ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 30 mg hard capsules
Ebilfumin 45 mg hard capsules
Ebilfumin 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ebilfumin 30 mg hard capsules

Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.
For the full list of excipients, see section 6.1.

Ebilfumin 45 mg hard capsules

Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.
For the full list of excipients, see section 6.1.

Ebilfumin 75 mg hard capsules

Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ebilfumin 30 mg hard capsules

The hard capsule consists of a rich yellow body and cap bearing the black imprint “OS 30”. Capsule size: 4
The capsule contains a white granulated powder.

Ebilfumin 45 mg hard capsules

The hard capsule consists of a white opaque body and cap bearing the black imprint “OS 45”. Capsule size: 4
The capsule contains a white granulated powder.

Ebilfumin 75 mg hard capsules

The hard capsule consists of a white opaque body and a rich yellow cap bearing the black imprint “OS 75”. Capsule size: 2
The capsule contains a white granulated powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Ebilfumin is indicated in adults and children including full-term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms.

Prevention of influenza

- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Ebilfumin for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

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

Ebilfumin is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Ebilfumin hard capsules are bioequivalent formulations. 75 mg doses can be administered as either:
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule.

Commercially manufactured oseltamivir powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

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

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

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

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

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

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

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

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

Paediatric population

Children 1 to 12 years of age

Ebilfumin 30 mg, 45 mg and 75 mg capsules are available for infants and children 1 year of age or older

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

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

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

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

Post-exposure prevention: The recommended post-exposure prevention dose of Ebilfumin is:

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

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

Infants 0 – 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults (see section 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**	**Recommended dose for 10 days**** Immunocompromised Patients
3 kg	9 mg twice daily	9 mg twice daily
4 kg	12 mg twice daily	12 mg twice daily
5 kg	15 mg twice daily	15 mg twice daily
6 kg	18 mg twice daily	18 mg twice daily
7 kg	21 mg twice daily	21 mg twice daily

8 kg	24 mg twice daily	24 mg twice daily
9 kg	27 mg twice daily	27 mg twice daily
10 kg	30 mg twice daily	30 mg twice daily

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient.
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
** The recommended duration in immunocompromised infants (0-12 months old) is 10 days. See Special Populations, Immunocompromised Patients for more information.

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

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen is recommended for infants 0 – 12 months of age (see Section 5.2 for exposure simulation):

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

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

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

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

Special populations

Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

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

*Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg once daily
> 10 to 30 (ml/min)	30 mg every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg once weekly

*Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

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

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

Immunocompromised patients

Treatment: For treatment of influenza, the recommended duration for immunocompromised patients is 10 days (see sections 4.4, 4.8 and 5.1). No dose adjustment is necessary. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

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

Method of administration

Oral use.

Patients who are unable to swallow capsules may receive appropriate doses of an oseltamivir suspension..

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

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

Severe concomitant condition

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

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

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

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

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

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

Excipient
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

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

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir.

However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza.

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

adolescents and 39 children) received oseltamivir for the treatment of influenza and 475 immunocompromised patients (including 18 children, of these 10 oseltamivir and 8 placebo) received oseltamivir or placebo for the prophylaxis of influenza.

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

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders. (Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions

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

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

The safety profile reported in subjects who received the recommended dose of oseltamivir for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.

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

System Organ Class (SOC)	**Adverse reactions according to frequency**			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis		
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions

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

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

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

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

System Organ Class (SOC)	**Adverse reactions according to frequency**			
	Very common	**Common**	**Uncommon**	**Rare**

Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders
Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

In patients with influenza who were receiving oseltamivir, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

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

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported adverse events (see section 5.2). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients "at risk" (patients at higher risk of developing complications associated with influenza, e.g. older people and patients with chronic cardiac or respiratory disease). In general, the safety profile in the patients "at risk" was qualitatively similar to that in otherwise healthy adults/adolescents.

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

No specific antidote is known.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

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

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population (p = 0.5976).

Treatment of influenza in pregnant women: No controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, however, there is evidence from post-marketing and retrospective observational studies showing benefit of the current dosing regimen in this patient population in terms of lower morbidity/mortality. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2, Pharmacokinetics, Special Population).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; p < 0.0001) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children (p = 0.013).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6 % were influenza-positive. In the oseltamivir treated group, the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo (p = 0.0148) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with oseltamivir in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

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

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

Treatment of influenza in immunocompromised patients: A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset, for a duration of 10 days. The treatment regimens were: standard dose (75 mg or weight adjusted dose for children) twice daily (73 adult patients, 4 adolescent patients and 4 children) or double dose (150 mg or weight-adjusted dose for children) twice daily (78 adult patients, 3 adolescent patients and 5 children) of oseltamivir.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95%

CI 63.9-140.0]). The TTRS for children was variable and the interpretation is limited by the small sample size. The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).
A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤12 years of age, n=30) receiving standard (75 mg or weight adjusted twice daily) vs. triple dose (225 mg or weight adjusted twice daily) oseltamivir for an adaptive dosing period of 5 to 20 days dependant on duration of viral shedding (mean treatment duration: 9 days). No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis).

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27 / 136) in the group not receiving prevention to 7 % (10 / 135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23 / 89) in the group not receiving prevention to 11 % (9 / 84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]). According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21 / 111) in the group not receiving prevention to 7 % (7 / 104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15 / 70) in the group not receiving prevention to 4 % (2 / 47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; $p = 0.0206$]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Prevention during an influenza pandemic has not been studied in controlled clinical studies in children 0-12 months of age. See Section 5.2 for exposure simulation details.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25 /519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; $p = 0.0006$])

during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50). A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

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

An overall higher incidence of oseltamivir-resistance was observed in adult and adolescent immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.5% (10/69) in standard dose group and 2.7% (2/74) in double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult and adolescent patients. The majority of adult patients that developed resistance were transplant recipients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most of the patients with oseltamivir-resistant virus were infected with influenza type A and had prolonged viral shedding.

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

Incidence of Oseltamivir Resistance in Clinical Studies

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

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza
There has been no evidence for emergence of drug resistance associated with the use of oseltamivir in clinical studies conducted to date in post-exposure (7 days), post-exposure within household groups

(10 days) and seasonal (42 days) prevention of influenza in immunocompetent patients. There was no resistance observed during a 12-week prophylaxis study in immunocompromised patients.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

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

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population

Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of oseltamivir have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 0 - 12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious with a safety profile comparable to that seen in older children and adults using the approved dose (see sections 4.1 and 4.2). The reported adverse events were consistent with the established safety profile in older children.

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

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:
Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis in infants aged <1 have been performed.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Elderly
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

Pregnant Women
A pooled population pharmacokinetic analysis indicates that the Ebilfumin dosage regimen described in Section 4.2 Posology and method of administration results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 4.6 Fertility, pregnancy and lactation).

Immunocompromised Patients
Population pharmacokinetic analyses indicate that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 4.2. Posology and method of administration) results in an increased predicted exposure (from approximately 5% up to 50%) to the active metabolite when compared to non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in patients due to their immunocompromised status. However, for immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2. Posology and method of administration.

Pharmacokinetic and pharmacodynamic analyses from two studies in immunocompromised patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

5.3 Preclinical safety data

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

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

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ebilfumin 30 mg hard capsules

Capsule core
Pregelatinised starch (derived from maize starch)
Talc

Povidone (K-29/32)
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac Glaze-45% (20% esterified)
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28% (E527)

Ebilfumin 45 mg hard capsules

Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone (K-29/32)
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac Glaze-45% (20% esterified)
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonium hydroxide 28% (E527)

Ebilfumin 75 mg hard capsules

Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone (K-29/32)
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Cap:
Gelatin
Yellow iron oxide (E172)
Titanium dioxide (E171)
Body:
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac Glaze-45% (20% esterified)
Black iron oxide (E172)
Propylene glycol (E1520)

Ammonium hydroxide 28% (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

6 years

Storage of the pharmacy compounded suspension

Shelf life of 3 weeks when stored below 25 °C.
Shelf life of 6 weeks at 2°C - 8°C.

6.4 Special precautions for storage

Store below 25°C.

For storage conditions of the pharmacy compounded suspension, see section 6.3.

6.5 Nature and contents of container

PVC/PE/PVdC/Al blisters or HDPE containers with LDPE lid (and a desiccant).
Pack-size 10 capsules.

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.

Extemporaneous formulation

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

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Ebilfumin capsules under “Making liquid Ebilfumin at home”.

Syringes of appropriate volume and grading should be provided for administering the pharmacy compounded suspension as well as for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding

Pharmacy compounded 6 mg/ml suspension prepared from capsules

Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules

This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis. For immunocompromised patients, a 10-day course of treatment is needed.

The pharmacist may compound a 6 mg/ml suspension from Ebilfumin 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

For immunocompromised patients, calculate the total volume needed to be compounded and dispensed to provide a 10-day course of treatment for the patient. The total volume needed is indicated in the table below for immunocompromised patients and is determined by the patient's weight. To allow for accurate volume withdrawal of up to 20 doses (2 withdrawals per daily treatment dose for 10 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight for 5-day treatment or 10-day prophylaxis course

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

*Depending on the capsule strength used.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight for 10-days of treatment for immunocompromised patients

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	100 ml	125 ml
> 15 kg to 23 kg	150 ml	187.5 ml
> 23 kg to 40 kg	200 ml	250 ml
> 40 kg	250 ml	300 ml

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

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 5 days of treatment or 10-days of prophylaxis)

Total volume of compounded suspension to be prepared	Required number of Ebilfumin capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
90 ml	Please use alternative capsule strength*	12 capsules (540 mg)	18 capsules (540 mg)	89 ml
100 ml	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98.5 ml
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
137.5 ml	11 capsules (825 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 10 days of treatment in immunocompromised patients)

Total volume of compounded suspension to be prepared	Required number of Ebilfumin capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
125ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
187.5ml	15 capsules (1120 mg)	25 capsules (1120 mg)	Please use alternative capsule strength*	185 ml
250ml	20 capsules (1500 mg)	Please use alternative capsule strength*	50 capsules (1500 mg)	246.5 ml
300ml	24 capsules (1800 mg)	40 capsules (1800 mg)	60 capsules (1800 mg)	296 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Third, follow the procedure below for compounding the 6 mg/ml suspension from Ebilfumin capsules:

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Ebilfumin capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Ebilfumin capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating "Shake Gently Before Use".
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Ebilfumin capsules for patients 1 year of age or older

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

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

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Infants less than 1 year of age
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis. For immunocompromised patients, a 10-day course of treatment for the patient is needed.

The pharmacist may compound a 6 mg/ml suspension from Ebilfumin 30 mg, 45 mg or 75 mg capsules using water containing 0.05 % w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed for each patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

For immunocompromised patients, calculate the total volume needed to be compounded and dispensed to provide a 10-day course of treatment for the patient. The total volume needed is indicated in the table below and is determined by the patient's weight. To allow for accurate volume withdrawal of up to 20 doses (2 withdrawals per daily treatment dose for 10 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight (for 5 days of treatment or 10-days of prophylaxis)

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

* Depending on the capsule strength used.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight (for 10-days of treatment in immunocompromised patients)

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
≤ 7 kg	up to 80 ml	100 ml
> 7 kg to 10 kg	100 ml	125 ml

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

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 5 days of treatment or 10-days of prophylaxis)

Total volume of compounded suspension to be prepared	**Required number of Ebilfumin capsules (mg of oseltamivir)**			**Required volume of vehicle**
	75 mg	**45 mg**	**30 mg**	
50 ml	4 capsules (300 mg)	Please use alternative capsule strength*	10 capsules (300 mg)	49.5 ml

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

*There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension (for 10-days of treatment in immunocompromised patients)

Total volume of compounded suspension to be prepared	Required number of Ebilfumin capsules (mg of oseltamivir)			Required volume of vehicle
	75 mg	45 mg	30 mg	
100 ml	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98.5 ml
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

Third, follow the procedure below for compounding the 6 mg/ml suspension from Ebilfumin capsules:

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Ebilfumin capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Ebilfumin capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Ebilfumin capsules for infants less than 1 year of age

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

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

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing tables above) on the oral syringe for each patient.

The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Home preparation

When commercially manufactured oseltamivir powder for oral suspension is not available, a pharmacy compounded suspension prepared from Ebilfumin capsules must be used (see detailed instructions above). If the commercially manufactured oseltamivir powder for oral suspension and the pharmacy compounded suspension is also not available, Ebilfumin suspension may be prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). The mixture should be stirred and given entirely to the patient. The mixture must be swallowed immediately after its preparation.

When only 75 mg capsules are available, and doses of 30 mg or 45 mg are needed, the preparation of Ebilfumin suspension involves additional steps. Detailed instructions can be found in the package leaflet of Ebilfumin capsules under “Making liquid Ebilfumin at home”.

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Ebilfumin 30 mg hard capsules

EU/1/14/915/001 (10 hard capsules blister)
EU/1/14/915/002 (10 hard capsules container)

Ebilfumin 45 mg hard capsules
EU/1/14/915/003 (10 hard capsules container)
EU/1/14/915/004 (10 hard capsules blister)

Ebilfumin 75 mg hard capsules

EU/1/14/915/005 (10 hard capsules blister)
EU/1/14/915/006 (10 hard capsules container)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 May 2014
Date of latest renewal: 12 February 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Balkanpharma-Dupnitsa AD
3 Samokovsko Shosse Str.
Dupnitsa 2600
Bulgaria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Label for HDPE tablet container and outer carton for tablet container and blister

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 30 mg hard capsules
oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/915/001 (10 hard capsules blister)
EU/1/14/915/002 (10 hard capsules container)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Only applicable for outer packaging:]
Ebilfumin 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

[Only applicable for outer packaging:]
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

[Only applicable for outer packaging:]
PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 30 mg hard capsules
oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Label for HDPE tablet container and outer carton for tablet container and blister

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 45 mg hard capsules
oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/915/003 (10 hard capsules container)
EU/1/14/915/004 (10 hard capsules blister)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Only applicable for outer packaging:]
Ebilfumin 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

[Only applicable for outer packaging:]
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

[Only applicable for outer packaging:]
PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 45 mg hard capsules
oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Label for HDPE tablet container and outer carton for tablet container and blister

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 75 mg hard capsules
oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/915/005 (10 hard capsules blister)
EU/1/14/915/006 (10 hard capsules container)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Only applicable for outer packaging:]
Ebilfumin 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

[Only applicable for outer packaging:]
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

[Only applicable for outer packaging:]
PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Ebilfumin 75 mg hard capsules
oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Ebilfumin 30 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ebilfumin is and what it is used for

- Ebilfumin is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Ebilfumin can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Ebilfumin may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Ebilfumin contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Ebilfumin

Do not take Ebilfumin:
- **if you are allergic** to oseltamivir or any of the other ingredients of this medicine (listed in section 6)**.**

Talk to your doctor if this applies to you. **Do not take Ebilfumin.**

Warnings and precautions
Talk to your doctor or pharmacist before taking Ebilfumin.
Before you take Ebilfumin, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Ebilfumin, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents. These may be signs of rare but serious side effects.

Ebilfumin is not a flu vaccine
Ebilfumin is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Ebilfumin will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Ebilfumin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Ebilfumin is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Ebilfumin is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Ebilfumin has no effect on your ability to drive or use machines.

Ebilfumin contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3. How to take Ebilfumin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Ebilfumin as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For patients with a weak immune system, treatment will continue for 10 days.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults and adolescents 13 years and over

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
40 kg or more	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For patients with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Children 1 to 12 years

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
10 to 15 kg	30 mg twice daily	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For children with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Infants less than 1 year (0 to 12 months)
Giving Ebilfumin to infants less than 1 year old for preventing flu during a flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg	3 mg per kg body weight**, twice daily	3 mg per kg body weight**, twice daily	3 mg per kg**, once daily

** For infants with a weak immune system, treatment is for 10 days.*

** mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is8 kg x 3mg per kg = 24 mg

Method of administration
Swallow the capsules whole with water. Do not break or chew the capsules.

Ebilfumin can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid form of this medicine (*oral suspension*). If you need an oral suspension but it's not available from your pharmacy, you can make a liquid form of Ebilfumin from these capsules. **See *Making Liquid Ebilfumin at home*** for instructions.

If you take more Ebilfumin than you should
Stop taking Ebilfumin and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when oseltamivir was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Ebilfumin for children and when administering Ebilfumin capsules or liquid Ebilfumin to children.

If you forget to take Ebilfumin
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Ebilfumin
There are no side effects when you stop Ebilfumin. But if Ebilfumin is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:
- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Ebilfumin are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects

mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During oseltamivir treatment, rare events have been reported that include
- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.
- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)
- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)
- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)
- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)
- Thrombocytopenia (low platelet count)

- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)
- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)
- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and nappy rash have been reported.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ebilfumin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ebilfumin contains
- Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.
- The other ingredients are:
  capsule contents: pregelatinized starch (derived from maize starch), talc, povidone (K-29/32), croscarmellose sodium, sodium stearyl fumarate
  capsule shell: gelatin, yellow iron oxide (E172) and titanium dioxide (E171)
  printing ink: shellac glaze-45% (20% esterified), black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide 28% (E527)

What Ebilfumin looks like and contents of the pack
The hard capsule consists of a rich yellow body and cap bearing the black imprint “OS 30”. Capsule size: 4.

Ebilfumin 30 mg hard capsules are available in blister packs or tablet containers of 10.

Marketing Authorisation Holder
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {MM/YYYY} {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, a liquid medicine may be available.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Ebilfumin capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make Ebilfumin suspension from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making Liquid Ebilfumin at home

- **If you have the right capsule** for the dose needed (a 30 mg or a 60 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making Ebilfumin suspension from capsules involves extra steps. This is suitable for younger children and babies: they usually need an Ebilfumin dose of less than 30 mg. **See the lower set of instructions**.

Children 1 to 12 years

To make a 30 mg or a 60 mg dose,
you need:

- **One or two 30 mg Ebilfumin capsule(s)**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are: chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

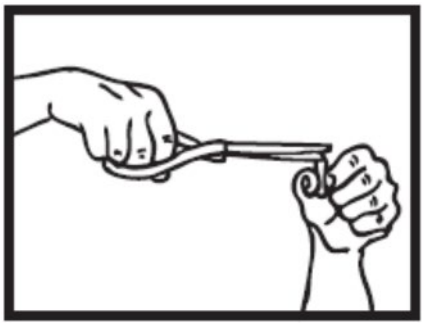
To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

You should use only 30 mg capsules for 30 mg and 60 mg doses. Do not try to make a 45 mg or 75 mg dose by using the contents of 30 mg capsules. Use the appropriate size capsule instead.

Weight	**Dose of Ebilfumin**	**Number of capsules**
Up to 15 kg	30 mg	1 capsule
~~15 kg up to 23 kg~~	~~45 mg~~	**Do not use 30 mg capsules**
23 kg up to 40 kg	60 mg	2 capsules

Step 2: Pour all the powder into a bowl

Hold a **30 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Open a second capsule for a 60 mg dose. Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.



Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Ebilfumin powder.
Stir the mixture well.

Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

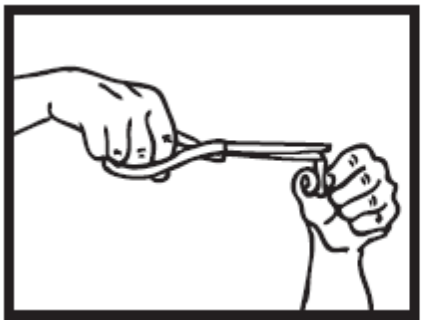
Infants less than 1 year

To make a smaller single dose, you need:

- **One 30 mg Ebilfumin capsule**
- **Sharp scissors**
- **Two small bowls** (use separate pairs of bowls for each child)
- **One large oral dose dispenser** to measure out water – a 5 or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the Ebilfumin.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.
  Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

Hold a **30 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.



Step 2: Add water to dilute the medicine

Use the larger dispenser to draw up **5 ml water.**

Add the water to the powder in the bowl.

Stir the mixture with the teaspoon for about 2 minutes.

Don't worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child's weight

Look up the child's weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

Infants less than 1 year (including full-term newborn babies)

Child's weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml
6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml

8.5 kg	4.3 ml
9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Step 4: Draw up the liquid mixture

Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.

Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Ebilfumin.
Mix the sweet food and Ebilfumin suspension well.

Give the whole contents of the second bowl (Ebilfumin suspension with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules:
Commercially manufactured oseltamivir powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that oseltamivir powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Ebilfumin capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Ebilfumin-water mixture. For measuring 5.0 ml of water, dispensers of 5 ml or 10 ml should be used.

The appropriate dispenser sizes for taking the correct volume of Ebilfumin suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full-term newborn babies):

Dose of Ebilfumin	Amount of Ebilfumin suspension	Dispenser size to use (grading 0.1 ml)
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Package Leaflet: Information for the user

Ebilfumin 45 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ebilfumin is and what it is used for

- Ebilfumin is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Ebilfumin can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Ebilfumin may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Ebilfumin contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Ebilfumin

Do not take Ebilfumin:
- **if you are allergic** to oseltamivir or any of the other ingredients of this medicine (listed in section 6)**.**

Talk to your doctor if this applies to you. **Do not take Ebilfumin.**

Warnings and precautions
Talk to your doctor or pharmacist before taking Ebilfumin.
Before you take Ebilfumin, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Ebilfumin, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents. These may be signs of rare but serious side effects.

Ebilfumin is not a flu vaccine
Ebilfumin is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Ebilfumin will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Ebilfumin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Ebilfumin is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Ebilfumin is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Ebilfumin has no effect on your ability to drive or use machines.

Ebilfumin contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3. How to take Ebilfumin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Ebilfumin as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For patients with a weak immune system, treatment will continue for 10 days.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults and adolescents 13 years and over

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
40 kg or more	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For patients with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Children 1 to 12 years

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
10 to 15 kg	30 mg twice daily	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For children with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Infants less than 1 year (0 to 12 months)
Giving Ebilfumin to infants less than 1 year old for preventing flu during a flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg	3 mg per kg body weight**, twice daily	3 mg per kg body weight**, twice daily	3 mg per kg**, once daily

** For infants with a weak immune system, treatment is for 10 days.*
** mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is8 kg x 3mg per kg = 24 mg

Method of administration

Swallow the capsules whole with water. Do not break or chew the capsules.

Ebilfumin can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid form of this medicine (*oral suspension*). If you need an oral suspension but it's not available from your pharmacy, you can make a liquid form of Ebilfumin from these capsules. **See *Making Liquid Ebilfumin at home*** for instructions.

If you take more Ebilfumin than you should
Stop taking Ebilfumin and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when oseltamivir was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Ebilfumin for children and when administering Ebilfumin capsules or liquid Ebilfumin to children.

If you forget to take Ebilfumin
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Ebilfumin
There are no side effects when you stop Ebilfumin. But if Ebilfumin is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:
- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Ebilfumin are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)

During oseltamivir treatment, rare events have been reported that include
- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.
- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)
- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)
- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)
- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)
- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects

(may affect more than 1 in 10 people)
- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)
- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and nappy rash have been reported.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ebilfumin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ebilfumin contains
- Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.
- The other ingredients are:

capsule contents: pregelatinized starch (derived from maize starch), talc, povidone (K-29/32), croscarmellose sodium, sodium stearyl fumarate
capsule shell: gelatin, titanium dioxide (E171)
printing ink: shellac glaze-45% (20% esterified), black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide 28% (E527)

What Ebilfumin looks like and contents of the pack
The hard capsule consists of a white opaque body and cap bearing the black imprint “OS 45”. Capsule size: 4.

Ebilfumin 45 mg hard capsules are available in blister packs or tablet containers of 10.

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This leaflet was last revised in {MM/YYYY} {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, a liquid medicine may be available.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Ebilfumin capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make Ebilfumin suspension from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making Liquid Ebilfumin at home

- **If you have the right capsule** for the dose needed (a 45 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making Ebilfumin suspension from capsules involves extra steps. This is suitable for younger, lighter children and babies: they usually need an Ebilfumin dose of less than 45 mg. **See the lower set of instructions**.

Children 1 to 12 years

To make a 45 mg dose,
you need:

- **One 45 mg Ebilfumin capsule**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are: chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

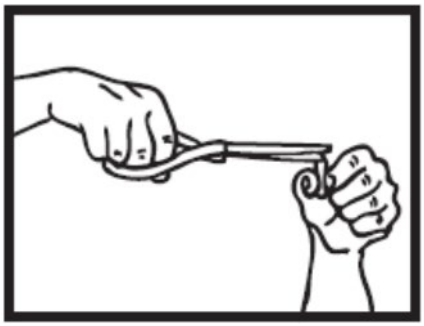
To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

You should use only 45 mg capsules for 45 mg doses. Do not try to make a 30 mg, 60 mg or 75 mg dose by using the contents of 45 mg capsules. Use the appropriate size capsule instead.

Weight	**Dose of Ebilfumin**	**Number of capsules**
~~Up to 15 kg~~	~~30 mg~~	**Do not use 45 mg capsules**
15 kg up to 23 kg	45 mg	1 capsule
~~23 kg up to 40 kg~~	~~60 mg~~	**Do not use 45 mg capsules**

Step 2: Pour all the powder into a bowl

Hold a **45 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.



Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Ebilfumin powder.
Stir the mixture well.

Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

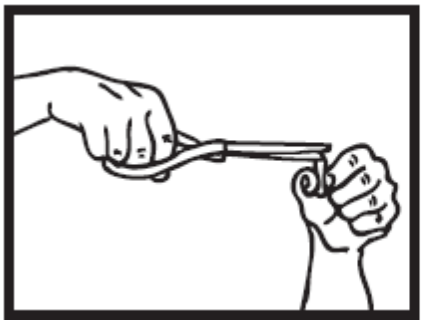
Infants less than 1 year

To make a smaller single dose, you need:

- **One 45 mg Ebilfumin capsule**
- **Sharp scissors**
- **Two small bowls** (use separate pairs of bowls for each child)
- **One large oral dose dispenser** to measure out water – a 5 ml dispenser or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the Ebilfumin.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.
  Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

Hold a **45 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.



Step 2: Add water to dilute the medicine

Use the larger dispenser to draw up **7.5 ml water.**

Add the water to the powder in the bowl.

Stir the mixture with the teaspoon for about 2 minutes.

Don't worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child's weight

Look up the child's weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

Infants less than 1 year (including full-term newborn babies)

Child's weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml
6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml
8.5 kg	4.3 ml

9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Step 4: Draw up the liquid mixture

Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.

Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Ebilfumin.
Mix the sweet food and Ebilfumin suspension well.

Give the whole contents of the second bowl (Ebilfumin suspension with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules:
Commercially manufactured oseltamivir powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that oseltamivir powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Ebilfumin capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Ebilfumin-water mixture. For measuring 5.0 ml of water, dispensers of 5 ml or 10 ml should be used.

The appropriate dispenser sizes for taking the correct volume of Ebilfumin suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full-term newborn babies):

Dose of Ebilfumin	Amount of Ebilfumin suspension	Dispenser size to use (grading 0.1 ml)
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Package Leaflet: Information for the user

Ebilfumin 75 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ebilfumin is and what it is used for

- Ebilfumin is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Ebilfumin can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Ebilfumin may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Ebilfumin contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Ebilfumin

Do not take Ebilfumin:
- **if you are allergic** to oseltamivir or any of the other ingredients of this medicine (listed in section 6)**.**

Talk to your doctor if this applies to you. **Do not take Ebilfumin.**

Warnings and precautions
Talk to your doctor or pharmacist before taking Ebilfumin.
Before you take Ebilfumin, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Ebilfumin, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents. These may be signs of rare but serious side effects.

Ebilfumin is not a flu vaccine
Ebilfumin is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Ebilfumin will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Ebilfumin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Ebilfumin is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Ebilfumin is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Ebilfumin has no effect on your ability to drive or use machines.

Ebilfumin contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3. How to take Ebilfumin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Ebilfumin as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For patients with a weak immune system, treatment will continue for 10 days.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults and adolescents 13 years and over

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
40 kg or more	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For patients with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Children 1 to 12 years

Body weight	**Treating flu:** dose for *5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose for *10 days*
10 to 15 kg	30 mg twice daily	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg** twice daily	75 mg** twice daily	75 mg** once daily

** For children with a weak immune system, treatment is for 10 days*
***75 mg can be made up of a 30 mg capsule plus a 45 mg capsule*

Infants less than 1 year (0 to 12 months)
Giving Ebilfumin to infants less than 1 year old for preventing flu during a flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Treating flu (Immunocompromised Patients):** dose *for 10 days**	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg	3 mg per kg body weight**, twice daily	3 mg per kg body weight**, twice daily	3 mg per kg**, once daily

** For infants with a weak immune system, treatment is for 10 days.*
** mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is8 kg x 3mg per kg = 24 mg

Method of administration

Swallow the capsules whole with water. Do not break or chew the capsules.

Ebilfumin can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid form of this medicine (*oral suspension*). If you need an oral suspension but it's not available from your pharmacy, you can make a liquid form of Ebilfumin from these capsules. **See *Making Liquid Ebilfumin at home*** for instructions.

If you take more Ebilfumin than you should
Stop taking Ebilfumin and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when oseltamivir was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Ebilfumin for children and when administering Ebilfumin capsules or liquid Ebilfumin to children.

If you forget to take Ebilfumin
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Ebilfumin
There are no side effects when you stop Ebilfumin. But if Ebilfumin is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:
- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Ebilfumin are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)

During oseltamivir treatment, rare events have been reported that include
- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.
- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)
- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)
- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)
- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)
- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects

(may affect more than 1 in 10 people)
- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)
- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and nappy rash have been reported.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ebilfumin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ebilfumin contains
- Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.
- The other ingredients are:

capsule contents: pregelatinized starch (derived from maize starch), talc, povidone (K-29/32), croscarmellose sodium, sodium stearyl fumarate
capsule shell: cap: gelatin, yellow iron oxide (E172) and titanium dioxide (E171), body: gelatin, titanium dioxide (E171)
printing ink: shellac glaze-45% (20% esterified), black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide 28% (E527)

What Ebilfumin looks like and contents of the pack
The hard capsule consists of a white opaque body and a rich yellow cap bearing the black imprint “OS 75”. Capsule size: 2.

Ebilfumin 75 mg hard capsules are available in blister packs or tablet containers of 10.

Marketing Authorisation Holder
Actavis Group PTC ehf.
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Iceland

Manufacturer
Balkanpharma-Dupnitsa AD
3 Samokovsko Shosse Str.
Dupnitsa 2600
Bulgaria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {MM/YYYY} {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, a liquid medicine may be available.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Ebilfumin capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make Ebilfumin suspension from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making Liquid Ebilfumin at home

- **If you have the right capsule strength** for the dose needed (a 75 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making Ebilfumin suspension from capsules involves extra steps. This is suitable for younger children and babies: they usually need an Ebilfumin dose of less than 30 mg. **See the lower set of instructions**.

Adults, adolescents 13 years and over, and children weighing 40 kg and over

To make a 75 mg dose, you need:

- **One 75 mg Ebilfumin capsule**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are: chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

You should use only 75 mg capsules for 75 mg doses. Do not try to make a 75 mg dose by using the contents of 30 mg or 45 mg capsules.

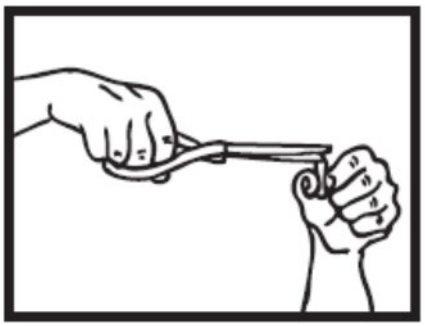
Weight	Dose of Ebilfumin	Number of capsules
40 kg and over	75 mg	1 capsule

Not for children who weigh less than 40 kg

You will need to prepare a dose of less than 75 mg for children who weigh less than 40 kg. *See below.*

Step 2: Pour all the powder into a bowl

Hold a **75 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.



Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Ebilfumin powder.
Stir the mixture well.

Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

Infants less than 1 year, and children weighing less than 40 kg

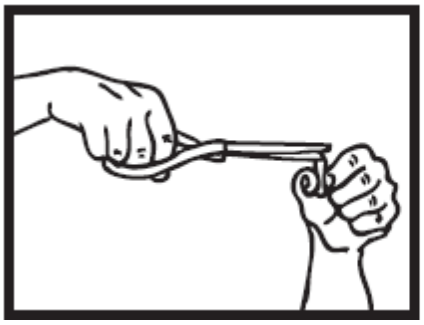
To make a smaller single dose, you need:

- **One 75 mg Ebilfumin capsule**
- **Sharp scissors**
- **Two small bowls**
- **One large oral dose dispenser** to measure out water – a 5 or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the Ebilfumin.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.

Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

Hold a **75 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.



Step 2: Add water to dilute the medicine

Use the larger dispenser to draw up 12.5 ml water.

Add the water to the powder in the bowl.

Stir the mixture with the teaspoon for about 2 minutes.

Don’t worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child’s weight

Look up the child’s weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

Infants less than 1 year (including full-term newborn babies)

Child’s weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml

6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml
8.5 kg	4.3 ml
9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Children 1 year or older, weighing less than 40 kg

Child's weight (nearest)	**How much mixture to draw up**
Up to 15 kg	5.0 ml
15 to 23 kg	7.5 ml
23 to 40 kg	10.0 ml

Step 4: Draw up the liquid mixture

Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.

Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Ebilfumin.
Mix the sweet food and Ebilfumin suspension well.

Give the whole contents of the second bowl (Ebilfumin suspension with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules:
Commercially manufactured oseltamivir powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that oseltamivir powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Ebilfumin capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Ebilfumin-water mixture. For measuring 12.5 ml of water, a 10 ml dispenser should be used.

The appropriate dispenser sizes for taking the correct volume of Ebilfumin suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full-term newborn babies):

Dose of Ebilfumin	Amount of Ebilfumin suspension	Dispenser size to use (grading 0.1 ml)
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Children 1 year or older, weighing less than 40 kg:

Dose of Ebilfumin	Amount of Ebilfumin suspension	Dispenser size to use (grading 0.1 ml)
30 mg	5.0 ml	5.0 ml (or 10.0 ml)
45 mg	7.5 ml	10.0 ml
60 mg	10.0 ml	10.0 ml