PRODUCT MONOGRAPH

PrNAT-OSELTAMIVIR

oseltamivir capsules

oseltamivir phosphate capsules, USP

30 mg, 45 mg and 75 mg oseltamivir (as oseltamivir phosphate)

oseltamivir powder for oral suspension
6 mg/mL oseltamivir (as oseltamivir phosphate) when reconstituted

Antiviral Agent

Natco Pharma (Canada) Inc.
2000 Argentia Road, Plaza 1, Suite 200
Mississauga, Ontario
L5N 1P7

Date of Revision:
September 18, 2020

Submission Control No: 223389

Table of Contents

[Pr]NAT-OSELTAMIVIR

oseltamivir (as oseltamivir phosphate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Capsules / 30 mg, 45 mg and 75 mg oseltamivir (as oseltamivir phosphate)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*
Oral	Powder for Oral Suspension / 6 mg/mL oseltamivir (as oseltamivir phosphate) when reconstituted	Sorbitol (see WARNINGS AND PRECAUTIONS) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Treatment of Influenza

NAT-OSELTAMIVIR (oseltamivir phosphate) is indicated for:

- The treatment of uncomplicated acute illness due to influenza infection in adults and adolescents (≥13 years) who have been symptomatic for no more than 2 days.

  The treatment indication is based on two Phase III clinical studies of naturally occurring influenza in adults in which the predominant infection was influenza A (95%) and a limited number with influenza B (3%) and influenza of unknown type (2%), reflecting the distribution of these strains in the community. The indication is also supported by influenza A and B challenge studies. No data are available to support the safety and efficacy of oseltamivir phosphate in adult patients who commenced treatment after 40 hours of onset of symptoms.

- The treatment of uncomplicated acute illness due to influenza in pediatric patients 1 year and older who have been symptomatic for no more than 2 days.

  The pediatric indication is based on one Phase III clinical study of naturally occurring influenza in pediatric patients aged 1 to 12 years in which 67% of influenza infected patients were infected with influenza A and 33% with influenza B.

NAT-OSELTAMIVIR, when taken as recommended for the treatment of influenza, alleviates the symptoms and reduces their duration, (see **CLINICAL TRIALS**).

Prevention/Prophylaxis of Influenza

The decision to administer NAT-OSELTAMIVIR for prophylaxis to close contacts should be based on the knowledge that influenza is circulating in the area and the index case demonstrates characteristic symptoms of influenza. NAT-OSELTAMIVIR is not effective in providing prophylaxis for respiratory infections other than influenza therefore a proper diagnosis of the index case is important.

NAT-OSELTAMIVIR is not a substitute for influenza vaccination. Vaccination is the preferred method of prophylactic prevention against influenza. The use of NAT-OSELTAMIVIR should not affect the evaluation of individuals for annual influenza vaccination, in accordance to "Health Canada. An Advisory Committee Statement on Influenza Vaccination for the Current Year/Season."

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations.

NAT-OSELTAMIVIR is indicated for:

- The prevention of influenza illness in adults and adolescents 13 years and older following close contact with an infected individual (the index case).

- The prevention indication is based on a phase III clinical study programme consisting of 4 Phase III clinical trials.

- The prevention of influenza illness in pediatric patients 1 year and older following close contact with an infected individual (the index case).

  This indication is based on a sub-study of pediatric patients in a Phase III clinical trial.

CONTRAINDICATIONS

- NAT-OSELTAMIVIR (oseltamivir phosphate) is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

No increased efficacy was demonstrated in adult subjects receiving 150 mg oseltamivir phosphate twice daily for 5 days compared to those receiving 75 mg twice daily for the treatment of influenza.

There is no evidence for efficacy of oseltamivir phosphate in any illness caused by agents other than influenza viruses Types A and B. Data on treatment of influenza B are limited.

Efficacy of oseltamivir phosphate in patients who begin treatment after 48 hours of symptoms has not been established.

Efficacy of oseltamivir phosphate 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. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

Safety and efficacy of repeated treatment or prevention courses have not been studied.

Efficacy of oseltamivir phosphate for treatment or prevention of influenza in immunocompromised patients has not been established.

Endocrine and Metabolism

A bottle of 13 g NAT-OSELTAMIVIR powder for oral suspension contains 11.147 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol which is unsuitable for subjects with hereditary fructose intolerance.

Hepatic

There have been post-marketing reports of elevated liver enzymes and hepatotoxicity including fulminant hepatitis/hepatic failure, in some cases with fatal outcome, where a causal relationship with oseltamivir could not be excluded, especially in patients with pre-existing liver disease.

The safety, efficacy and pharmacokinetics of oseltamivir in patients with severe hepatic impairment have not been studied (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment, Hepatic Impairment**).

Neuropsychiatric

There have been post-marketing reports of delirium and self-injury, in some cases resulting in fatal outcomes, in patients with influenza who were receiving oseltamivir phosphate. Because these events were reported voluntarily during clinical practice, estimate of frequency cannot be made but they appear to be uncommon based on oseltamivir phosphate usage data. These events were reported primarily among pediatric patients. The contribution of oseltamivir phosphate to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient (see **ADVERSE REACTIONS: Post-Market Adverse Drug Reactions, Neurologic, Psychiatric**).

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.

Renal

Renal Impairment: For dose adjustments in patients with renal impairment (for both treatment and prevention) - see **DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment.**

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.

Resistance

In clinical studies of naturally acquired infection, the cumulative incidence of oseltamivir-resistant virus by phenotyping alone or by phenotyping and genotyping was 0.32% (4/1245) or 0.4% (5/1245) respectively in adult/adolescent patients. In children with naturally acquired influenza virus infection, resistance was determined in 6 clinical studies WV15731 (0%; 0/5), WV15758 (8%; 15/183), WV15759/WV15871 (0%, 0/60), JV16284 (19%, 8/43), WV16193 (0%, 0/147), NV16871 (8%, 2/26). From the data obtained in these studies, the cumulative incidence of oseltamivir resistance in pediatric patients aged 1 to 12 years was 4.1% (19/464) based on phenotyping and 5.4% (25/464) based on phenotyping and genotyping (full genotyping was not performed on all patients). The patients cleared the virus normally and showed no clinical deterioration.

There has been no evidence for emergence of drug resistance associated with the use of oseltamivir phosphate in clinical studies conducted to date in post-exposure (7 days), post-exposure within the household groups (10 days) and seasonal (42 days) prophylaxis of influenza in immunocompetent persons (see **MICROBIOLOGY: Resistance**).

Insufficient information is available to fully characterize the risk of emergence of resistance to oseltamivir phosphate in clinical use (see **MICROBIOLOGY: Resistance**).

Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions have been reported since marketing in patients treated with oseltamivir phosphate (see **ADVERSE REACTIONS: Post-Market Adverse Drug Reactions**).

Special Populations

Pregnant Women: At present, insufficient data are available in pregnant women taking oseltamivir phosphate to enable an evaluation of the potential for oseltamivir phosphate to cause fetal malformations or fetal toxicity. NAT-OSELTAMIVIR should therefore be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No controlled clinical trials have been conducted on the use of oseltamivir phosphate in pregnant women. Results from a pooled pharmacokinetic analysis indicate a lower exposure to the active metabolite in pregnant women compared to non-pregnant women; however, this predicted exposure is expected to have clinical benefits and there are insufficient pharmacokinetic and safety data to recommend a dose adjustment in pregnant women who are justified to use oseltamivir phosphate.

Studies for effects on embryo-fetal development were conducted in rats (50, 250 and 1500

mg/kg/day) and rabbits (50, 150 and 500 mg/kg/day) by the oral route. Relative exposures at these doses were, respectively, 2, 13 and 100 times human exposure in the rat and 4, 8 and 50 times human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. An increased incidence of abortion was seen in the 500 mg/kg/day group. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal individual abnormalities and variants in the exposed offspring in these studies. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied. In view of the isolated nature of this finding it was considered to be of doubtful toxicological significance. For the results of administration of oseltamivir to juvenile rats see **WARNINGS AND PRECAUTIONS, Nursing Women**.

Nursing Women: Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. In lactating rats, oseltamivir and the active metabolite are excreted in 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 sub-therapeutic dose to the infant. Considering this information, and the pathogenicity of the circulating influenza virus strain, administration of oseltamivir may be considered where the potential benefit to the lactating mother justifies the potential risk to the nursing infant.

Pediatrics (< *1* year of age): NAT-OSELTAMIVIR should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity). The efficacy of NAT-OSELTAMIVIR in infants younger than 1 year of age have not been established (see CLINICAL TRIALS).

Geriatrics (≥ *65* years of age): Efficacy of oseltamivir phosphate in the treatment of elderly patients has not been evaluated. Safety data in 372 elderly patients (≥ 65 years old) showed no overall difference between these subjects and younger adults. Based on drug exposure and tolerability, dosage adjustments are not anticipated for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Geriatrics**).

Safety has been demonstrated in elderly residents of nursing homes who took oseltamivir phosphate for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season (see **CLINICAL TRIALS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In adult/adolescent treatment studies with oseltamivir phosphate the most frequently reported adverse events were nausea and vomiting. In the prevention studies adverse events were qualitatively very similar to those seen in the treatment studies. In the pediatric treatment and prophylaxis studies the most frequently reported adverse event was vomiting.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates

observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult Treatment Studies

In a total of 4624 patients, including patients on placebo and 75 mg b.i.d. oseltamivir phosphate, in adult/adolescent phase III studies in the treatment of influenza, the most frequently reported adverse events were nausea and vomiting. These events were transient and generally occurred with first dosing. These events did not lead to patient discontinuation of study drug in the vast majority of instances. At the recommended dose of 75 mg twice daily, the most frequently reported adverse events that led to patient withdrawal were nausea and vomiting.

In adult/adolescent phase III treatment studies, some adverse events occurred more frequently in patients taking oseltamivir phosphate compared to those taking placebo. The adverse events that occurred with an incidence of ≥1% at the recommended dose, either for treatment or prophylaxis, are shown in Table 1. This summary includes healthy young adults and "at risk" patients (patients at higher risk of developing complications associated with influenza e.g. elderly patients and patients with chronic cardiac or respiratory disease). Those events with an incidence of ≥ 1% and which were reported more frequently in patients taking oseltamivir phosphate compared with placebo, irrespective of causality, were nausea, vomiting, abdominal pain and headache.

Table 1: Most Frequent Adverse Events in Studies in Naturally Acquired Influenza for Adults/Adolescents for Treatment or Prophylaxis

Adverse Event **System Organ Class (MedDRA)**	**Treatment***				**Prevention**			
	Oseltamivir Phosphate 75 mg twice daily for 5 days N=2647		**Placebo N=1977**		**Oseltamivir Phosphate 75 mg once daily N=1945**		**Placebo N=1588**	
Ear and Labyrinth Disorders								
Dizziness (incl.Vertigo)*	54	(2.0%)	49	(2.5%)	28	(1.4%)	24	(1.5%)
Gastrointestinal Disorders								
Nausea (without vomiting)	263	(9.9%)	118	(6.0%)	156	(8.0%)	66	(4.2%)
Vomiting	205	(7.7%)	63	(3.2%)	46	(2.4%)	19	(1.2%)
Diarrhea*	149	(5.6%)	147	(7.4%)	66	(3.4%)	66	(4.2%)
Abdominal pain (incl. upper abdominal pain)*	62	(2.3%)	51	(2.6%)	47	(2.4%)	31	(2.0%)
Dyspepsia*	12	(0.5%)	9	(0.5%)	29	(1.5%)	23	(1.4%)

Adverse Event System Organ Class (MedDRA)	Treatment*				Prevention			
	Oseltamivir Phosphate 75 mg twice daily for 5 days N=2647		Placebo N=1977		Oseltamivir Phosphate 75 mg once daily N=1945		Placebo N=1588	
General Disorders and Administration Site Reactions								
Fatigue*	14	(0.5%)	9	(0.5%)	142	(7.3%)	107	(6.7%)
Pain *	8	(0.3%)	5	(0.3%)	70	(3.6%)	43	(2.7%)
Pyrexia*	6	(0.2%)	9	(0.5%)	33	(1.7%)	33	(2.1%)
Pain in limb*	5	(0.2%)	1	(0.1%)	20	(1.0%)	5	(0.3%)
Influenza like illness*	—	—	1	(0.1%)	21	(1.1%)	24	(1.5%)
Infections and Infestations								
Bronchitis	70	(2.6%)	72	(3.6%)	10	(0.5%)	14	(0.9%)
Sinusitis*	35	(1.3%)	22	(1.1%)	15	(0.8%)	12	(0.8%)
Herpes simplex*	27	(1.0%)	23	(1.2%)	11	(0.1%)	9	(0.6%)
Nasopharyngitis*	4	(0.2%)	2	(0.1%)	80	(4.1%)	68	(4.3%)
Upper respiratory tract infections*	5	(0.2%)	1	(0.1%)	60	(3.1%)	51	(3.2%)
Influenza*	—	—	—	—	46	(2.4%)	41	(2.6%)
Nervous System Disorders								
Headache	45	(1.7%)	27	(1.4%)	335	(17.2%)	260	(16.4 %)
Insomnia*	31	(1.2%)	17	(0.9%)	22	(1.1%)	14	(0.9%)
Respiratory, Thoracic and Mediastinal Disorders								
Cough*	42	(1.6%)	38	(1.9%)	94	(4.8%)	90	(5.7%)
Nasal congestion*	27	(1.0%)	22	(1.1%)	134	(6.9%)	113	(7.1%)
Sore throat*	25	(0.9%)	14	(0.7%)	100	(5.1%)	86	(5.4%)
Rhinorrhea*	6	(0.02%)	5	(0.3%)	29	(1.5%)	19	(1.2%)
Musculosceletal, Connective Tissue and Bone Disorders								
Back pain*	13	(0.5%)	9	(0.5%)	41	(2.1%)	41	(2.6%)
Arthralgia*	4	(0.2%)	3	(0.2%)	28	(1.4%)	39	(2.5%)
Myalgia*	7	(0.3%)	4	(0.2%)	20	(1.0%)	21	(1.3%)
Disorders of Reproductive System and Breast								

Adverse Event System Organ Class (MedDRA)	Treatment*		Prevention	
	Oseltamivir Phosphate 75 mg twice daily for 5 days N=2647	Placebo N=1977	Oseltamivir Phosphate 75 mg once daily N=1945	Placebo N=1588
Dysmenorrhea*	— —	— —	53 (2.7%)	51 (3.2%)

* These events may be related to the underlying influenza infection because they occurred either more frequently in patients on placebo compared to patients on oseltamivir phosphate, or the difference in frequency between the two arms was less than 1%.

Additional adverse events occurring in <1% of patients receiving oseltamivir phosphate for treatment included unstable angina, anemia, pseudomembranous colitis, humerus fracture, pneumonia, pyrexia, and peritonsillar abscess.

Adult Prevention Studies
A total of 3533 subjects (adolescents, healthy adults and elderly) participated in 3 phase III prevention studies, of whom 1480 received the recommended dose of 75 mg once daily. Adverse events were qualitatively similar to those seen in the treatment studies (see Table 1). There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received oseltamivir phosphate or placebo, compared with the younger population (aged up to 65 years).

In another study, an additional 399 subjects received 75 mg of oseltamivir phosphate once daily for 10 days following the identification of a household index case. Similar to previous studies, nausea (8.3%), vomiting (4.5%), diarrhea (0.8%) and headache (7.8%) were among the most commonly reported adverse events.

Pediatric Treatment Studies
A total of 1480 pediatric patients aged 1 to 12 years (including 698 otherwise healthy pediatric patients aged 1 to 12 and 334 asthmatic pediatric patients aged 6 to 12) participated in clinical studies of oseltamivir phosphate given for the treatment of influenza. A total of 858 pediatric patients received treatment with oseltamivir phosphate oral suspension.

Adverse events occurring in ≥ 1% of pediatric patients receiving oseltamivir phosphate are listed in Table 2. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric patients treated with oseltamivir phosphate included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the vast majority of cases.
The adverse event profile in adolescents is similar to that described for adult patients and pediatric patients aged 1 to 12 years.

Table 2: Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza

Adverse Event System Organ Class (MedDRA)	Treatment[a]		Prophylaxis[b]	
	Oseltamivir Phosphate 2 mg/kg twice daily N=858	Placebo N=622	Prophylaxis with Oseltamivir Phosphate[c] N=148	No Prophylaxis[b] N=87
Nervous System Disorders				
Headaches	3 (0.3%)	5 (0.8%)	5 (3.4%)	1 (1.1%)
Blood and Lymphatic system Disorders				
Lymphadenopathy *	5 (0.6%)	8 (1.3%)	-	-
Ear and Labyrinth Disorders				
Earache*	10 (1.2%)	4 (0.6%)	1 (0.7%)	-
Tympanic membrane disorder*	4 (0.5%)	6 (1.0%)	-	-
Eye Disorders				
Conjunctivitis (incl. red eyes, eye discharge and eye pain)*	9 (1.0%)	2 (0.3%)	-	-
Gastrointestinal Disorders				
Vomiting	140 (16.3%)	51 (8.2%)	12 (8.1%)	2 (2.3%)
Diarrhea*	63 (7.3%	49 (7.9%)	1 (0.7%)	-
Abdominal pain(incl. upper abdominal pain)*	29 (3.4%)	21 (3.4%)	3 (2.0%)	-
Nausea	32 (3.7%)	27 (4.3%)	6 (4.1%)	1 (1.1%)
Dyspepsia*	2 (0.2%)	-	3 (2.0%)	-
Infections and Infestations				
Otitis media *	43 (5.0%)	51 (8.2%)	3 (2.0%)	2 (2.3%)
Pneumonia*	29 (3.4%)	19 (3.1%)	-	1 (1.1%)
Bronchitis *	14 (1.6%)	15 (2.4%)	-	2 (2.3%)
Sinusitis *	11 (1.3%)	13 (2.1%)	1 (0.7%)	-
Nasopharyngitis*	2 (0.2%)	2 (0.3%)	2 (1.4%)	4 (4.6%)
Upper respiratory tract infection*	3 (0.3%)	3 (0.5%)	2 (1.4%)	3 (3.4%)
Respiratory, Thoracic and Mediastinal Disorders				
Cough*	8 (0.9%)	4 (0.6%)	18 (12.2%)	23 (26.4%)
Nasal congestion*	3 (0.3%)	-	16 (10.8%)	17 (19.5%)
Asthma (including aggravated)	22 (2.6%)	25 (4.0%)	2 (1.4%)	1 (1.1%)
Epistaxis*	18 (2.1%)	14 (2.3%)	1 (0.7%)	-
Rhinorrhoea*	2 (0.3%)	2 (0.3%)	2 (1.4%)	1 (1.1%)
Skin and Subcutaneous Tissue Disorders				
Dermatitis *	9 (1.0%)	11 (1.8%)	-	-

Adverse Event System Organ Class (MedDRA)	Treatment[a]		Prophylaxis[b]	
	Oseltamivir Phosphate 2 mg/kg twice daily N=858	Placebo N=622	Prophylaxis with Oseltamivir Phosphate[c] N=148	No Prophylaxis[b] N=87
General Disorders and Administration Site Reactions				
Pyrexia *	2 (0.2%)	2 (0.3%)	3 (2.0%)	6 (6.9%)

a Pooled data from Phase III trials of Oseltamivir phosphate treatment of naturally acquired influenza.
b Subjects participating in an uncontrolled household transmission study (in which household contacts received either oseltamivir phosphate for prophylaxis (once-daily dosing for 10 days) or no prophylaxis but Oseltamivir phosphate treatment if they became ill), who remained on no prophylaxis and did not receive treatment with Oseltamivir phosphate.
c Pooled data from pediatric prophylaxis studies. Unit dose = age-based dosing (see DOSAGE AND ADMINISTRATION).
* These events may be related to the underlying influenza infection because they occurred either more frequently in patients on placebo compared to patients on Oseltamivir phosphate, or the difference in frequency between the two arms was less than 1%.

Pediatric Prevention Studies

Amongst the 148 pediatric patients aged 1 to 12 years who received the recommended dose of Oseltamivir phosphate once daily, in a post-exposure prophylaxis study in households (N=99), and in a separate 6 week pediatric prophylaxis study (n=49), gastrointestinal events, particularly vomiting was the most frequently reported adverse event. Other events reported more frequently by pediatric patients who received oseltamivir phosphate for prophylaxis are nausea, abdominal pain, dyspepsia and earaches. Oseltamivir phosphate was well tolerated in these studies and the adverse events noted were consistent with those previously observed in pediatric treatment studies (see Table 2).

Immunocompromised Patients: In a 12-week prophylaxis study in 475 immunocompromised subjects, including 18 children 1-12 years of age, the safety profile in the 238 subjects receiving oseltamivir phosphate was consistent with that previously observed in oseltamivir phosphate prophylaxis clinical trials.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-marketing use of oseltamivir phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to oseltamivir phosphate exposure.

Skin and hypersensitivity reactions: dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson-Syndrome, toxic epidermal necrolysis, anaphylactic/anaphylactoid reactions and face edema

Liver and biliary system: elevated liver enzymes, hepatotoxicity including fulminant hepatitis/hepatic failure, in some cases with fatal outcome

Gastro-intestinal disorders: gastro-intestinal bleeding, hemorrhagic colitis

Neurologic: seizure

Psychiatric: delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior leading to self-injury, delusions, hallucinations, agitation, anxiety, nightmares (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrated that neither oseltamivir nor the active metabolite are good substrates for P450 mixed-function oxidases or for glucuronyl transferases.

Drug-Drug Interactions

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

Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. Co-administration of probenecid results in an approximate two-fold increase in exposure to the active metabolite due to a decrease in active anionic tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when co-administering with probenecid. Other drugs excreted via anionic tubular secretion have not been evaluated.

Co-administration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

In six subjects, co-administration with acetaminophen did not alter plasma levels of oseltamivir, its active metabolite, or acetaminophen.

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

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid, warfarin, rimantadine, amantadine, cimetidine or with antacids (magnesium and aluminum hydroxides and calcium carbonates).

In phase III treatment and prophylaxis clinical studies, oseltamivir phosphate has been administered with commonly used drugs such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide), antibiotics (penicillin), H_2-receptor blockers (cimetidine), and analgesic agents (acetylsalicylic acid, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of oseltamivir phosphate with these compounds.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Tests
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hepatic Impairment: The safety, efficacy and pharmacokinetics in patients with severe hepatic impairment have not been studied. No studies have been carried out in pediatric patients with hepatic impairment.

Infants: The efficacy of oseltamivir phosphate in infants younger than 1 year of age has not been established. NAT-OSELTAMIVIR should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity).

For information on renal impairment and elderly patients see Dosage Adjustment section.

Recommended Dose – Treatment of Influenza
Treatment should begin no more than two days after the onset of symptoms of influenza.

Adults and Adolescents (≥ 13 years): The recommended oral dose of NAT-OSELTAMIVIR capsules for the treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily, for 5 days.

Pediatrics (1 to 12 years): The recommended oral dose of NAT-OSELTAMIVIR oral suspension for pediatric patients 1 year and older is shown in the table below. NAT-OSELTAMIVIR oral suspension may also be used by adult patients who cannot swallow a capsule. If oseltamivir phosphate oral suspension is not available, NAT-OSELTAMIVIR capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. For children old enough to safely swallow capsules, the 30 and 45 mg capsules can also be taken as outlined in the table below.

Body Weight in kg	Body Weight in lbs	Recommended Dose for 5 Days	Amount of Oral Suspension (6 mg/mL)
≤ 15 kg	≤ 33 lbs	30 mg twice daily	5.0 mL twice daily
> 15 kg to 23 kg	> 33 lbs to 51 lbs	45 mg twice daily	7.5 mL twice daily
> 23 kg to 40 kg	> 51 lbs to 88 lbs	60 mg twice daily	10.0 mL twice daily
> 40 kg	> 88 lbs	75 mg twice daily	12.5 mL twice daily

Use an appropriate oral dosing dispenser to measure the amount of the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.

Recommended Dose – Prevention of Influenza

Therapy should begin within 2 days of exposure after the onset of symptoms in the index case and continue for at least ten days. Viral shedding may continue for up to 14 days in children and elderly after the onset of influenza illness. Therefore, if the index case is a child or an elderly person, therapy with NAT-OSELTAMIVIR for prevention may continue for up to 14 days.

Patients should be instructed to complete the entire course of therapy.

Adults and Adolescents (≥ 13 years): The recommended oral dose of NAT-OSELTAMIVIR for prevention of influenza following close contact with an infected individual (the index case) is 75 mg once daily.

Safety has been demonstrated for up to 12 weeks in immunocompromised patients.

Pediatrics (1 to 12 years): The recommended dose of NAT-OSELTAMIVIR oral suspension for prevention in pediatric patients 1 year and older is shown in the table below. NAT-OSELTAMIVIR oral suspension may also be used by adult patients who cannot swallow a capsule. If Oseltamivir phosphate oral suspension is not available, NAT-OSELTAMIVIR capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. For children old enough to safely swallow capsules, the 30 and 45 mg capsules also be taken as outlined in the table below.

Body Weight in kg	Body Weight in lbs	Recommended Dose for 10 Days	Amount of Oral Suspension (6 mg/mL)
≤ 15 kg	≤ 33 lbs	30 mg once daily	5.0 mL once daily
> 15 kg to 23 kg	> 33 lbs to 51 lbs	45 mg once daily	7.5 mL once daily
> 23 kg to 40 kg	> 51 lbs to 88 lbs	60 mg once daily	10.0 mL once daily
> 40 kg	> 88 lbs	75 mg once daily	12.5 mL once daily

Use an appropriate oral dosing dispenser to measure the amount of oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.

Dosage Adjustment

Hepatic Impairment: No dose adjustment is required in adult patients with mild or moderate hepatic impairment (See **ACTIONS AND CLINICAL, PHARMACOLOGY: Special Populations and Conditions, Hepatic Impairment**).

Renal Impairment: No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. Dosage adjustments for adult patients with creatinine clearance ≤ 60 mL/min are as indicated below. Note that the dosage adjustments are based primarily on population pharmacokinetic modeling data. Clinical safety and efficacy studies at these doses have not been performed.

Treatment of Influenza: In adult patients with a creatinine clearance of >30-60 mL/min, it is recommended that the dose be reduced to 30 mg of NAT-OSELTAMIVIR twice daily for 5 days.
In adult patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 30 mg of NAT-OSELTAMIVIR once daily for 5 days.

Treatment of Influenza for patients undergoing routine hemodialysis: In adult patients an initial dose of 30 mg of NAT-OSELTAMIVIR 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 of NAT-OSELTAMIVIR should be administered after every hemodialysis session, over a period of 5 days.

For adult patients on continuous ambulatory peritoneal dialysis (CAPD) a single 30 mg dose of NAT-OSELTAMIVIR administered prior to the start of dialysis is recommended for treatment.

Prevention of influenza: In adult patients with a creatinine clearance of >30-60 mL/min, it is recommended that the dose be reduced to 30 mg of NAT-OSELTAMIVIR once daily for 10-14 days.
In adult patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 30 mg of NAT-OSELTAMIVIR every other day for a period of 10-14 days.

Prevention of Influenza for patients undergoing routine hemodialysis: In adult patients an initial dose of 30 mg of NAT-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 hemodialysis session for a period of 10-14 days.
For adult patients on peritoneal dialysis an initial dose of 30 mg of NAT-OSELTAMIVIR administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days, for a period of 10-14 days, is recommended for prophylaxis.

Note that 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.

Elderly Patients: No dose adjustment is required for elderly patients with normal renal function (See **WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics**).

Missed Dose

The missed dose should be taken as soon as remembered, then the regular dosing schedule should be continued. Two doses of NAT-OSELTAMIVIR should not be taken at the same time.

Administration

NAT-OSELTAMIVIR may be taken with or without food (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Absorption**). However, taking with food may enhance tolerability in some patients.

Reconstitution of Oral Suspension:

It is recommended that NAT-OSELTAMIVIR powder for oral suspension be reconstituted by the pharmacist prior to dispensing to the patient.

1. Tap the closed bottle several times to loosen the powder.
2. Measure 55 mL of water in a graduated cylinder.
3. Add the total amount of water for reconstitution to the bottle and shake the closed bottle well for 15 seconds. (The bottle containing 390 mg oseltamivir will contain 65 mL of suspension at a final concentration of 6 mg/mL of oseltamivir (as oseltamivir phosphate) when reconstituted.)
4. Remove the child-resistant cap and push bottle adapter into neck of bottle.
5. Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

Dispense with enclosed patient information leaflet, a 10 mL oral syringe and a universal or 28 mm press-in bottle adaptor. It is recommended to write the date of expiration of the reconstituted suspension on the bottle label. (The shelf life of the reconstituted suspension is 10 days if stored at room temperature (not above 25°C) or 17 days if stored in a refrigerator (2-8°C)).

A bottle of 13 g NAT-OSELTAMIVIR powder for oral suspension contains 11.147 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol which is unsuitable for subjects with hereditary fructose intolerance (see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism).

Note: Shake the NAT-OSELTAMIVIR oral suspension well before each use.

Emergency Compounding of an Oral Suspension from NAT-OSELTAMIVIR Capsules (Final Concentration 6 mg/mL)

The following directions are provided for use only during emergency situations. These directions are not intended to be used if the Health Canada-approved, commercially manufactured oseltamivir phosphate for Oral Suspension is readily available from wholesalers or the manufacturer.

Compounding an oral suspension with this procedure will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

Commercially manufactured oseltamivir phosphate for Oral Suspension (6 mg/mL) is the preferred product for pediatric and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that oseltamivir phosphate for Oral Suspension is not available, the pharmacist may compound a suspension (6 mg/mL) from NAT-OSELTAMIVIR (oseltamivir phosphate) Capsules 75 mg using one of the following vehicles: Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), simple syrup OR purified water containing 0.05% w/v sodium benzoate added as preservative. Other vehicles have not been studied. This compounded suspension should not be used for convenience or when the Health Canada-approved oseltamivir phosphate for Oral Suspension is commercially available.

First, calculate the Total Volume of an oral suspension needed to be compounded and dispensed for each patient. The Total Volume required is determined by the weight of each patient. Refer to Table 3.

Table 3: Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the Patient's Weight

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤ 15 kg	≤ 33 lbs	75 mL
16 to 23 kg	34 to 51 lbs	100 mL
24 to 40 kg	52 to 88 lbs	125 mL
≥41 kg	≥89 lbs	150 mL

Second, determine the number of capsules and the amount of vehicle (Cherry Syrup (Humco®), Ora-Sweet SF, simple syrup OR purified water containing 0.05% w/v sodium benzoate added as preservative) that are needed to prepare the Total Volume (calculated from Table 3: 75 mL, 100 mL, 125 mL, or 150 mL) of compounded oral suspension (6 mg/mL). Refer to Table 4.

Table 4: Number of NAT-OSELTAMIVIR 75 mg Capsules and Amount of Vehicle (Cherry Syrup (Humco®), Ora-Sweet SF, simple syrup OR purified water containing 0.05 % w/v sodium benzoate added as preservative) Needed to Prepare the Total Volume of a Compounded Oral Suspension (6 mg/mL)

Total Volume of Compounded Oral Suspension needed to be Prepared	75 mL	100 mL	125 mL	150 mL

Required number of NAT-OSELTAMIVIR 75 mg Capsules*	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Required volume of water	5 mL	7 mL	8 mL	10 mL
Required volume of vehicle Cherry Syrup (Humco®) OR simple syrup OR Ora-Sweet SF (Paddock Laboratories)	69 mL	91 mL	115 mL	137 mL

* Includes overage to ensure all doses can be delivered,

Total Volume of Compounded Oral Suspension needed to be Prepared	75 mL	100 mL	125 mL	150 mL
Required number of NAT-OSELTAMIVIR 75 mg Capsules*	**6 capsules (450 mg oseltamivir)**	**8 capsules (600 mg oseltamivir)**	**10 capsules (750 mg oseltamivir)**	**12 capsules (900 mg oseltamivir)**
purified water containing 0.05% w/v sodium benzoate added as preservative	74 mL	98 mL	123 mL	147 mL

* Includes overage to ensure all doses can be delivered

Third, follow the procedure below for compounding the oral suspension (6 mg/mL) from NAT-OSELTAMIVIR Capsules 75 mg:

1. If using Cherry Syrup (Humco®), Ora-Sweet SF, or simple syrup as a vehicle, place the specified amount of water into an amber glass or amber polyethyleneterephthalate (PET) bottle, see Table 4. [Alternatively, if using purified water containing 0.05% w/v sodium benzoate (added as preservative) as a vehicle, start at Step 2.]
2. Carefully separate the capsule body and cap and transfer the contents of the required number of NAT-OSELTAMIVIR 75 mg capsules into a clean mortar.
3. Triturate the granules to a fine powder.
4. Add one-third (1/3) of the specified amount of vehicle and levigate the powder until a uniform suspension is achieved.
5. Transfer the suspension to an amber glass or amber PET bottle (if using Cherry Syrup (Humco®), Ora-Sweet SF, or simple syrup as a vehicle, use the same amber glass or amber PET bottle from step 1). A funnel may be used to eliminate any spillage.
6. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
7. Repeat the rinsing (Step 6) with the remainder of the vehicle.
8. Close the bottle using a child-resistant cap.

9. Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: The active drug, oseltamivir phosphate, readily dissolves in the specified vehicle. The suspension is caused by some of the inert ingredients of NAT-OSELTAMIVIR Capsules which are insoluble in the vehicle.)
10. Put an ancillary label on the bottle indicating "Shake Gently Before Use". [This compounded suspension should be gently shaken prior to administration to minimize the tendency for air entrapment.]
11. Instruct the parent or guardian that any remaining material following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
12. Place an appropriate expiration date label according to storage condition (see below).

STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:

Compounded with Ora-Sweet®SF, simple syrup or cherry syrup:

- Room temperature storage conditions: Stable for five days (5 days) when stored at 25°C.
- Refrigerated storage conditions: Stable for 5 weeks (35 days) when stored in a refrigerator at 2-8°C.

Compounded with purified water containing 0.05% w/v sodium benzoate added as preservative:

- Room temperature storage conditions: Stable for 10 days when stored at room temperature. Do not store above 25°C.
- Refrigerated storage conditions: Stable for 49 days when stored at 2-8°C.

Note: The storage conditions are based on stability studies of compounded oral suspensions, using the above mentioned vehicle, which were placed in amber glass and amber polyethyleneterephthalate (PET) bottles. Stability studies have not been conducted with other vehicles or bottle types.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, and drug name and any other required information to be in compliance with all Provincial and Federal Pharmacy Regulations. **Refer to Table 5 for the proper dosing instructions.**

Table 5: Dosing Chart for Pharmacy-Compounded Suspension from NAT-OSELTAMIVIR Capsules 75 mg

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose 6 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤ 15 kg	≤ 33 lbs	30 mg	5 mL	5 mL two times a day	5 mL once daily
16 to 23 kg	34 to 51 lbs	45 mg	7.5 mL	7.5 mL two times a day	7.5 mL once daily

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose 6 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
24 to 40 kg	52 to 88 lbs	60 mg	10 mL	10 mL two times a day	10 mL once daily
≥41 kg	≥89 lbs	75 mg	12.5 mL	12.5 mL two times a day	12.5 mL once daily

Note: 1 teaspoon = 5 mL

Consider dispensing the 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. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.

For the suspension compounded with purified water containing 0.05% w/v sodium benzoate added as a preservative, the appropriate dose must be withdrawn from the dispensed bottle by the caregiver. Using a separate container, the withdrawn dose must be mixed with an equal amount of sweetened liquid, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Reports of overdoses with oseltamivir phosphate have been received from clinical trials and during post- marketing experience. These overdose cases included single or repeated overdose, accidental or intended. The majority of overdose cases were reported in children.

A subset of 114 overdose cases was evaluated in detail, where overdose was defined as receiving more than twice the recommended dose. From the 114 patients, 31% ingested oseltamivir phosphate in an overdose amount ranging from >2 to <4 fold the recommended dose (on single or multiple occasions), 49% experienced an overdose between 4 and <9 fold the recommended dose, and 17% experienced a 9-fold or higher overdose. In the remaining 3% of patients, enough information was not provided to determine the exact amount of overdose.

The most frequently reported adverse events were gastrointestinal disorders, followed by psychiatric and nervous disorders. In the majority of cases reporting overdose, no adverse events

were reported. Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of oseltamivir phosphate, described in ADVERSE REACTIONS.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active metabolite, oseltamivir carboxylate. The active metabolite is a selective inhibitor of influenza A and B virus neuraminidase enzymes which are glycoproteins found on the virion surface. Viral neuraminidase is primarily important for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. The proposed mechanism of action of oseltamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. It has also been suggested that neuraminidase can play a role in viral entry into uninfected cells.

Oseltamivir is readily absorbed after oral administration and converted by hepatic esterases to its active metabolite. The mean volume of distribution (V_{ss}) of the active metabolite is approximately 23 L. The active metabolite is not further metabolized and is eliminated in the urine. The half-life of elimination of this metabolite is 6 to 10 hours. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h), indicating that tubular secretion in addition to glomerular filtration occurs. Also, the prodrug which reaches the systemic circulation (less than 5%) is eliminated by renal excretion. The binding of oseltamivir to human plasma protein is 42% and that of the active metabolite is negligible, approximately 3%.

Exposure to the active metabolite is inversely proportional to declining renal function.

Pharmacokinetics

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. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the prodrug is less than 5% relative to the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are not significantly affected by co-administration with food (see DOSAGE AND ADMINISTRATION).

Distribution*:* The mean volume of distribution (Vss) of the active metabolite is approximately 23 litres in humans.

The binding of oseltamivir to human plasma protein is 42% and that of the active metabolite is negligible, approximately 3%.

Metabolism*:* Oseltamivir 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.

Excretion: Absorbed oseltamivir is primarily (>90%) eliminated by conversion to the active

metabolite. The active metabolite is not further metabolized and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline with a half-life of 6 to 10 hours in most subjects. The active drug 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 radiolabelled dose is eliminated in feces.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in pediatric patients aged 1 to 16 years. Multiple dose pharmacokinetics were studied in a small number of pediatric patients aged 3-12 years enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adults resulting in 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 capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age is similar to those in adults.

NAT-OSELTAMIVIR should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity).

Geriatrics: Exposure to the active metabolite at steady-state was 25% to 35% higher in elderly patients (age range 65 to 78) compared to young adults given comparable doses of oseltamivir phosphate. Half-lives observed in the elderly patients were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients for either treatment or prevention (see DOSAGE AND ADMINISTRATION: Dosage Adjustment).

Hepatic Impairment: The safety, efficacy and pharmacokinetics of oseltamivir phosphate in patients with severe hepatic impairment have not been studied (See WARNINGS AND PRECAUTIONS: Hepatic). In a clinical study of adult patients with moderate hepatic impairment (N=11), compared with healthy volunteers (N=23), metabolic conversion of oseltamivir into the active metabolite oseltamivir carboxylate was not significantly altered (see DOSAGE AND ADMINISTRATION: Dosage Adjustment, Hepatic Impairment). No studies have been carried out in pediatric patients with hepatic impairment.

Renal Impairment: Administration of 100 mg of oseltamivir phosphate 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.

STORAGE AND STABILITY

NAT-OSELTAMIVIR (oseltamivir phosphate) Capsules: Store at 15-25°C.

NAT-OSELTAMIVIR Powder for Oral Suspension: Store dry powder at 15-25°C.
Store reconstituted suspension:

a) at room temperature (not above 25°C). Discard unused portion within 10 days of reconstitution.

or

b) in a refrigerator (2-8°C). Discard unused portion within 17 days of reconstitution.
Do not freeze reconstituted suspension.

NAT-OSELTAMIVIR Pharmacy-Compounded Suspension:
Store reconstituted suspension:
Compounded with Ora-Sweet®SF, simple syrup or cherry syrup:

- Room temperature storage conditions: Stable for five days (5 days) when stored at 25°C.
- Refrigerated storage conditions: Stable for 5 weeks (35 days) when stored in a refrigerator at 2-8°C.

Compounded with purified water containing 0.05% w/v sodium benzoate added as preservative:

- Room temperature storage conditions: Stable for 10 days when stored at room temperature. Do not store above 25°C.
- Refrigerated storage conditions: Stable for 49 days when stored at 2-8°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NAT-OSELTAMIVIR (oseltamivir phosphate) 30 mg, 45 mg and 75 mg Capsules

Composition

NAT-OSELTAMIVIR (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg and 75 mg oseltamivir for oral use in the form of oseltamivir phosphate. In addition to the active ingredient, each capsule contains pregelatinized starch, croscarmellose sodium, povidone K30, sodium stearyl fumarate and talc. The 30 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide. The 45 mg capsule shell contains gelatin, black iron oxide and titanium dioxide. The 75 mg capsule shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide and titanium dioxide. Each capsule is printed with blue ink, which includes shellac, propylene glycol and FD&C Blue No. 2 aluminum lake as a colorant.

Availability

NAT-OSELTAMIVIR 30 mg capsules are available as white to off white powder filled in size ‘4’ capsules with yellow colour cap imprinted with ‘30 mg’ with blue colour ink and yellow colour body imprinted with ‘NAT’ with blue colour ink.

NAT-OSELTAMIVIR 45 mg capsules are available as white to off white powder filled in size ‘4’ capsules with grey colour cap imprinted with ‘45 mg’ with blue colour ink and grey colour body imprinted with ‘NAT’ with blue colour ink.

NAT-OSELTAMIVIR 75 mg capsules are available as 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.

All three strengths are available in blister packages of 10s.

NAT-OSELTAMIVIR Powder for Oral Suspension (6 mg/mL)

Composition

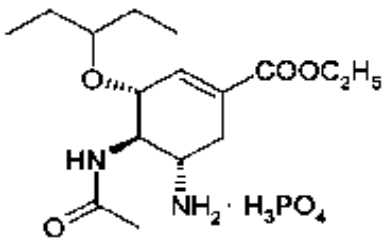
NAT-OSELTAMIVIR powder for oral suspension contains 390 mg oseltamivir as oseltamivir phosphate per bottle, which when reconstituted contains 65 mL of suspension at a final concentration of 6 mg/mL oseltamivir. The non-medicinal ingredients are: monosodium citrate, saccharin sodium, sodium benzoate, sorbitol, titanium dioxide, tutti-frutti flavoring, xanthan gum and colloidal silicon dioxide.

Availability
NAT-OSELTAMIVIR powder for oral suspension is available as a white to off-white granular powder blend for reconstitution to a white to off-white tutti-frutti-flavored suspension. Available in 100 mL glass bottles with a 10 mL oral syringe and a universal or 28 mm press-in bottle adapter, provided by a dispensing pharmacist. Net contents after reconstitution: 65 mL containing oseltamivir phosphate equivalent to 390 mg oseltamivir base.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	oseltamivir phosphate
Chemical Name	Ethyl (3R, 4R, 5S)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate, phosphate (1:1)
Molecular Formula	$C_{16}H_{28}N_2O_4 \cdot H_3PO_4$
Molecular Weight	312.4 g/mol for oseltamivir free base and 410.4 g/mol for oseltamivir phosphate salt
Structural Formula	
Physical Form	White crystalline solid
Solubility	Freely soluble in water and methanol, slightly soluble in dimethylformamide and ethanol, and practically insoluble in acetone, 2-propanol and non-polar organic solvents.
pKa and pH values	pKa: 7.75
Partition Co-efficient	1-octanol/aqueous phosphate buffer: logP=0.36
Melting Point	192-195°C with degradation

CLINICAL TRIALS

Comparative Bioavailability Studies

Study 1:
An open label, randomized, two treatment, two period, two sequence, single dose, crossover comparative oral bioavailability study of NAT-OSELTAMIVIR 75 mg capsules with Tamiflu® 75 mg capsules of Roche Laboratories Inc., was conducted in 23 normal, healthy, adult male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Oseltamivir (1 × 75 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	NAT-OSELTAMIVIR*	TAMIFLU®	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng•h/mL)	155.6 161.9 (29.6)	155.8 160.2 (24.0)	99.9	93.7 - 106.6
$AUC_{0-\infty}$ (ng•h/mL)	161.9 168.1 (29.0)	162.6 167.0 (23.5)	99.6	93.8 - 105.8
C_{max} (ng/mL)	67.2 70.8 (33.1)	66.5 73.6 (47.0)	101.0	87.0 - 117.3
T_{max}§ (h)	1.1 (79.1)	1.1 (88.4)		
$T_{½}$§ (h)	1.6 (30.4)	1.6 (29.1)		

* Test Product: NAT-OSELTAMIVIR 75 mg capsule (Natco Pharma (Canada) Inc.)
α Reference Product: TAMIFLU® 75 mg capsule (Roche Laboratories Inc., purchased from the USA)
§ Expressed as the arithmetic mean (CV%) only

Study 2:
An open label, randomized, balanced, two treatment, two period, two sequence, single dose, crossover, oral bioequivalence study of NAT-OSELTAMIVIR (oseltamivir phosphate) Powder for Oral Suspension, 6 mg/mL (75 mg in 12.5 mL) of Natco Pharma (Canada) Inc. compared with that of TAMIFLU® (oseltamivir phosphate) Powder for Oral Suspension, 6 mg/mL (75 mg in 12.5 mL) distributed by Genentech, Inc. a Member of the Roche Group was conducted in 72 healthy, adult Asian male subjects under fasting conditions. The results of the 65 subjects included in the final analysis are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Oseltamivir (1 x 75 mg dose administered as 12.5 mL of 6 mg/mL) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng*h/mL)	125.35 127.62 (19.19)	126.86 129.43 (19.67)	98.86	95.85 – 101.97
$AUC_{0-\infty}$ (ng*h/mL)	129.89 132.21 (19.03)	131.44 133.85 (18.86)	98.90	95.86 – 102.04
C_{max} (ng/mL)	32.64 33.75 (26.45)	32.81 34.46 (31.22)	99.48	93.41 – 105.94
T_{max} (h) §	2.38 (45.22)	2.32 (46.51)		
$T_{½}$ (h) §	3.65 (81.62)	3.27 (62.03)		

* NAT-OSELTAMIVIR (oseltamivir phosphate) Powder for Oral Suspension, 6 mg/mL (Natco Pharma (Canada) Inc.)
† TAMIFLU® (oseltamivir phosphate) Powder for Oral Suspension, 6 mg/mL (Genentech USA, Inc. A Member of the Roche Group), purchased from the USA
§ Expressed as the arithmetic mean (CV%) only

Treatment of Influenza

Adult Patients: Phase III clinical trials evaluated the safety and efficacy of oseltamivir phosphate for the treatment of naturally occurring influenza during a period when influenza virus was known to be circulating in the community. A total of 1418 patients received any treatment (oseltamivir phosphate or placebo) of whom 476 patients received 75 mg oseltamivir phosphate twice daily for 5 days. Patients started treatment with oseltamivir phosphate within 40 hours after reported onset of symptoms. The primary efficacy parameter was the time to alleviation of all symptoms. The population used in the primary analyses was the intent-to-treat-infected (ITTI) population. This population included only subjects who received at least one dose of study treatment and who had laboratory confirmed influenza. An intent-to-treat (ITT) population included all subjects who took at least one dose of study medication, regardless of whether they proved to have influenza. The results for two pivotal studies are shown in the table below.

Table 3: Median Time (Hours) to Alleviation of All Symptoms in the ITTI and ITT Populations

Study	Population	Placebo (95% CI)	Oseltamivir Phosphate 75 mg twice daily (95% CI)	*p*-value*
WV15670	ITTI	n=161 116.5 (101.5 to 137.8)	n=157 87.4 (73.3 to 104.7)	0.017

Study	Population	Placebo (95% CI)	Oseltamivir Phosphate 75 mg twice daily (95% CI)	*p*-value*
	ITT	n=235 116.1 (99.8 to 129.5)	n=240 97.6 (79.1 to 115.3)	0.051
WV15671	ITTI	n=128 103.3 (92.6 to 118.7)	n=121 71.5 (60.0 to 83.2)	< 0.0001
	ITT	n=200 97.0 (86.3 to 113.6)	n=204 76.3 (66.3 to 89.2)	0.004

ITT intent-to-treat
ITTI intent-to-treat infected
* difference between medians

Treatment with oseltamivir phosphate significantly reduced the duration by 1.3 days, of clinically relevant symptoms of influenza. The seven symptoms assessed were: feverish feeling, muscle aches or myalgia, headache, sore throat, cough, overall discomfort, and nasal stuffiness or runny nose.

Pediatric Patients: One double-blind placebo controlled treatment trial was conducted in pediatric patients, aged 1 to12 years (mean age 5.3), who had fever (>100°F) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. In this study 67% of influenza-infected patients were infected with influenza A and 33% with influenza B. Treatment with Oseltamivir phosphate, started within 48 hours of onset of symptoms, significantly reduced the duration of illness by 1.5 days compared to placebo. Duration of illness was defined as time to alleviation of cough, alleviation of coryza, resolution of fever, and return to normal health and activity.
Pediatric patients receiving Oseltamivir phosphate returned to normal health and activity almost 2 days earlier than those receiving placebo.

Prevention of Influenza
Adult Patients: The efficacy of oseltamivir phosphate in preventing naturally occurring influenza illness has been proven in four separate trials which are summarized below and in Table 5.

In a phase III study (WV15799) in adult and adolescent contacts of a household case of influenza, 75 mg of oseltamivir phosphate once daily, started within 2 days of onset of symptoms in the household case and continued for 7 days, significantly reduced the incidence of influenza illness occurring in the contacts by 92% (*p* value = < 0.001).

In a double blind placebo controlled study (WV15673) conducted in unvaccinated otherwise healthy adults 18-65 years of age, 75 mg of oseltamivir phosphate administered once daily significantly reduced the incidence of clinical influenza by 76% (*p* value = 0.0006) during a community outbreak of influenza. The subjects in this study received oseltamivir phosphate for a period of 42 days. No additional benefit was demonstrated in this study using 75 mg of oseltamivir phosphate twice daily.

In a double blind placebo controlled study (WV15825) in elderly residents of nursing homes,

many of whom had chronic cardiac disease and/or respiratory disease, 80% received vaccine in the season of the study. The vaccine was a good match for circulating strains. The administration of 75 mg of oseltamivir phosphate once daily significantly reduced the incidence of clinical influenza illness in these patients by 92% (p value = 0.0015). In the same study, oseltamivir phosphate significantly reduced the incidence of influenza associated bronchitis, pneumonia and sinusitis by 86% (p value = 0.037). The subjects in this study received oseltamivir phosphate for a period of 42 days.

In all three of these clinical trials, approximately 1% of subjects taking oseltamivir phosphate for prevention developed influenza during the dosing period.

In a fourth phase III study (WV16193) it was demonstrated that oseltamivir phosphate effectively prevents the secondary spread of influenza within households. In this study, the index case was treated with oseltamivir phosphate and household contacts were randomized (by household) to receive either prophylaxis (P) with oseltamivir phosphate or treatment (T) with oseltamivir phosphate upon emergence of influenza-like illness. In households with infected index cases where subjects who were already shedding virus at baseline were excluded (ITTIINAB population) there was a 78.8% (p =0.0008) reduction in the incidence of laboratory-confirmed influenza in P versus T. Amongst contacts, the outcome was analogous to that seen for households with a significantly lower number of infected contacts in P versus T (84.5% reduction, p =0.0002, ITTIINAB population). No virus shedding was detected in any subject in the prophylaxis group while 7% of contact in the treatment group (ITTIINAB) shed virus.

Oseltamivir phosphate also significantly reduced the incidence of virus shedding and successfully prevented virus transmission in families.

Table 4: Clinical Summary of Prevention Studies

Study	Number of Subjects	Dose	Reduction in Clinical Influenza (Protective Efficacy)
Seasonal Studies			
			ITT Population
WV15673/WV15697 Adults	1559	Placebo 75 mg o.d. 75 mg b.i.d. 42 days	76%, p = 0.00055 72%, p = 0.00125
WV15825 Elderly	548	Placebo 75 mg o.d. 42 days	92%, p = 0.00153
Post-exposure Studies			
			ITTIINAB Population
WV15799 Adult/adolescent contacts, index case not treated	405	Placebo 75 mg o.d., 7 days	92%, p =0.000076
WV16193	89**	Prophylaxis: 75 mg	78.8%, p = 0.0008

Study	Number of Subjects	Dose	Reduction in Clinical Influenza (Protective Efficacy)
Index case treated, age 1 year		o.d., 10 days Treatment: 75 mg b.i.d., 5 days	
WV16193 (children 1-12 years)	117	Prophylaxis: 30 mg (1-2 years) 45 mg (3-5 years) 60 mg (6-12 years) o. d., 10 days Treatment: 30 mg (1-2 years) 45 mg (3-5 years) 60 mg (6-12 years) b. i. d., 5 days	80.1 % (22.0-94.9), p = 0.0206

*Pediatric dosing adjusted according to age
** Number of households
ITT=Intent to treat
ITTIINAB=Intent to treat, index infected, not infected at baseline

Pediatric Patients: In the post-exposure prophylaxis study in the family (WV16193; see 'Adult Prevention Studies') there were 215 pediatric contact cases (>1 to 12 years of age). There was an even distribution of boys and girls with the majority being Caucasian. The mean age was 8 years (range 1 to 12). The data from this subset of pediatric patients was examined to determine if oseltamivir was effective in the prevention of influenza infection in this setting. When subjects who were already shedding virus at baseline were excluded (ITTIINAB population, 117), 17 pediatric contacts became infected, 2 in the prophylaxis group and 15 in the treatment group (see Table 4). The protective efficacy in the pediatric contacts was similar to that achieved in the overall population in this study.
The dosing schedule in this study was by age. The majority of children received the now recommended schedule of treatment by weight in children (see DOSAGE AND ADMINISTRATION). There were, however, some children who were under- or over-dosed (23% and 9%, respectively) in this study.

Prophylaxis of influenza in Immunocompromised Patients

A double-blind, placebo-controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects (including 18 pediatric subjects 1 to 12 years of age) who had received solid organ (n=388; liver, kidney, liver and kidney) or hematopoietic stem cell transplants (n=87). Median time since transplant for solid organ transplant recipients was 1105 days for the placebo group and 1379 days for the oseltamivir group. Median time since transplant for hematopoietic stem cell transplant recipients was 424 days for the placebo group and 367 days for the oseltamivir group. Approximately 40% of subjects received influenza vaccine prior to entering the study. The primary efficacy endpoint for this study was the incidence of confirmed, clinical influenza, defined as oral temperature >99.0°F/37.2°C plus cough and/or

coryza, all recorded within 24 hours, plus either a positive virus culture or a four-fold increase in virus antibody titers from baseline. The incidence of confirmed clinical influenza was 3% (7/238) in the group not receiving oseltamivir phosphate compared with 2% (5/237) in the group receiving oseltamivir phosphate; this difference was not statistically significant. A secondary analysis was performed using the same clinical symptoms and RT-PCR for laboratory confirmation of influenza. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR confirmed clinical influenza was 3% (7/231) in the group not receiving oseltamivir phosphate and <1% (1/232) in the group receiving oseltamivir phosphate.

DETAILED PHARMACOLOGY

Animal Pharmacology

Oseltamivir phosphate produced effects in the non-clinical safety pharmacology studies only at oral doses well in excess of any clinically relevant therapeutic levels. These effects in the rat, were reduced gastrointestinal transit and gastric emptying at 1000 mg/kg. In the rodent toxicology studies these effects were not reported as any sign of gastrointestinal disturbance. Additionally, there were increases in excretion of electrolytes at 100 and 1000 mg/kg and increased urine production at 1000 mg/kg. Increases in electrolyte excretion were reported in a 27-week rat toxicology study at 1000 mg/kg/day and attributed to a high phosphate intake due to the salt of the test material. In the same study less pronounced effects were seen at 200 mg/kg/day, while in another rat toxicology study no significant effects were seen at 100 mg/kg/day. A statistically significant increase in response to a painful stimulus was seen but this was neither time nor dose related and therefore not thought to be of pharmacological significance.

The intravenous infusion of the active metabolite at 2, 15 and 100 mg/kg cumulatively produced statistically significant changes in heart rate, QT and QTc interval, QRS duration and pCO2 when compared with time matched controls in the anaesthetized dog. The effects on heart rate and pCO2 were at isolated time points and the decrease in QRS duration was not accompanied by any other relevant physiological changes and so not likely to be due to the drug treatment. The statistical differences in QT and QTc interval between the active metabolite and vehicle treated groups was seen in the predose and just after the start of the infusion suggesting no pharmacological significance. Because of this, significance was tested for by comparing percentage changes from predose values within the active metabolite treatment group. There were no significant differences detected. However, on comparison with the absolute values significant differences were seen during the infusion of the 100 mg/kg/dose. To clarify this situation a further test was performed in an isolated sheep Purkinje fibre study where no significant effects were observed on cardiac action potential parameters. Other than these findings, no additional effects were seen on the cardiovascular and respiratory dynamics of the anaesthetized dog.

In conclusion, oseltamivir phosphate produced significant pharmacological effects only at doses much greater than would be of clinical relevance. It is therefore concluded that oseltamivir phosphate and the active metabolite produced no clinically relevant pharmacological effects on the central nervous, cardiovascular, respiratory, gastrointestinal, smooth muscle, renal, hepatic and immune systems tested.

Human Pharmacology
QT/QTc: A retrospective analysis of ECGs from 8 clinical pharmacology studies (n=182 subjects including 30 placebo) concluded that oseltamivir phosphate does not cause prolongation of QT intervals in humans. Although some individuals were found to have some alterations in QTc measurements, none were of clinical significance and the frequency was similar among placebo and subjects treated with oseltamivir phosphate.

In a study on ECG intervals in which healthy volunteers received daily doses of either 75, 225 or 450 mg oseltamivir phosphate b.i.d. orally for 5 days, treatment with oseltamivir phosphate had no impact on any ECG parameters

MICROBIOLOGY

Virology: Oseltamivir was also tested for its effect on human T cell proliferation *in vitro*. Both antigen specific T cell lines and peripheral blood lymphocytes were isolated from whole blood. There was a slight but significant inhibition of influenza specific T cell line proliferation in the presence of 1 and 10 μM active metabolite, while there was no effect on antigen stimulation of peripheral blood lymphocytes. This slight effect (<20 %) on T cell proliferation is unlikely to compromise the long-term immune status of the patient with respect to subsequent influenza infection.

The active metabolite inhibits neuraminidases of influenza viruses of both types A and B. Inhibitory concentrations *in vitro* are in the low nanomolar range. The 50% inhibitory concentration (IC_{50}) was in the range of 0.1 to 2.6 nM. The relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established. The active metabolite also inhibits influenza virus infection and replication *in vitro* and inhibits influenza virus replication and pathogenicity in animal models.

Resistance:
In vitro
Extensive *in vitro* work has been completed with the active metabolite. Resistance to this compound does not arise readily *in vitro*. Several different resistance mutations in the viral neuraminidase have been selected *in vitro* in Roche studies or reported in the published literature. Resistance mutations tend to be viral sub-type specific. The degree of reduced sensitivity differs markedly for different mutations from 2 fold for I222V in N1 to 30,000 fold for R292K in N2. Influenza A virus H1N1 strains are associated with a histidine to tyrosine change at position 274 (H274Y) on the enzyme. In H3N2 subtypes the genetic alteration of interest is an arginine to lysine at position 292 (R292K) on the enzyme. *In vitro* these mutant viruses exhibit reduced growth potential compared to wild-type virus.

In vivo
In vivo experiments of infectivity and pathogenicity have been conducted with mutated viruses in mice and ferrets. These experiments have demonstrated that the H274Y H1N1 mutant and the R292K H3N2 mutant have reduced ability to infect susceptible animals compared to wild-type virus and that infection is not associated with clinical evidence of pathogenicity in the ferret.

Correlation of *in vitro* resistance patterns to resistance *in vivo* are not known. Viruses with resistant neuraminidase genotypes have varying degrees of loss of fitness compared to wild-type.

Clinical Studies

The risk of emergence of influenza viruses with reduced susceptibility or resistance to oseltamivir has been examined during Roche-sponsored clinical studies. Patients who were found to carry oseltamivir-resistant virus generally did so transiently, and showed no worsening of the underlying symptoms. In some pediatric patients, oseltamivir-resistant virus was detected for a prolonged period compared to patients carrying oseltamivir-sensitive virus; however these patients showed no prolongation of influenza symptoms.

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

* Full genotyping was not performed in all studies.

Insufficient information is available to fully characterize the risk of emergence of resistance to oseltamivir phosphate in clinical use.

There has been no evidence for emergence of drug resistance associated with the use of oseltamivir phosphate in clinical studies conducted to date in post-exposure (7 days), post-exposure within household contacts (10 days) and seasonal (42 days) prevention of influenza in immunocompetent subjects.

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir phosphate. For example, in 2008 the oseltamivir phosphate resistance-associated substitution H275Y was found in > 99 % of circulating 2008 H1N1 influenza isolates in Europe, while the 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir. Resistant strains have also been isolated from both immunocompetent and immunocompromised patients treated with oseltamivir. The susceptibility to oseltamivir and the prevalence of such viruses appears to vary seasonally and geographically. Oseltamivir resistance has also been reported in patients with pandemic H1N1 influenza in connection with both therapeutic and prophylactic regimens.

The rate of emergence of resistance may be higher in the youngest age groups, and in immunocompromised patients. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific.

Prescribers should consider available information on influenza virus drug susceptibility patterns for each season when deciding whether to use oseltamivir phosphate (for latest information, please refer to WHO and/or local government websites).

Cross resistance: Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir phosphate-resistant influenza mutants has been observed *in vitro*.

Due to the limitations in the assays available to detect drug-induced shifts in virus susceptibility due to mutations in the viral hemagglutinin, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, one of the three oseltamivir-induced mutations in the viral neuraminidase from clinical isolates is the same as one of the three mutations in the viral neuraminidase from clinical isolates observed in zanamivir-resistant virus.

Insufficient information is available to fully characterize the risk of emergence of resistance or cross-resistance to oseltamivir phosphate in clinical use.

TOXICOLOGY

Acute Dose Toxicity

Acute oral administration was well tolerated by male and female adult rodents (mice and rats) and unweaned 14-day old male and female rats at 2000 mg/kg (~1000-fold the highest clinical dose). Single oral administration of 500 mg/kg (free base, corresponding to 657 mg/kg phosphate salt dose) or higher to juvenile 7-day old rats resulted in treatment-related mortality together with functional observation battery findings (FOB) and clinical signs indicative of general toxicity and imminent mortality (including low arousal, tremors, convulsions, alterations in general body posture, respiration, mucous membrane and skin coloration, and/or hypoactivity) and reduced body weight gain. The no effect level was 300 mg/kg (free base, corresponding to 394 mg/kg phosphate salt dose; ~150-fold the highest clinical dose) in juvenile rats in that study.
An intravenous range-finding study in mice (n=1/sex/dose) produced convulsions immediately after intravenous dosing with 250 mg/kg. The male died and the female recovered after 40 minutes. The maximum non-lethal dose of 100 mg/kg was confirmed in a further five males and five females observed for two weeks. Other than some evidence of a local reaction in the tail of two females, there were no significant adverse effects in this group.

Multiple Dose Toxicity

In multiple dose rat studies, doses up to 500 mg/kg/day (2 weeks), 650 mg/kg/day (4 weeks), and 200 mg/kg/day (27 weeks) were generally well tolerated, with no significant toxicologic effects.

A dose of 1000 mg/kg/day in a two week range finding rat study in unweaned 7-9 day old rats resulted in a high rate of mortality (18/24). At 500 mg/kg, no adverse effects were seen in the 7-9 day old rats or repeated treatment (500 mg/kg/day administered from 7 to 21 days post partum). In multiple dose rat studies, the highest doses examined (≥1000 mg/kg/day) also induced two renal changes. One consisted of cortico-medullary mineralisation in the proximal tubules due to the imbalance of the calcium/phosphate ratio in the diet caused by dosing high levels of a phosphate salt. The second was a mild enhancement of chronic progressive nephropathy; rats are specifically sensitive to both these changes. A dose of 1000 mg/kg/day in the rat results in approximately 70 and 520 times the clinical exposure in humans, to the active metabolite and prodrug, respectively. In clinical studies, there was no biochemical evidence of renal effects in

humans.

Marked gastrointestinal irritation was observed in marmosets at 2000 mg/kg/day, but not in four- and 39-week studies at 2 x 500 mg/kg/day. Emesis occurred at 500 mg/kg/day and above in marmosets, probably related to the concentration of the oral formulation. A reduction in incidence was associated with dividing the doses and halving the concentrations administered. This effect was seen at approximately 100 and 200 times the exposure values following clinical use in human, of the active metabolite and prodrug, respectively.

In the 39-week marmoset study, one 2 x 25 mg/kg/day group and two 2 x 100 mg/kg/day group animals were sacrificed prematurely. All three showed evidence of osteomalacia before dosing commenced, at autopsy and at the histopathological examination of the bones. No animal in the 2 x 500 mg/kg/day group was affected. Review of the clinical safety database, including the elderly, failed to reveal any biochemical evidence of skeletal effects in humans.

Reproduction and Teratology

Fertility, teratology and pre- and post-natal studies were conducted to cover all phases of the reproductive process. There was no evidence of adverse effects on fertility or embryo-foetal development up to the highest dose of 1500 mg/kg/day in rats, or for teratogenicity testing in rabbits up to 500 mg/kg/day. These dose levels were associated with maternal toxicity. In rabbits mortalities occurred at 750 and 1500 mg/kg/day during a non-pregnant tolerance study. Some rabbits were sacrificed in the teratology range-finding and main studies at 500 mg/kg/day due to abortions associated with maternal toxicity. In the regulatory pre- and post-natal study in rats, maternal deaths occurred (9/25) at or immediately prior to delivery in the 1500 mg/kg/day group; prolonged parturition was also observed. Two further studies were therefore undertaken; although only 1/125 maternal deaths at parturition were seen in the combined 1500 mg/kg/day groups, extension of parturition was confirmed by these studies. It was concluded that the drug alone was not responsible for the maternal deaths in the first pre- and post-natal study. At 1500 mg/kg/day in the rat teratology study, there was a slightly increased incidence of incomplete ossification of the 3rd sternebra in the exposed offspring, when compared to controls. Statistical significance was achieved, however, the majority of incidences occurred in one litter, where a general reduction in ossification was observed. In view of the isolated nature of this finding it was considered to be of doubtful toxicological significance.

Mutagenicity and Carcinogenicity

There was no evidence of mutagenic potential in any study (doses up to 5000µg/plate), with or without metabolic activation. Separate bacterial cell gene mutation (Ames) tests were conducted for the pro-drug and active metabolite. A mouse lymphoma cell mutation test examined the active metabolite. The pro-drug was tested in a chromosome analysis assay with human lymphocytes, and in an *in vivo* micronucleus test in mice (oral dose of up to 2000 mg/kg). All the study systems were verified as sensitive by positive controls, and all the results were negative.

Two year rat and mouse studies and a six month transgenic Tg: AC mouse assay performed with the active metabolite were negative.

The tables presented on the following pages provide the findings of the main toxicology,

reproductive, mutagenicity and various special studies performed with oseltamivir phosphate.

Table 5 Acute Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
Mouse CD-1 1 Dose	Oral gavage: 2000 5/sex	Mortality, clinical signs, bodyweight, food consumption, histopathology of gross lesions	2000: No deaths. ↓ Bodyweight gain (F)
Mouse CD-1 1 Dose	Intravenous: 5, 50, 100, 250 2/sex range-finder, 5/sex at MNLD	Mortality, clinical signs, bodyweight, autopsy, histopathology of gross lesions	250: 1/1 death (M). 1/1 M, 1/1F convulsed immediately, F recovered + 40 mins. 100: No systemic effects in 5M, 5F.
Rat Han-Wistar 1 Dose	Oral gavage: 2000 5/sex	Mortality, clinical signs, bodyweight, food consumption, histopathology of gross lesions	2000: No adverse effects
Rat (2w.old, unweaned) SD: CD 1 Dose	Oral gavage: 0, 250, 500, 1000, 1500, 2000 5/sex:	Mortality, clinical signs, bodyweight, autopsy, histopathology of gross lesions	2000: No adverse effects
Rat (7-day old, unweaned) SD:CD 1 Dose	Oral gavage: 0, 300, 500, 600, 700, 850, 1000 (free base, corresponding to 394, 657, 788, 920, 1117, and 1314 mg/kg phosphate salt dose) 10/sex + toxicokinetic satellites	Mortality, clinical signs, functional observational battery (FOB), bodyweight, necropsy, histopathology of gross lesions	300: No effects 500 and higher: lethality, FOB and/or behavioral findings indicative of general toxicity and imminent mortality (e.g., low arousal, tremors, convulsions, alterations in general body posture, respiration, mucous membrane and skin coloration, and/or hypoactivity), reduced body weight gain

Table 6: Multiple Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
Mouse CD-1 4 Weeks	Oral gavage: 0, 50, 250, 500, 1000, 1500 12/sex + toxicokinetic satellites	Mortality, clinical signs, bodyweight, food consumption, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights,	50-1000: No adverse effects. 1500: ↑ Hb conc., RBC count, PCV (M). ↓ Plasma Na and Cl (M). ↑ Plasma cholesterol (M,F). ↑ Focal nephropathy (M,F).

Table 6: Multiple Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
		histopathology	
Rat SD: CD 2 Weeks	Oral gavage: 0, 125, 500, 2000 10/sex + toxicokinetic satellites	Mortalities, clinical signs, bodyweights, food consumption, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	125: No adverse effects 500: ↑ Salivation post dosing (M,F). ↓ Bodyweight gain (transient, M). ↑ Relative liver weight (F). 2000: ↑++ Salivation post dosing (M,F). ↑+Discolouration of peri-urinogenital fur, second week (M,F). ↓ Bodyweight gain (M), (transient, F). ↑ Hb conc., RBC count, PCV, RBC distribution width (M,F). ↑ WBC count, segmented neutrophils (M). ↓ APTT (M). ↑ Plasma BUN, Ca, P, total protein, globulin (M,F). ↑ Plasma Cholesterol, glucose (M). ↑ plasma Creatinine, albumin (F). ↓ K, Cl (M,F). ↓ Na (F). ↑ Relative liver weight (F). ↑ Relative kidney weight (M,F). ↑ Renal tubule mineralisation (8/10 M). ↑ Alveolar macrophage accumulation (M,F).
Rat SD: CD 4 Weeks (+ 2w recovery)	Oral gavage: 0, 50, 250, 1500 10/sex + toxicokinetic satellites	Mortalities, clinical signs, bodyweight, food and water consumption, ophthalmoscopy, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	50: No adverse effects 250: Salivation post dosing. 1500: ↑+ Salivation post dosing ↑ Water consumption. ↑ WBC count, lymphocytes, neutrophils, monocytes. ↓ APTT (F) ↑ Plasma urea. ↑ Urine NAG/creatinine ratio (M,F). ↓ Urine pH. ↑ Urine protein. ↑ Relative kidney weight (M,F). ↑+ Cortico-medullary mineralisation of kidneys (7/8 M). ↑++ Cortico-medullary mineralisation (F). ↑+ Tubular basophilia, dilatation, granular casts (M,F).
Rat SD:CD 4 Weeks	Oral dietary: 0, 250, 650, 1500, 2500 6/sex	Mortalities, clinical signs, bodyweight, food and water consumption, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	250: ↑ Fur staining, rough hair-coat (M,F). ↑ Urinary phosphate (F). ↑ Cortico-medullary mineralisation of kidneys (F). ↑ Focal nephropathy (F). 650: ↑ Fur staining, rough hair-coat (M,F). ↓ Bodyweight gain (M). ↑ Urine phosphate (F). ↑ Renal cortico-medullary mineralisation (F). ↑ Focal nephropathy (F) 1500: ↑ + Fur staining, rough hair-coat (M,F). ↓ Bodyweight gain (M,F), ↑ Plasma Na (M). ↓ Plasma phosphate (M). ↑ Urine phosphate (F). ↑ Renal cortico-medullary mineralisation (M,F). ↑ Focal nephropathy (F) 2500: ↑+ Fur staining, rough hair-coat (M,F). ↓+ Bodyweight gain (M,F). ↓ + Food consumption. ↑ Plasma Na, ALP (M). ↑ Plasma Phosphate (M). ↑ Urine phosphate (F). ↑ Adjusted liver, kidney weights (M). ↑ + Renal cortico-medullary mineralisation (M). ↑++ Renal cortico-medullary

Table 6: Multiple Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
			mineralisation (F). ↑ Focal nephropathy (F).
Rat SD:CD 27 Weeks (+ 8w recovery + t/kinetic satellites maintained off treatment for 26 weeks)	Oral gavage: 0, 50, 200, 1000 20/sex + toxicokinetic satellites	Mortalities, clinical signs, bodyweight, ophthalmoscopy, neurology, food and water consumption, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	50: ↑ WBC count, lymphocytes, neutrophils (M). ↑ Serum globulin (F). ↓ A/G ratio (F). 200: ↑ WBC count, lymphocytes, neutrophils (M). ↑ Serum globulin (F). ↓ A/G ratio (F). ↓ Urine pH (M). ↑ Urine Ca, Mg P (M). ↑ Relative kidney weights (M,F). ↑ Relative liver weight (M). 1000: ↑ Unkempt, discoloured fur anogenital region (M,F). ↑+ Water consumption (M). ↑ Water consumption (F). ↑ WBC count, lymphocytes, neutrophils, RBC distribution width, platelets (M). ↑ Serum ALP, P (F). ↑ Serum bilirubin, BUN, albumin (M). ↑ Serum cholesterol, total protein, globulin, Mg (M,F). ↓ A/G ratio (F). ↓Serum Na (M). ↓ Serum Cl (M,F). ↓ Urine pH (M). ↑ ++ Urine volume (M). ↑ Urine volume (F). ↓ Urine creatinine (M,F). ↓ Urine Ca (F). ↑ Urine P, Na, K, Cl (M,F). ↑ Urine Ca, Mg (M). ↑ NAG/creatinine ratio (M,F). ↑ Relative kidney, liver weights (M,F). ↑ Relative adrenal weights (F). ↑ Renal cortico-medullary mineralisation (M,F). ↑ Chronic progressive nephropathy (M).
Marmoset 7 Days	Oral gavage: 0, 100, 500, 1000, 2000 2/sex	Mortalities, clinical signs, bodyweight, food consumption, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	100: No adverse effects. 500/2x250: ↑Emesis 1000/2x500: ↑+ Emesis. ↑+ Gastric mucosal atrophy (1/4). 2000: Death (1/4). Sacrificed in extremis (3/4). ↑++ Gastric mucosal degeneration (4/4). ↑++ Small intestinal mucosal degeneration (1/4).
Marmoset 4 Weeks (+2 w recovery)	Oral gavage: 2x0, 2x50, 2x150, 2x500 6/sex (control & high), 4/sex (low & mid)	Mortalities, clinical signs, bodyweight, food consumption, ECG, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	2x50: ↑ Salivation 2x150: ↑ Salivation 2x500: ↑+ Salivation. ↑ Reddening at angle of mouth. ↑ Emesis.
Marmoset 39 Weeks (+ 9w recovery)	Oral gavage: 2x0, 2x25, 2x100, 2x500 5/sex	Mortalities, clinical signs, bodyweight, food and water consumption, ECGs, ophthalmoscopy,	2x25: ↓ Heart rate (from Week 26). 2x100: ↓ Heart rate (from Week 26) 2x500: ↑+ Emesis. ↓ Bodyweight gain (F). ↓ Heart rate (from Week 26). ↑Urine volume. ↓ Urine Cl, K, Mg. ↓ Plasma total protein, albumin, K.

Table 6: Multiple Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
		urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	
Rat (1w.old, unweaned) SD:CD 2 Weeks	Oral gavage: 0, 50, 150, 500, 1000 12/sex	Mortality, clinical signs, bodyweight, urinalysis, haematology, clinical chemistry, autopsy, organ weights, histopathology	5: No Adverse effects. 150: No Adverse effects. 500: No Adverse effects. 1000: Deaths, acute (8/12 M, 10/12 F). ↑ Cyanosis (3/8M, 3/10 F mortalities). ↑ Pulmonary oedema (4/8 M, 5/10 F mortalities) ↑ Hepatocyte vacuolation (18/24 mortalities).
Rat (7, 14, 24, 42 days old) Crl:CD (SD)	Toxicity Phase Oral gavage: 500, 700 or 1000mg/kg/day 3 groups: 7/sex single dose on day 7 3 groups: 7/sex single dose on day 14 Toxicokinetic Phase 28/sex single dose 1000/mg/kg on day 7 3 groups 14/sex single dose 1000mg/kg on day 14, 24 or 42 post-partum	Mortality, morbidity, bodyweight. In the Toxicity Phase, histological examination of selected tissues for inter-current mortalities, controls and high dose group animals	<u>Toxicity Phase</u> **Day 7 Post-Partum** 500: No clinical signs observed. 700: 1 F death, acute. 1 F prematurely sacrificed exhibiting signs of prostration, coldness and slow breathing. Clinical signs observed in 2 M and 2 F (hypoactivity, cold and slow and/or irregular breathing). 1000: 2 M deaths, acute. 1 M prematurely sacrificed exhibiting signs of prostration, coldness and slow breathing. 5 M developed hypoactivity and coldness. 5 M developed slow and/or irregular breathing. 7 F developed slow or irregular breathing, coldness and hypoactivity. Of these females, 1 F exhibited tremors while a second was prostrate. **Day 14 Post-Partum** 500: No clinical signs observed. 700: No clinical signs observed. 1000: 3 M cold, 2 of which were also hypoactive. 1 F cold. Toxicokinetic Phase - 1000 mg/kg/day **Day 7 Post-Partum:** 7 deaths (5 M and 2 F). 6 pups (3 M and 3 F) observed to have clinical signs including coldness, pallor and hypoactivity. **Day 14 Post-Partum:** 1 death (F). No other clinical observations observed. **Day 24 Post-Partum:** 1 death (M) at dosing exhibiting no clinical signs. No other clinical observations observed. Day 42 Post-Partum: No clinical signs observed.
Rat	Oral gavage:	Mortality, clinical	50: No adverse effects.

Table 6: Multiple Dose Toxicity

Species Strain Duration	Route/Doses (mg/kg) No./Group	Parameters Monitored	Treatment Related Effects
(1w.old, unweaned) SD:CD 2 Weeks (+4w recovery)	0, 50, 150, 500 24/sex (control & high), 20/sex (low & mid)	signs, bodyweight, urinalysis haematology, clinical chemistry, toxicokinetics, autopsy, organ weights, histopathology	150: ↓ Testes (M). ↓ Uterus (F). 500: ↓ Testes, thymus (M). ↓ Uterus (F). All findings of no toxicological significance, NOAEL = 500 mg/kg/day
Rat (3 w.old, weaned) SD:CD 4 Weeks (+4w recovery)	Oral gavage: 0, 50, 150, 500 24/sex (control & high), 20/sex (low & mid)	Mortality, clinical signs, bodyweight, food consumption, urinalysis, haematology, clinical chemistry, toxicokinetics, autopsy, organs weights, histopathology	50: ↓ Urine creatinine (M,F). 150: ↓ Urine creatinine (M,F). ↑ Urine volume, Na, K, Cl (M,F). ↑ Serum P, Ca (M,F). ↑ Serum Mg, K, globulin (F). ↓ A/G ratio (F). 500: ↓ Urine creatinine (M,F). ↑+ Urine volume, Na, K, Cl, Ca, Mg (M,F). ↑+ Urine P (M). ↑ Serum P, Na, Ca (M,F). ↑ Serum Mg, K, globulin (F). ↓ A/G ratio (F). All findings of no toxicological significance, NOAEL = 500 mg/kg/day.

Table 7: Reproductive Toxicity Studies

Study Type Species Strain	Route No./Group	Doses (mg/kg/day)	Treatment Related Effects
Fertility and Early Embryonic Development Rat SD:CD	Oral 20/sex	0, 50, 250, 1500	50: ↓Bodyweight gain (M). 250: ↓Bodyweight gain (M). ↑ Salivation post dosing (M,F). 1500: ↑+ Salivation post dosing, fur staining, rough coat. ↓ Bodyweight gain (M,F). ↑ Food consumption (F). No adverse effects on fertility, mating or early embryonic development.
Teratology Range finding Rat SD:CD	Oral 7 mated females + toxicokinetic satellites	0. 50, 250, 1500	50: No adverse effects. 250: ↓ Bodyweight gain, food consumption. 1500: ↓ Bodyweight gain, food consumption. No adverse effects on pregnancy and foetal parameters.
Teratology Rat SD:CD	Oral 22 mated females	0. 50, 250, 1500	50: No adverse effects. 250: No adverse effects. 1500: ↓ Bodyweight gain, food consumption. No adverse effects on pregnancy parameters. Incomplete ossification of 3rd sternebra, mainly in one litter.
Tolerance Rabbit NZW	Oral 3 females (non-pregnant)	0, 50, 250, 500, 750, 1500	50: No adverse effects. 250: No adverse effects. 500: ↓+ Food consumption, faecal output (2/3). ↓

Table 7: Reproductive Toxicity Studies

Study Type Species Strain	Route No./Group	Doses (mg/kg/day)	Treatment Related Effects
			Bodyweight (1/3). ↓ Bodyweight gain (2/3). 750: Death (1/3). ↓++ Food consumption, faecal output (3/3). ↑ ++ Reddening, mucosal erosions, ulceration of stomach, intestinal fluid distension (1/3). ↑ Fur in stomach, liquid caecal contents (2/3). ↑ + Reddened areas on gastric mucosa (1/3). 1500: Killed in extremis (3/3). ↑ ++ Hypoactivity, prostration, hunched posture, salivation (3/3). ↑ ++ Bodyweight, food intake, faecal output. ↑ ++ Reddening, mucosal erosion, ulceration of stomach, intestinal fluid distension (3/3). ↓++ Faecal pellets in colon.
Teratology Range-finding Rabbit NZW	Oral 6 mated females + toxicokinetic satellites	0, 50, 250, 500	50: No adverse effects. 250: No adverse effects. 500: Abortion, premature sacrifice (1/8). ↓ Bodyweight gain, food consumption. ↓+ Faecal output No adverse effects on pregnancy and foetal parameters.
Teratology Rabbit NZW	Oral 23 mated females + toxicokinetic satellites	0, 50, 150, 500	50: No adverse effects 150: ↓ + Bodyweight gain, food consumption, faecal output. 500: Abortion and premature sacrifice (5/26). Premature sacrifice (2/26). ↓ ++ Bodyweight gain, food consumption, faecal output. No adverse effects on pregnancy parameters. No teratogenicity
Pre-and Post-Natal Rat SD:CD (regulatory)	Oral 25 mated females	0, 50, 250, 1500	50: No adverse effects. 250: No adverse effects. 1500: Deaths (3/25). Killed in extremis (6/25). All 9/25 showed some or all of: convulsions, hypoactivity, abnormal respiration, cold body surface, partly closed eyes. Deaths/KIE occurred day before, or day of expected parturition. ↑ + Salivation post dosing. ↑ + Duration of parturition (16/25). ↓ Pup viability. ↓ Pup bodyweight gain
Pre-and Post-Natal Rat Wistar RORO (investigatory)	Oral 21 mated females + satellites	0, 50, 500, 1500, 1500 to Day 19 of pregnancy	50: No adverse effects 500: ↑ Salivation post dosing 1500: ↑ + Salivation post dosing. ↓ Bodyweight gain, food consumption. ↑ + Urine volume. ↑ + Duration of parturition. ↓ Maternal care. ↓ Pup birthweights. ↓ Pup viability. ↓ + Pup bodyweight gain. ↓ Developmental tests. 1500 (to DG19): Deaths at parturition (1/18 with

Table 7: Reproductive Toxicity Studies

Study Type Species Strain	Route No./Group	Doses (mg/kg/day)	Treatment Related Effects
			exceptional litter size of 19). ↑ + Salivation post dosing. ↓ Bodyweight gain, food consumption. ↑ + Urine volume. ↑ Delay in developmental tests. No mortalities at parturition occurred.
Pre-and Post-Natal Rat SD:CD (investigatory)	Oral 20 mated females (treated groups) 30 mated females (controls) + satellites	0, 500, 1500, 1500+, 1500+, 1500+ a	500: No adverse effects 1500: ↑ Salivation post dosing. ↓ Bodyweight gain and food consumption. ↑ + Duration of parturition 1500: ↑ Salivation post dosing. ↓ Bodyweight gain and food consumption. ↑ + Duration of parturition 1500: ↑ Salivation post dosing. ↓ Bodyweight gain and food consumption. One found dead Day 2 post-partum. ↑ + Duration of parturition 1500: ↑ Salivation post dosing. ↓ Bodyweight gain and food consumption. There were no maternal deaths at parturition related to compound dosed at 1500 mg/kg/day

+ = Mechanistic investigations (all dosed Day 6 of pregnancy to Day 21 of lactation) a = dosed from Day 6 to 17 of pregnancy

Table 8: Mutagenicity Studies

Test	Compound	Concentration/Dose	Treatment Related Effects
Bacterial Cell Gene Mutation (Ames Test)	Pro-drug (hydrochloride)	100-5000 mcg/plate ± S9 mix	No evidence of mutagenicity.
Bacterial Cell Gene Mutation (Ames Test)	Active compound	50-5000 mcg/plate ± S9 mix	No evidence of mutagenicity.
Mouse Lymphoma Cell Mutation	Active compound	23.4-3000 mcg/ml ± S9 mix	No evidence of mutagenicity.
Chromosome Aberrations in Human Lymphocytes	Pro-drug	62.5-2000 mcg/plate -S9 mix 500-4990 mcg/ml +S9 mix	No evidence of mutagenicity.
Micronucleus Test in Mice	Pro-drug	500, 100, 2000 mg/kg Evaluated 24, 48, 72 hours	No evidence of mutagenicity.

Table 9: Special Studies

Study Type	Treatment Related Effects
Rabbit Primary Eye Irritation	Reversible reddening, hyperaemia, swelling of conjunctivae (3/3). Reversible hyperaemia of sclera, watery/mucous discharge (3/3). Reversible iridic vascularisation and corneal opacity (1/3). Primary irritation score 4.11 (≡ "not irritating", EU guidelines). Potential irritant to the eye in humans.
Guinea pig Skin Sensitisation	First challenge: Erythema in 56% (24h) and 78% (48h) animals Second challenge: Erythema in 44% (24h) and 56% (48h) animals. Potential for skin sensitisation in humans.
Dog 7 Day Gastrointestinal Tract Local Tolerance (75 mg capsule)	Erosion of the epithelium above a Peyer's patch (1/2). Clinical relevance not known.
Antigenicity (pro-drug and active compound)	No immunogenicity potential (ASA, PCA tests). No specific antibodies (ELISA). No anaphylaxis elicited in ASA tests. Weak PCA elicited by pro-drug and active compound.

REFERENCES

1. Bardsley-Elliot A and Noble S. Oseltamivir. Drugs 1999;58(5):851-860.

2. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. NEJM 1999;341(18):1336-43.

3. Hayden FG, Treanor J, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: Randomized, controlled trials for prevention and treatment. JAMA 1999;282(13):1240-1246.

4. He G, et al. Summary of the clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite (Ro 64-0802). Clinical Pharmacokinetics. 1999; 37:471-84.

5. Massarella JW, He G, et al. The pharmacokinetics and tolerability of the influenza neuraminidase inhibitor oseltamivir (Ro 64-0796/GS4104) in healthy adults and elderly volunteers. J Clin Pharmacol. 2000; 40:836-43.

6. Nicholson KG, Aoki FY, Osterhaus ADME, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. The Lancet 2000; 355:1845-50.

7. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. JAMA 2000; 283:1016-24.

8. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001; 20:127-33.

9. Welliver R, Monto AS, et al. Effectiveness of oseltamivir in preventing influenza in household contact: a randomized controlled trial. JAMA 2001; 285:748-54.

10. Peters PH, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001; 49:1025-1031.

11. Hayden F.G., Belshe R, Villanueva C, et al. Management of influenza in households: A prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004, 189:440-449.

12. Product Monograph, TAMIFLU®, Hoffman-La Roche Limited. Date of Revision February 27, 2017, control number 199480.

PART III: CONSUMER INFORMATION

PrNAT-OSELTAMIVIR
oseltamivir (as oseltamivir phosphate)

This leaflet is part III of a three-part "Product Monograph" published when NAT-OSELTAMIVIR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NAT-OSELTAMIVIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the flu is:
The flu, or influenza, is an infection caused by influenza viruses. It is most common in the fall and winter. The flu is highly contagious. The virus usually enters the body through the mouth, nose or eyes. When a person with the flu coughs or sneezes, the virus becomes airborne and can be inhaled by anyone nearby.

Flu occurs in local outbreaks which happen once or twice per year, usually in the winter.

What the difference is between the flu and a cold:
Both the flu and a cold are viral infections and can cause symptoms such as coughing and sore throat. A cold is a minor viral infection of the nose and throat. The flu however is usually more severe, has rapid onset of symptoms, and is associated with higher fever and aches and pains.

What the medication is used for:
NAT-OSELTAMIVIR is a prescription medication (a viral neuraminidase inhibitor) used to treat or prevent the onset of flu.

What it does:
NAT-OSELTAMIVIR works by inhibiting an enzyme necessary for the flu virus to spread through your body.

In two large clinical treatment trials, flu patients who took oseltamivir phosphate recovered 1.3 days (30%) faster than flu patients who did not take oseltamivir phosphate. NAT-OSELTAMIVIR should also alleviate your symptoms, and help you feel better soon.

In a large clinical trial for prevention of flu in families with children 13 years and older, oseltamivir phosphate, started within 2 days of the first family member getting sick and taken for 7 days, prevented over 90% of the flu illnesses in the rest of the family.

When NAT-OSELTAMIVIR should not be used:

- Do not use NAT-OSELTAMIVIR if you are allergic or sensitive to oseltamivir phosphate or any ingredient in this formulation (See "What the non- medicinal ingredients are")
- NAT-OSELTAMIVIR should not be used in children under 1 year age.

What the medicinal ingredient is:
NAT-Oseltamivir is available as capsules containing 30 mg, 45 mg or 75 mg of the active ingredient oseltamivir as oseltamivir phosphate.

The oral suspension contains 6 mg/mL of the active ingredient oseltamivir as oseltamivir phosphate.

What the non-medicinal ingredients are:
NAT-OSELTAMIVIR capsules contain the following non- medicinal ingredients: pregelatinized starch, croscarmellose sodium, gelatin, iron oxides (red, black and yellow), povidone K 30, sodium stearyl fumarate, talc, titanium dioxide, shellac, propylene glycol and FD&C Blue No. 2 Aluminum lake.

NAT-OSELTAMIVIR oral suspension contains the following non-medicinal ingredients: monosodium citrate, saccharin sodium, sodium benzoate, sorbitol, titanium dioxide, tutti-frutti flavoring, xanthan gum and colloidal silicon dioxide.

What dosage forms it comes in:
30 mg, 45 mg and 75 mg capsules
NAT-OSELTAMIVIR 30 mg capsules are available as white to off white powder filled in size '4' capsules with yellow colour cap imprinted with '30 mg' with blue colour ink and yellow colour body imprinted with 'NAT' with blue colour ink.

NAT-OSELTAMIVIR 45 mg capsules are available as white to off white powder filled in size '4' capsules with grey colour cap imprinted with '45

mg' with blue colour ink and grey colour body imprinted with 'NAT' with blue colour ink.

NAT-OSELTAMIVIR 75 mg capsules are available as 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.

6 mg/mL suspension
NAT-OSELTAMIVIR is also available as a liquid suspension (liquid form with a dosing dispenser (provided by your pharmacist) called oral suspension). The suspension will be prepared by your pharmacist and will be a thick white to off-white fruit-flavored liquid.

WARNINGS AND PRECAUTIONS

BEFORE you use NAT-OSELTAMIVIR talk to your doctor or pharmacist if:

- you ever had a bad reaction to oseltamivir phosphate (NAT-OSELTAMIVIR) or any of the non-medicinal ingredients
- you have hereditary fructose intolerance, as the NAT-OSELTAMIVIR oral suspension contains sorbitol and you should not use the suspension if you have this condition
- you are allergic to other medicines, food and dyes
- you are taking any other medicines, including those not prescribed by your doctor
- you have any type of kidney disease
- you are pregnant, plan on becoming pregnant, breast-feeding or planning to breast-feed.

This information will help your doctor and you decide whether you should use NAT-OSELTAMIVIR and what extra care may need to be taken while you are on the medicine.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

PROPER USE OF THIS MEDICATION

Your doctor has prescribed NAT-OSELTAMIVIR after diagnosing your flu condition. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your NAT-OSELTAMIVIR to anyone else.

NAT-OSELTAMIVIR is not a substitute for the flu shot. If you are at high risk of developing complications, you should continue to get your flu shot as recommended by your doctor. You might be surprised to find that you are still susceptible to flu even though you got your annual flu shot.

Treatment with NAT-OSELTAMIVIR (adults, adolescents and children (≥1 year))

Treatment with NAT-OSELTAMIVIR should begin **no more than two days** after flu symptoms have started to appear. Typical symptoms of flu include sudden onset of fever, headache, tiredness, muscular weakness, runny or stuffy nose, sore throat and cough.

Usual dose:

- NAT-OSELTAMIVIR should be taken twice daily (once in the morning and once in the evening) for five days.
- It is important that you begin your treatment with NAT-OSELTAMIVIR as soon as possible from the first appearance of your flu symptoms. If flu symptoms, most notably fever, do not begin to improve in the first day or two after you start your treatment with NAT-OSELTAMIVIR, speak with your doctor.
- NAT-OSELTAMIVIR can be taken with food. As with many medicines, if taken with a light snack, milk, or a meal, possible stomach upset may be reduced.
- You must complete the entire treatment recommended by your doctor, even if you are feeling better.
- Take this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than prescribed by your doctor. Never share NAT-OSELTAMIVIR with anyone, even if they have the same symptoms.

- If your doctor has prescribed NAT-OSELTAMIVIR liquid Suspension, follow the directions below to ensure proper dosing.

1. Shake closed bottle well for about 5 seconds before each use.
2. Open the bottle by pushing downward on the child resistant bottle cap and twisting it in the direction of the arrow.
3. Measure the oral suspension with a pharmacy provided 10 mL oral syringe to be sure you get the correct dose.
4. Dispense the full contents of oral dosing dispenser directly into the mouth.
5. Close the bottle with child-resistant cap after each use.
6. Disassemble oral dispenser, rinse under running tap water and air dry prior to next use.

Emergency Home Preparation of an Oral Suspension from NAT-OSELTAMIVIR Capsules:

When oseltamivir phosphate oral suspension is not available, and if directed by your doctor or pharmacist, you may mix the contents of NAT-OSELTAMIVIR capsules with sweetened liquids to prepare an oral suspension for children, immediately before dosing.

Please follow your doctor's (pharmacist's) instructions carefully to ensure proper dosing:

- Holding one capsule over a small bowl, carefully pull the capsule open and pour the complete contents of the capsule into the bowl.
- Add a small amount of a sweetened liquid such as chocolate syrup (regular or sugarfree) that the child will consume completely.
- Stir the mixture and give the entire dose to the child.
- Rinse the bowl with a bit of sweetened liquid and administer the rinse to the child.

Prevention with NAT-OSELTAMIVIR (adults, adolescents and children (≥1 year))

Therapy should begin **within 2 days** after coming into contact with someone with flu symptoms. Typically, about one in ten get the flu during an outbreak, although this varies. If someone close to you (like someone living in your home) has the flu your chance of getting it yourself is higher (around one in five).

Usual dose:

- NAT-OSELTAMIVIR should be taken once daily for 10 days or longer as recommended by your doctor if you have contacted someone who has flu. It is important that you begin your treatment with NAT-OSELTAMIVIR as soon as possible after you are exposed.
- NAT-OSELTAMIVIR can be taken with food. As with many medicines, if taken with a light snack, milk, or a meal, possible stomach upset may be reduced.
- The duration of dosing was tailored by your doctor. You must complete the entire course of therapy that your doctor has prescribed for you.
- Take this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than prescribed by your doctor.

Overdose:

If you think you have taken too much NAT-OSELTAMIVIR, contact your healthcare professional, hospital emergency department or Regional Poison Control Centre, even if there are no symptoms.

Missed Dose:

If you forget to take a dose of NAT-OSELTAMIVIR take it as soon as possible, then just carry on with the regular times you take your medication. Do not take double the amount if you miss one dose.
If you have missed several doses, inform your doctor and follow the advice given to you. Do not change your dose of NAT-OSELTAMIVIR unless instructed to do so by your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking NAT-OSELTAMIVIR.

NAT-OSELTAMIVIR is generally well tolerated.

The most common/possible unwanted effects are:

- nausea
- vomiting
- abdominal pain
- headache

Taking NAT-OSELTAMIVIR with food may reduce possible stomach upset.

Severe skin and hypersensitivity reactions have been reported since the marketing of oseltamivir phosphate. Symptoms of skin reactions include flushing, rash, itching or swelling. Symptoms of hypersensitivity reactions include dizziness or breathing problems.

Cases of liver toxicity have also been reported, symptoms of which include, yellowing of skin or eyes and dark urine.

People with the flu, particularly children and adolescents, may be at an increased risk of seizures, confusion, delirium, hallucinations, agitation, anxiety or other abnormal behaviour early during their illness. These events may occur shortly after beginning NAT-OSELTAMIVIR or may occur when flu is not treated. These events are uncommon but may result in self-injury to the patient, sometimes fatal. Therefore, patients should be observed for signs of unusual behaviour and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behaviour.
Some unwanted effects may go away during treatment as your body adjusts to the medicine. If you are concerned about these or any other unexpected effects while on NAT-OSELTAMIVIR, talk with your doctor or pharmacist.

These are not all the possible side effects you may feel when taking NAT-OSELTAMIVIR. If you experience any side effects not listed here, contact your healthcare professional.

HOW TO STORE IT

- Keep out of reach and sight of children.
- Store away from heat.
- Keep NAT-OSELTAMIVIR capsules in their original labeled container at room temperature at 15- 25°C and keep them in a dry place.
- Keep NAT-OSELTMAIVIR dry powder between 15-25ºC.
- Keep NAT-OSELTAMIVIR liquid suspension in its original labeled container:
  - at room temperature (not above 25ºC). Discard unused portion within 10 days of reconstitution.

    OR

  - in a refrigerator at 2-8ºC. Discard unused portion within 17 days of reconstitution. Do not freeze reconstituted solution.
- The pharmacist will write the date of expiration on the bottle label.
- Do not use this medicine after the expiry date on the package

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

This leaflet does not provide all known information about NAT-OSELTAMIVIR. If you have any questions or concerns about your treatment, please speak with your doctor or pharmacist.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html for information on how to report online, by mail or by fax; or
- Calling toll-free 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about NAT-

IMPORTANT: PLEASE READ

OSELTAMIVIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website www.natcopharma.ca, or by calling 1-800-296-9329.

This leaflet was prepared by Natco Pharma (Canada) Inc.

Last Revised: Sep-18-2020