NATFLU (OSELTAMIVIR PHOSPHATE) CAPSULES 75MG

Description and Composition:

White to off white powder filled in size '2' capsules with yellow colour cap imprinted with '75 mg' with blue colour ink and grey colour body imprinted with 'NAT' with blue colour ink.

Each capsule contains: Oseltamivir Phosphate USP equivalent to Oseltamivir 75mg.

Pharmacodynamic:

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

Pharmacokinetic:

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 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.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.

Infants and children 1 year of age or older : 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

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.

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.

Hepatic impairment

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.

Pregnant Women

Natflu dosage regimen described in Dosage Section 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 and at a therapeutic level for a range of influenza virus strains. Dose adjustments are not recommended for pregnant women in the treatmentor prophylaxis of influenza.

Immunocompromised Patients

The treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir 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 Dosage and Method of administration sections.

Immunocompromised patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

Indication:

Treatment of influenza

Natflu is indicated for the treatment of influenza in children 6 to 12 months of age during a pandemic influenza outbreak

Natflu is indicated for the treatment of influenza in adults and children ≥ 1 year of age. Treatment should commence as soon as possible but no later than forty-eight hours after the onset of the initial symptoms of infection.

Prophylaxis of influenza
Natflu is indicated for post exposure prophylaxis in adults and children ≥ 1 year following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

Posology and method of administration:

NATFLU IS AVAILABLE IN ONLY ONE STRENGTH OF 75MG. NOT ONLY THE APPROVED DOSE REGIMEN OF OSELTAMIVIR WILL BE DELIVERED; OTHER APPROVED DOSAGE FORMS AND STRENGTHS OF OSELTAMIVIR SHOULD BE USED IN SUCH CASES.

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	75mg 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 75mg 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	75mg twice 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 special populations, immunocompromised patients for more information).

Paediatric population

<u>Children 1 to 12 years of age</u>

Oseltamivir 75 mg capsule is 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	75mg 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.

<u>Post-exposure prevention:</u> The recommended post-exposure prevention dose of Natflu is:

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	75mg twice daily

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

<u>Infants 6 – 12 months of age</u>

<u>Treatment:</u> The recommended treatment dose for infants 6 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 6 - 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. The following dosing regimen is recommended for treatment of infants 6 - 12 months of age:

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

For instructions on preparing the extemporaneous formulation

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 (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis sesssion
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

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

from APD to CAPD if considered necessary by a nephrologist.

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

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) 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 (suspension or capsules) 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. 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.

Method of administration

Oral use.
Patients who are unable to swallow capsules may receive appropriate doses of Oseltamivir suspension.

Contraindication:
Oseltamivir is contraindicated in patients with known hypersensitivity to Oseltamivir phosphate or to any components of the product.

Precautions/Warning:
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.

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

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.

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.

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.

Neuropsychiatric events

Neuropsychiatric events have been reported during administration of Natflu 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.

Interaction with other medicaments:

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems, 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).

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 indicate no malformative nor feto/neonatal toxicity by oseltamivir.

However, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive.

The use of Natflu may be considered during pregnancy if necessary and after considering the available safety and benefit information, and the pathogenicity of the circulating influenza virus strain.

Breastfeeding

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

There is no evidence that Natflu has an effect on male or female fertility.

Side effects/adverse reactions:

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea, vomiting and nausea. 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.

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.

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*).

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, despite a longer duration of dosing in the prophylaxis.

Table 1 Adverse reaction in studies investigating Natflu 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, Convulsion	
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, Hepatitis
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:

Table 2 shows the most frequently reported ARs for pediatrics.

Table 2 Adverse reactions of 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)

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational 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

In general, the safety profile in the patients "at risk" was qualitatively similar to that in otherwise healthy adults/adolescents.

Immunocompromised patients

The most frequent adverse reaction reported in immunocompromised children was vomiting (28%).

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.

Over dosage and treatment:
Experience on over dosage of Oseltamivir has not been experienced yet. However, acute overdosage of Oseltamivir is expected to cause nausea, with or without accompanying emesis. Apart from nausea and/or vomiting, high doses of Oseltamivir in single dose (up to 1000mg) are well tolerated.

Special precautions for disposal and other handling:

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

Extemporaneous formulation

When Natflu powder for oral suspension is not available

In the event that commercially manufactured Natflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Natflu 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 Natflu capsules under "Making liquid Natflu 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 solution 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 is needed.

The pharmacist may compound a 6 mg/ml suspension from Natflu 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	150ml	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 Natflu capsules (mg of Oseltamivir)			Required volume of vehicle
	75mg	45mg	30mg	
60ml	Please use alternative capsule strength*	8 capsules (360mg)	12 capsules (360mg)	59.5ml
75ml	6 capsules (450mg)	10 capsules (450mg)	15 capsules (450mg)	74ml
90ml	Please use alternative capsule strength*	12 capsules (540mg)	18 capsules (540mg)	89ml
100ml	8 capsules (600mg)	Please use alternative capsule strength*	20 capsules (600mg)	98.5ml
125ml	10 capsules	Please use	25 capsules	123.5ml

	(750mg)	alternative capsule strength*	(750mg)	
137.5ml	11 capsules (825mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136ml

*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 Natflu capsules (mg of Oseltamivir)			Required volume of vehicle
	75mg	45mg	30mg	
125ml	10 capsules (750mg)	Please use alternative capsule strength*	25 capsules (750mg)	123.5ml
187.5ml	15 capsules (1120mg)	25 capsules (1120mg)	Please use alternative capsule strength*	185ml
250ml	20 capsules (1500mg)	Please use alternative capsule strength*	50 capsules (1500mg)	246.5ml
300ml	24 capsules (1800mg)	40mg capsules (1800mg)	60 capsules (1800mg)	296ml

*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 Natflu capsules:

1. In a glass beaker of suitable size place the stated amount of water containing 0.05% w/v sodium benzoate added as preservative.
2. Open the stated amount of Natflu 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 Natflu 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 the therapy must be discarded. It is recommended that this information be provided by 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.

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 Natflu 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*)** Immunocompromised 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**.

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 6-12 months 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 Natflu 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 patients 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
≤ 7kg	Upto 80ml	100ml
> 7kg to 10 kg	100ml	125ml

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 Natflu capsules (mg of Oseltamivir)			Required volume of vehicle
	75mg	45mg	30mg	
50ml	4 capsules (300mg)	Please use alternative capsule strength*	10 capsules (300mg)	49.5ml
60ml	Please use alternative capsule strength	8 capsules (360mg)	12 capsules (360mg)	59.5ml
75ml	6 capsules (450mg)	10 capsules (450mg)	15 capsules (450mg)	74ml

* 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 Natflu capsules (mg of Oseltamivir)			Required volume of vehicle
	75mg	45mg	30mg	
100ml	8 capsules (600mg)	Please use alternative capsule strength*	20 capsules (600mg)	98.5ml
125ml	10 capsules (750mg)	Please use alternative capsule strength*	25 capsules (750mg)	123.5ml

* 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 Natflu 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 Natflu 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 Natflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethylene etere phthalate (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 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.

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 Natflu capsules for infants 6-12 months of age (3 mg/kg body weight)

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*)** Immunocompromised 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	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	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml twice daily	2.5 ml once	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	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	5.0 ml

7 kg	21 mg	3.5 ml	3.5 ml twice daily	3.5 ml twice daily	3.5 ml once	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	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml twice daily	4.0 ml once	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	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml twice daily	4.5 ml once	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	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml twice daily	5.0 ml once	5.0 ml

* The recommended duration in immunocompromised infants (6-12 months old) is 10 days.

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 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 Natflu oral suspension is not available, a pharmacy compounded suspension prepared from Natflu capsules must be used (see detailed instructions above). If the commercially manufactured Natflu oral suspension and the pharmacy compounded suspension is also not available, Natflu 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 Natflu suspension involves additional steps. Detailed instructions can be found in the Natflu Patient Information Leaflet or Risalah Ubat Untuk Pesakit (RiMUP).

Storage:

Store below 30ºC. Protect from light.

Shelf life: 48 months.

Presentation: One box contains 10 capsules in a blister pack (PVC/Aclar/PVC, sealed with peel push foil).

Manufactured By:

Natco Pharma Ltd
Kothur – 509 228
Ranga Reddy District,
Telangana, India.

Product Registration Holder:
Perniagaan Normahas Sdn Bhd
1-5-10, Block G,
Diamond Square,
Jalan 1/50, melalui Jalan Gombak,
53000 Kuala Lumpur, Malaysia

Revised on: June 2023