age. Exposure to metabolites differed more in the youngest neonates. Available data suggest that the exposure provided by the 3 mg/kg dose in neonates 0-12 months of age 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 from older children. There are no data on post-exposure influenza prophylaxis in infants less than 1 year of age. There are no studies on prevention during the influenza epidemic in children under 12 years of age.

Pregnant women

Joint population pharmacokinetic studies show that exposure to the active metabolite is lower in pregnant women than in non-pregnant women at the current oseltamivir dose regimen (mean 30% across all trimesters). However, the expected low exposure remains above the inhibitory concentration (IC95) and at the therapeutic level for influenza virus. In addition, there is evidence from observational studies that the current dose regimen provides benefits in this patient population. Therefore, dose adjustment is not recommended in pregnant women for the treatment or prophylaxis of influenza (see Section 4.6).

5.3 Preclinical safety data

Preclinical data reveal no hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Based on the findings of conventional rodent carcinogenicity studies, there is a dose-dependent trend of increased incidence of some tumors typical for the rodent species used. These findings do not alter the benefit-risk ratio of FLUZAVIR in the therapeutic indications adopted, considering the exposure limits in relation to the expected exposure in human use.

Teratology studies were performed in rats and rabbits at maximum doses of 1500 mg/kg/day and 500 mg/kg/day, respectively. There were no effect observed on fetal development. A fertility study in rats at a maximum dose of 1500 mg/kg/day revealed no adverse effects for either sex. Prenatal and postnatal rat studies noted delayed delivery at 1500 mg/kg/day. The safety margin between human exposure and the no-effect dose in rats (500 mg/kg/day) is 480 times for oseltamivir and 44 times for the active metabolite, respectively. Fetal exposure in rats and rabbits comprised approximately 15 to 20% of maternal rat exposure.

Oseltamivir and the active metabolite were excreted in milk in lactating rats. It is not known whether oseltamivir or its active metabolite is excreted in human milk. Extrapolation of animal data yields estimates of 0.01 mg/day and 0.3 mg/day for both compounds, respectively.

A potential for skin sensitization to oseltamivir was identified in a "maximization" study in guinea pigs. Approximately 50% of animals treated with unformulated active ingredient showed erythema following detection of induced animals. Reversible irritation was detected in the eyes of rabbits.

Very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1310 mg/kg), had no adverse reactions in adult rats, while these doses resulted in toxicities, including death, in 7-day-old juvenile rat pups. These reactions were seen at doses of 657 mg/kg and higher.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Monosodium citrate
Xanthan gum
Titanium dioxide
Sodium benzoate
Saccharin sodium
Tutti Frutti flavor

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store the dry powder at room temperature below 25°C before reconstitution. The prepared suspension should be used within 10 days if stored at room temperature below 25°C or within 17 days if stored between 2°C and 8°C (in the refrigerator).

6.5 Nature and contents of container

FLUZAVIR is available in a 125 mL honey colored glass bottle with a white cap and a 5 mL PP syringe. These bottles are packed in cardboard boxes. One cardboard box contains 1 glass bottle, 5 ml PP syringe and instructions for use.

6.6 Special precautions for disposal and other handling

Preparation of oral suspension

It is recommended that FLUZAVIR suspension is prepared by a pharmacist immediately before administration to the patient (see Section 4.2).

Only the syringe included in the pack should be used.

1. Tap the sealed bottle several times until the powders are released.
2. Add drinking water up to the level of the marked point on the bottle.
3. Shake the sealed vial vigorously for 15 seconds to suspend the powder.
4. The cap of the bottle is opened and the syringe is pushed in.

The Instructions for Use and the oral dose syringe should be given to the patient. It is recommended to write the expiry date of the reconstituted suspension on the bottle label.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

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9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 14.05.2024
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT: