PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE:

FLUMITEV 30, hard capsules

FLUMITEV 45, hard capsules

FLUMITEV 75, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

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

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

Sugar free.

For full list of excipients, see **section 6.1**.

3 PHARMACEUTICAL FORM:

Capsules, hard

FLUMITEV 30 mg:

Each 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.

FLUMITEV 45 mg:

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.

FLUMITEV 75 mg:

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:

FLUMITEV is indicated for the treatment of influenza in adults and children ≥ 1 year of age (see **sections 4.2** and **4.4**).

Pandemic use only: FLUMITEV is indicated for the treatment of infants 6 - 12 months of age during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see **sections 4.4** and **5.2**).

Prophylaxis:

FLUMITEV is indicated for the prophylaxis of influenza in adults and children ≥1 year of age.

4.2 Posology and method of administration:

Posology:

FLUMITEV may be taken with or without food (see **section 5.2**). However, FLUMITEV taken with food may enhance tolerability in some patients.

Treatment of influenza

Treatment should begin within the first or second day of onset of symptoms of

influenza.

Adults and adolescents: The recommended oral dose of FLUMITEV capsules in adults and adolescents ≥ 13 years is a 75 mg capsule twice daily, for 5 days.

Children: Children weighing > 40 kg who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily or one +30 mg capsule plus one 45 mg capsule twice a day.

The recommended oral dose of FLUMITEV for children ≥ 1 year of age is:

Body Weight	**Recommended treatment dose for 5 days**	
	Capsules	**Pharmacy compounded 6 mg/ml suspension compounded from capsules** (see **section 6.6**)
≤ 15 kg	30 mg twice daily	5,0 ml twice daily
> 15 to 23 kg	45 mg twice daily	7,5 ml twice daily
> 23 kg to 40 kg	60 mg twice daily	10,0 ml twice daily
> 40 kg	75 mg twice daily	12,5 ml twice daily

The 75 mg dose can be measured using a combination of 30 mg and 45 mg.

The recommended oral dose of FLUMITEV for children 6 - 12 months of age:

Based on limited pharmacokinetic data currently available, a dosage of 3 mg/kg twice daily in children 6 - 12 months of age provides plasma exposure to the active metabolite in the majority of patients similar to that shown to be clinically efficacious in older children and adults.

Recommended volumes of the pharmacy compounded suspension (3 mg/kg body weight) are shown in the table below:

Body Weight (kg)	**FLUMITEV (mg)**	**Volume per dose (6 mg/ml) Pharmacy compounded suspension [1])**
6	18	3 ml

7	21	3,5 ml
8	24	4 ml
9	27	4,5 ml
≥ 10	30	5 ml

[1)] A pharmacy compounded 6 mg/ml suspension can be prepared from the capsules. See **section 6.6: *Pharmacy compounding***.

The recommended treatment dose for infants 6 - 12 months is 3 mg/kg twice daily for 5 days, during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see **section *5.2: Special Populations***).

Prophylaxis of influenza:

Adults and adolescents:

The recommended oral dose of FLUMITEV for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for at least 10 days. Therapy should begin within two days of exposure.

The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts for as long as dosing is continued.

Children ≥ 1 year of age:

Children weighing > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once a day, for 10 days. As an alternative to the capsules, the pharmacy compounded 6 mg/ml suspension can be prepared from the capsules. See **section 6.6: *Pharmacy compounding***.

The recommended prophylactic oral dose of FLUMITEV for children ≥ 1 year of age is:

Body Weight	**Recommended treatment dose for 10 days**	
	Capsules	**Pharmacy compounded (6 mg/ml) Pharmacy compounded suspension [1)]**
≤ 15 kg	30 mg twice daily	5,0 ml twice daily
> 15 to 23 kg	45 mg twice daily	7,5 ml twice daily
> 23 kg to 40 kg	60 mg twice daily	10,0 ml twice daily
> 40 kg	75 mg twice daily [2)]	12,5 ml twice daily

[1)] A pharmacy compounded 6 mg/ml suspension can be prepared from the capsules. See **section 6.6: *Pharmacy compounding***.

[2)] The 75 mg dose can be measured using a combination of 30 mg and 45 mg.

Special populations:

Patients with renal impairment:

Treatment of influenza: No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min.

Dose adjustment is recommended for patients with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	**Recommended dose for treatment**
> 30 to 60 (mL/min)	30 mg twice daily for 5 days
> 10 to 30 (mL/min)	30 mg once daily for 5 days

In patients undergoing routine haemodialysis an initial dose of 30 mg FLUMITEV can be administered prior to the start of dialysis if influenza symptoms develop during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered

after every haemodialysis session.

For peritoneal dialysis an initial dose of 30 mg of FLUMITEV administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see **section 5.2: *Special Populations*** and **4.4**). The pharmacokinetics of FLUMITEV have not been studied in patients with "endstage renal disease" (i.e. creatinine clearance < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

Prophylaxis of influenza: No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min.

Dose adjustment is recommended for patients with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	**Recommended dose for prevention**
> 30 to 60 (mL/min)	30 mg once daily
> 10 to 30 (mL/min)	30 mg every second day

In patients undergoing routine haemodialysis an initial dose of 30 mg of FLUMITEV can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of FLUMITEV administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see **section *5.2: Special Populations*** and **4.4**). The pharmacokinetics of FLUMITEV have not been studied in patients with "end-stage renal disease" (i.e., creatinine clearance < 10 mℓ/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

Patients with hepatic impairment:

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza (see **section *5.2: Special Populations***). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immuno-compromised patients:

Seasonal prophylaxis in immuno-compromised patients 1 year of age and older is recommended for 12 weeks. No dose adjustment is necessary.

Elderly:

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see **section *5.2: Special Populations***).

Paediatric population:

The safety and efficacy of FLUMITEV in children under 1 year has not been established (see **section 5.2: *Special Populations***). FLUMITEV should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

Method of administration:

For oral administration.

Patients who are unable to swallow capsules may receive appropriate extemporaneous formulation, see **section 6.6** for preparation.

4.3 Contraindications:

- Hypersensitivity to oseltamivir phosphate or to any excipient of FLUMITEV as listed in **section 6.1.**

4.4 Special warnings and precautions for use:

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

FLUMITEV is not a substitute for influenza vaccination:

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

Resistance of influenza viruses to FLUMITEV have been reported. The prevalence of virus resistance and virus strains on subtypes differs between countries and seasons. The resistance of the predominant virus to FLUMITEV generally changes from season to season. Updated local surveillance data from the National Institute for Communicable Diseases (NICD) should be consulted for information on seasonal prevalence of medicine resistant viruses.

Severe concomitant condition:

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

Immunocompromised patients:

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

Cardiac / respiratory disease:

Efficacy of FLUMITEV 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**).

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 such as convulsions, abnormal and inappropriate behaviour, disturbances in consciousness, hallucinations and delirium have been reported during FLUMITEV administration in patients with influenza. In some cases, the delirium resulted in accidental self-injury and death. These events occurred mostly within the first few days of taking FLUMITEV.

Patients, and especially paediatric and adolescent patients, taking FLUMITEV should be carefully monitored for signs of abnormal behaviour.

Paediatric population:

Based on limited pharmacokinetic and safety data, FLUMITEV may only be used in infants 6 – 12 months of age for treatment during a pandemic influenza outbreak. The treating medical practitioner should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure that there is a potential benefit to the child.

FLUMITEV should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

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

4.5 Interaction with other medicines 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 FLUMITEV in subjects when taking co-excreted medicines 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 FLUMITEV with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

There is no mechanistic basis for an interaction with oral contraceptives.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic medicines has no effect on plasma levels of FLUMITEV or its active metabolite.

Co-administration with paracetamol does not alter plasma levels of FLUMITEV, its active metabolite, or paracetamol.

FLUMITEV has been administered with commonly used medicines such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide), antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H_2-receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines

(theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators, and analgesic medicines (aspirin, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of FLUMITEV with these compounds.

4.6 Fertility, pregnancy and lactation:

Animal reproductive studies in rats and rabbits, no teratogenic effect was observed.

Pregnancy:

Safety in pregnancy has not been established.

No controlled clinical trials have been conducted on the use of FLUMITEV in pregnant women.

Breastfeeding:

Safety in lactation has not been established.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited information is available on infants breastfed by mothers taking FLUMITEV and on excretion of FLUMITEV in breast milk. Limited data demonstrated that low levels of oseltamivir and the active metabolite were detected in breast milk. Safety in humans has not been demonstrated in children of breastfeeding women using FLUMITEV. Mothers on treatment with FLUMITEV should not breastfeed their infants.

Fertility:

No human data available.

4.7 Effects on ability to drive and use machines:

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

4.8 Undesirable effects:

a. Summary of the safety profile:

In adults/adolescents, the most frequently 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 adverse reactions did not lead to discontinuation of FLUMITEV.

The following serious adverse reactions have been less frequently reported since FLUMITEV 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.)**

b. Tabulated summary of adverse reactions:

Treatment and prevention of influenza in adults and adolescents:

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

Table 1 Adverse reactions reported in the treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	*Frequent*	Bronchitis, herpes simplex, nasopharyngitis, upper respiratory tract infections, sinusitis, influenza
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopenia
Immune system disorders	*Less frequent*	Hypersensitivity reactions, anaphylactic reactions, anaphylactoid reactions
Psychiatric disorders	*Less frequent*	Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury
Nervous system disorders	*Frequent*	Headache, insomnia
	Less frequent	Altered level of consciousness, convulsion
Eye disorders	*Less frequent*	Visual disturbance
Cardiac disorders	*Less frequent*	Cardiac dysrhythmia
Respiratory, thoracic and mediastinal disorders	*Frequent*	Cough, sore throat, rhinorrhoea, nasal congestion
Gastrointestinal disorders	*Frequent*	Nausea, vomiting, abdominal

MedDRA system organ class	**Frequency**	**Adverse reactions**
		pain (incl. upper abdominal pain), dyspepsia, diarrhoea
	Less frequent	Gastrointestinal bleedings, haemorrhagic colitis
Musculoskeletal and connective tissue disorders	*Frequent*	Back pain, arthralgia, myalgia
Reproductive system and breast disorders	*Frequent*	Dysmenorrhoea
Hepato-biliary disorders	*Less frequent*	Elevated liver enzymes, fulminant hepatitis, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	*Less frequent*	Eczema, dermatitis, rash, urticaria, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
General disorders and administration site conditions	*Frequent*	Pain, dizziness (incl. vertigo), fatigue, pyrexia, pain in limb, influenza-like illness

Treatment and prevention of influenza in children:

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

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	*Frequent*	Otitis media, bronchitis, pneumonia, sinusitis
Blood and lymphatic system disorders	*Frequent*	Lymphadenopathy
Nervous system disorders	*Frequent*	Headache
Eye disorders	*Frequent*	Conjunctivitis (including red eyes, eye discharge and eye pain)
Ear and labyrinth disorders	*Frequent*	Earache
	Less frequent	Tympanic membrane disorder
Respiratory, thoracic and mediastinal disorders	*Frequent*	Cough, nasal congestion, rhinorrhoea, asthma (including aggravated asthma), epistaxis
Gastrointestinal disorders	*Frequent*	Vomiting, abdominal pain (incl. upper abdominal pain), dyspepsia, nausea, diarrhoea
Skin and subcutaneous tissue disorders	*Less frequent*	Dermatitis (including allergic and atopic dermatitis)

Post-Marketing Experience:

Psychiatric disorders/Nervous system disorders: Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, including abnormal motor

behaviour, disturbances in consciousness, hallucinations and delirium have been reported. In some cases, the delirium resulted in accidental self-injury and death. More events were reported in males than in females. These neuropsychiatric events occurred mostly within the first few days of administration of FLUMITEV. Patients, especially paediatric and adolescent patients should therefore be carefully monitored for abnormal behaviour for the first few days. Convulsions and psychiatric symptoms have also been reported in patients with influenza who were not taking FLUMITEV.

Immune system disorders: allergy, anaphylactic/anaphylactoid reactions and face oedema have been reported.

Skin and subcutaneous tissue disorders: Cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis have been reported.

Hepato-biliary disorders: Hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving FLUMITEV.

Gastrointestinal disorders: Gastrointestinal bleedings, in particular, haemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with FLUMITEV was interrupted.

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

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.

e. Other special populations:

Paediatric population (infants less than one year of age):

Safety information available on oseltamivir e.g. FLUMITEV administered for treatment of influenza in infants less than 1 year of age from prospective and retrospective observational trials (comprising together more than 2 400 children of that age class), epidemiological database research and postmarketing reports suggest that the safety profile in children less than 1 year of age is similar to the established safety profile of children aged 1 year and above.

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 safety profile of oseltamivir observed in 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.

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

In overdose, symptoms may be the exacerbation or exaggeration of side effects. Treatment is supportive and symptomatic.

No specific antidote is known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors

ATC code: J05AH02

Oseltamivir phosphate is a pro-drug and selective inhibitor of influenza virus neuraminidase enzymes. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells, and the further spread of infectious virus.

The active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B.

The active metabolite also inhibits influenza virus growth in vitro and inhibits influenza virus replication and pathogenicity in vivo. The active metabolite reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

5.2 Pharmacokinetic properties:

Absorption:

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to the active metabolite. Plasma concentrations of the active metabolite are measurable within 30 minutes, reach

near maximal levels in 2 to 3 hours post dose, and substantially exceed (> 20-fold) those of the pro-drug. At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are unaffected by co-administration with food (see **section 4.2**).

Distribution:

The mean volume of distribution (Vss) of the active metabolite is approximately 23 litres in humans. The active moiety reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit. In these studies, antiviral concentrations of the active metabolite were seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea following oral administration of doses of oseltamivir phosphate.

The binding of the active metabolite to human plasma protein is negligible (approximately 3 %). The binding of the pro-drug to human plasma protein is 42 %. These levels are insufficient to cause significant medicine interactions.

Biotransformation:

Oseltamivir phosphate is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite are substrates for or inhibitors of cytochrome P450 isoforms (see **section 4.5**).

Elimination:

Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to the active metabolite. The active metabolite is not further metabolised and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline, with a half-life of 6 - 10 hours in most subjects. The active medicine is eliminated entirely

(> 99 %) by renal excretion. Renal clearance (18,8 L/h) exceeds glomerular filtration rate (7,5 L/h) indicating that tubular secretion in addition to glomerular filtration occurs. Less than 20 % of an oral radio-labelled dose is eliminated in faeces.

Pharmacokinetics in Special Populations:

Patients with renal impairment:

Administration of 100 mg of oseltamivir twice daily for five days to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to declining renal function.

Treatment of influenza:

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 - 60 mL/min, it is recommended that the dose be reduced to 30 mg of oseltamivir twice daily for 5 days. In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily for 5 days.

In patients undergoing routine haemodialysis an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis in patients with influenza symptoms during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see **sections 4.2** and **4.4**). The pharmacokinetics of oseltamivir have not been studied in patients with “end-stage renal disease” (i.e., creatinine clearance of < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

Prophylaxis of influenza:

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 - 60 mL/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily. In patients with creatinine clearance between 10 and 30 mL/min receiving oseltamivir it is recommended that the dose be reduced to 30 mg of oseltamivir every other day. In patients undergoing routine haemodialysis an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see **sections 4.2** and **4.4**). The pharmacokinetics of oseltamivir have not been studied in patients with “end-stage renal disease” (i.e., creatinine clearance of < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

Patients with hepatic impairment:

In-vitro studies have shown 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 mild or moderate hepatic impairment (see **section 4.2**). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Elderly:

Exposure to the active metabolite at steady state was 25 - 35 % higher in elderly (age range 65 - 78) compared to young adults who were given comparable doses

of oseltamivir. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of medicine exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza (see **section 4.2**).

Children ≥ 1 year of age:

The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics was studied in a small number of children aged 3 - 12 years enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in children than in adults, resulting in lower exposure in these children for a given mg/kg dose. The rate of clearance of the active metabolite increased with decreasing age over the age range 3 to 16 years. Doses of 2 mg/kg yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

Paediatric population:

Infants 6 to 12 months of age:

Limited pharmacokinetic and safety data are available for infants less than 2 years of age. Pharmacokinetic modelling was undertaken using these data in addition to data from studies in adults and children older than 1 year of age. The results demonstrate that doses of 3 mg/kg twice daily for infants aged 6 to 12 months provide exposures similar to those shown to be clinically efficacious in adults and children > 1 year of age (see **sections 4.1** and **4.2**).

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

FLUMITEV 30 mg hard capsules:

Capsule core

Croscarmellose sodium

Povidone (K-29/32)

Sodium stearyl fumarate

Starch pregelatinized (maize)

Talc

Water, purified

Capsule shell

Gelatine

Iron oxide yellow (E172)

Titanium dioxide (E171)

Printing ink

Shellac** Glaze – 45 % (20 % esterified) in ethanol**

Ammonium hydroxide 28 % (E527)

Iron oxide black (E172)

Propylene glycol (E1520)

FLUMITEV 45 mg hard capsules:

Capsule core

Croscarmellose sodium

Povidone (K-29/32)

Sodium stearyl fumarate

Starch pregelatinized (maize)

Talc

Water, purified

Capsule shell

Gelatine

Titanium dioxide (E171)

Printing ink

Shellac** Glaze – 45 % (20 % esterified) in ethanol**

Ammonium hydroxide 28 % (E527)

Iron oxide black (E127)

Propylene glycol (E1520)

FLUMITEV 75 mg hard capsules:

Capsule core

Croscarmellose sodium

Povidone (K-29/32)

Sodium stearyl fumarate

Starch pregelatinized (maize)

Talc

Water, purified

Capsule shell

Titanium dioxide (E171)

Titanium dioxide (E172)

Gelatine

Printing ink

Shellac** Glaze – 45 % (20 % esterified) in ethanol**

Ammonium hydroxide 28 % (E527)

Iron oxide black (E172)

Propylene glycol (1520)

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 at or below 25 °C.

Protect from light.

Keep original container until required for use.

6.5 Nature and contents of container:

FLUMITEV will be packed in PVC/PE/PVdC/Al blisters or HDPE containers with LDPE lid (and a desiccant).

Pack size: 10 or 100 capsules.

6.6 Special precautions for disposal and other handling:

Any unused medicine 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

FLUMITEV 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 patient information leaflet of FLUMITEV capsules under “Making liquid FLUMETEV 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.

The pharmacist may compound a 6 mg/ml suspension from FLUMITEV 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.

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

Body Weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	50 ml	60 ml or 75 ml*
> 15 kg to 23 kg	75 ml	90 ml or 100 ml*
> 23 kg to 40 kg	100 ml	125 ml
> 40 kg	125 ml	137,5 ml (or 150 ml)*

* Depending on the capsule strength used.

Second, determine the number of capsules and the amount of vehicle (water containing 0,05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

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

Total volume of compounded suspension to be prepared	**Required number of FLUMITEV capsules (mg of oseltamivir)**			**Required volume of vehicle**
	75 mg	**45 mg**	**30 mg**	
60 ml	Please use alternative	8 capsules (360 mg)	12 capsules (360 mg)	59,5 ml

	capsule strength*			
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.

Third, follow the procedure below for compounding the 6 mg/ml suspension from FLUMITEV 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 FLUMITEV 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 FLUMITEV capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethylene terephthalate (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 FLUMITEV capsules for infants and children 1 year of age or older:

Body weight (kg)	**Dose (mg)**	**Volume per dose 6 mg/ml**	**Treatment dose (for 5 days)**	**Prophylaxis dose (for 10 days)**
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7,5 ml	7,5 ml twice daily	7,5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12,5 ml	12,5 ml twice daily	12,5 ml once daily

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

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

Infants less than 1 year of age:

This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medication for a 5-day course of treatment.

The pharmacist may compound a 6 mg/ml suspension from FLUMITEV 30 mg, 45 mg or 75 mg capsules using water containing 0,05 % w/v sodium benzoate added as a preservative.

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

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

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

*Depending on the capsule strength used.

Second, determine the number of capsules and the amount of vehicle (water containing 0,05 % w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

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

Total volume of compounded	**Required number of FLUMITEV capsules (mg of oseltamivir)**			**Required volume of vehicle**
	75 mg	**45 mg**	**30 mg**	

suspension to be prepared				
50 ml	4 capsules (300 mg)	Please use alternative capsule strength*	10 capsules (300 mg)	49,5 ml
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59,5 ml
75 ml	6 capsules (450 mg)	10 capsules (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.

Third, follow the procedure below for compounding the 6 mg/ml suspension from FLUMITEV 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 FLUMITEV 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 FLUMITEV capsules, which are insoluble.)

4. Transfer the suspension to an amber glass or amber polyethylene terephthalate (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 FLUMITEV capsules for infants less than 1 year of age:

Body weight (kg)	**Dose (mg)**	**Volume per dose 6 mg/ml**	**Treatment dose (for 5 days)**
6 kg	18 mg	3 ml	3 ml twice daily
7 kg	21 mg	3,5 ml	3,5 ml twice daily
8 kg	24 mg	4 ml	4 ml twice daily
9 kg	27 mg	4,5 ml	4,5 ml twice daily
≥ 10 kg	30 mg	5 ml	5 ml twice daily

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing 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 FLUMITEV 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, FLUMITEV 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 FLUMITEV suspension involves additional steps.

Detailed instructions can be found in the patient information leaflet of FLUMITEV capsules under “Making liquid FLUMITEV at home”.

7 HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

2090

South Africa

8 REGISTRATION NUMBER(S):

FLUMITEV 30: 56/20.2.8/1035

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FLUMITEV 75: 56/20.2.8/1037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

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10 DATE OF REVISION OF THE TEXT: