NEW ZEALAND DATA SHEET
Tamiflu (oseltamivir)

1. PRODUCT NAME
Tamiflu 75mg capsules
Tamiflu 45 mg capsules
Tamiflu 30 mg capsules
Tamiflu 6mg/mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tamiflu 30mg capsules
Each capsule contains 39.4 mg oseltamivir phosphate equal to 30mg oseltamivir

Tamiflu 45mg capsules
Each capsule contains 59.1 mg oseltamivir phosphate equal to 45mg oseltamivir

Tamiflu 75mg capsules
Each capsule contains 98.5 mg oseltamivir phosphate equal to 75mg oseltamivir

Tamiflu 6mg/mL powder for oral suspension
Each mL of reconstituted suspension contains 0.5122 g oseltamivir phosphate which when constituted with 55 mL water makes 65 mL of 6mg/mL oseltamivir. One bottle of reconstituted suspension (65 ml) contains 390 mg of oseltamivir.

Excipients with known effect
Tamiflu 6mg/mL powder for oral suspension
5 ml oseltamivir suspension delivers 0.9 g of sorbitol.
7.5 ml oseltamivir suspension delivers 1.3 g of sorbitol.
10 ml oseltamivir suspension delivers 1.7 g of sorbitol.
12.5 ml oseltamivir suspension delivers 2.1 g of sorbitol.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Tamiflu 30 mg hard capsules
The hard capsule consists of a light yellow opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “30 mg”. Imprints are blue.

Tamiflu 45 mg hard capsules
The hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a grey opaque cap bearing the imprint “45 mg”. Imprints are blue.

Tamiflu 75 mg hard capsules
The hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “75 mg”. Imprints are blue.

Tamiflu 6mg/mL powder for oral suspension
The powder is a granulate or clumped granulate with a white to light yellow colour.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tamiflu is indicated for the treatment of influenza in adults and children 2 weeks of age and older who have been symptomatic for no more than 2 days (see section 4.4 Special warnings and precautions for use).

Tamiflu is indicated for the prophylaxis of influenza in adults and children ≥1 years of age. Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Standard dosage

Treatment of influenza

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

Adults and adolescents

The recommended oral dose of Tamiflu for adults and adolescents ≥13 years is 75 mg twice daily, for 5 days. Adults and adolescents ≥13 years of age can take Tamiflu capsules. Patients unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules) to achieve a 75 mg dose.

Infants and Children ≥ 1 to < 13 years of age

The recommended weight adjusted dosing regimens of Tamiflu for children ≥1 year of age are:

Body weight	Recommended dose for 5 days	Volume of 6 mg/mL oral suspension
≤ 15 kg	30 mg twice daily	5.0 mL twice daily
> 15 to 23 kg	45 mg twice daily	7.5 mL twice daily
> 23 kg to 40 kg	60 mg twice daily	10.0 mL twice daily
> 40 kg	75 mg twice daily	12.5 mL twice daily

Infants and children ≥ 1-year-old may receive the required Tamiflu dose in the form of capsules. Patients unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules).

Infants 2 weeks to <1 year of age:

The recommended oral dose of Tamiflu for infants 2 weeks to less than 1 year of age is 3 mg/kg twice daily, for 5 days. These dosing recommendations are not intended for infants who have a post-conceptual age of less than 36 weeks.

The recommended oral dose of Tamiflu for infants 2 weeks to less than 1 year of age is*:

Body weight	Recommended dose for 5 days	Amount of 6mg/mL oral suspension
3 kg	9 mg twice daily	1.5 mL twice daily
4 kg	12 mg twice daily	2.0 mL twice daily
5 kg	15 mg twice daily	2.5 mL twice daily
6 kg	18 mg twice daily	3.0 mL twice daily
7 kg	21 mg twice daily	3.5 mL twice daily
8 kg	24 mg twice daily	4.0 mL twice daily
9kg	27 mg twice daily	4.5 mL twice daily
10kg	30 mg twice daily	5.0 mL twice daily

* This table is not intended to contain all possible weights for this population. For all infants 2 weeks to less than 1 year of age, 3mg/kg should be used to determine dose regardless of the weight of the patient.

It is recommended that Tamiflu powder for oral suspension be reconstituted by a pharmacist prior to dispensing to the patient (see section 6.6 Special precautions for disposal and other handling).

Prophylaxis of influenza
Adults and adolescents
The recommended oral dose of Tamiflu for adults and adolescents ≥ 13 years for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Adults and adolescents ≥ 13 years of age can take capsules. Therapy should begin within two days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts for as long as dosing is continued.

Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules).

Infants and Children ≥ 1 to < 13 years of age
The recommended weight-adjusted prophylactic oral dosing regimens of Tamiflu for children ≥ 1 year of age are:

Body weight	Recommended dose for 10 days	Volume of 6 mg/mL oral suspension
≤ 15 kg	30 mg once daily	5.0 mL once daily
> 15 to 23 kg	45 mg once daily	7.5 mL once daily
> 23 kg to 40kg	60 mg once daily	10.0 mL once daily
> 40 kg	75 mg once daily	12.5 mL once daily

Infants and children ≥ 1-year-old may receive the required Tamiflu dose in the form of capsules but those who are unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see below, Patients unable to swallow capsules).

It is recommended that Tamiflu powder for oral suspension be reconstituted by a pharmacist prior to dispensing to the patient (see section 6.6 Special precautions for disposal and other handling).

Patients unable to swallow capsules

When commercially manufactured Tamiflu powder for oral suspension is not readily available, adults, adolescents, children and infants (≥ 1 year of age) who are unable to swallow capsules may receive appropriate doses of Tamiflu either prepared at home by caregivers or prepared by a pharmacist.

Home-prepared, extemporaneous preparation of capsules

This procedure describes the preparation of a **15 mg/mL** solution.

Adults and adolescents (13 years and older)

Adults and adolescents who are unable to swallow capsules may receive a 75 mg dose of Tamiflu by following the instructions below.

1. Hold one Tamiflu 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder into the bowl,
2. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey, light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste of the medication.
3. Stir the mixture well and give the entire contents to the patient. The mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture. It is not necessary to administer any undissolved white powder as this is inert material.

Children (1 year and older); 15 mg/mL solution

Children who are unable to swallow capsules and require a dose different to that available in capsule form may receive appropriate doses of Tamiflu by following the instructions below.

1. Hold one Tamiflu 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder into the bowl.

2. Using a graduated syringe, add 5 mL water to the powder. Stir for about two minutes.

3. Draw up into the syringe the correct amount of mixture from the bowl (see table below). The recommended dose is body weight dependent.

   Push down on the plunger of the syringe, to empty its entire contents into a second bowl. Discard any unused mixture.

Body weight	Recommended dose	Amount of Tamiflu mixture for one dose (15 mg/mL)
≤ 15 kg	30 mg	2 mL
> 15 to 23 kg	45 mg	3 mL
> 23 kg to 40kg	60 mg	4 mL
> 40 kg	75 mg	5 mL

Note: This compounding procedure results in a 15 mg/mL mixture, which is different from the commercially available Tamiflu Oral Suspension.

4. In the second bowl, add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children one year or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to the mixture to mask the bitter taste of the medication.

5. Stir this mixture well and give the entire contents of the second bowl to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture.

Pharmacy-compounded oral suspension from Tamiflu capsules (final concentration 6 mg/mL) for adults, adolescents, children and infants ≥ 2 weeks of age

Commercially manufactured Tamiflu for oral suspension (6 mg/mL) is the preferred product for paediatric patients ≥ 2 weeks of age and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that Tamiflu for oral suspension is not available, the pharmacist may compound a suspension (**6 mg/mL**) from Tamiflu capsules.

This procedure describes the preparation of a **6 mg/mL** suspension, which will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a suspension (**6 mg/mL**) from Tamiflu 75 mg capsules using water containing 0.05% w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume of compounded Tamiflu **6 mg/mL** suspension required is determined by the weight of the patient according to the recommendation in the table below:

Volume of pharmacy compounded suspension (6 mg/mL) required for a 5 day course based on the patient's weight

Body Weight (kg)	Total Volume to Compound per Patient Weight (mL)
up to 5kg	25mL
>5 to 6 kg	30 mL
>6 – 15 kg	50 mL
> 15 - 23 kg	75 mL
> 23 - 40 kg	100mL
> 40 kg	125 mL

Second, determine the number of capsules and the amount of vehicle (water containing 0.05% w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above: 25 mL, 50 mL, 75 mL, 100 mL or 125 mL) of compounded Tamiflu **6 mg/m**L suspension as shown in the table below:

Total Volume of Compounded Suspension to be Prepared	Required Number of Tamiflu 75 mg Capsules (mg of oseltamivir)	Required Volume of Vehicle
25 mL	2 capsules (150 mg)	24.5 mL
50 mL	4 capsules (300 mg)	49.5 mL
75 mL	6 capsules (450 mg)	74 mL
100 mL	8 capsules (600 mg)	98.5 mL
125 mL	10 capsules (750 mg)	123.5 mL

Third, follow the procedure below for compounding the suspension (6 mg/mL) from Tamiflu capsules:

1. Transfer the contents of the stated amount of Tamiflu capsules into the bottle and add the stated amount of sodium benzoate solution (see Table above).
2. Close the bottle with the cap and shake for two minutes.
3. Put an ancillary label on the bottle indicating "Shake Gently Before Use".
4. Instruct the parent or caregiver to discard any remaining solution after the patient has completed the full course of therapy.
5. Place an appropriate expiration date label according to storage condition (see below).

Storage of the Pharmacy-compounded suspension (6 mg/mL)
Room temperature storage conditions: stable for 3 weeks (21 days) when stored at room temperature 'do not store above 25°C'.

Refrigerated storage conditions: stable for 6 weeks when stored at 2 - 8 ºC

Pharmacy-compounded Tamiflu suspension should not be frozen.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, medicine name and any other required information to be in compliance with local pharmacy regulations.

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

Special dosage instructions

Patients with renal impairment

Treatment of influenza

In adults, no dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 – 60 mL/min, it is recommended that the dose be reduced to 30 mg of Tamiflu twice daily for 5 days. In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose is reduced to 30 mg of Tamiflu once daily for 5 days. In patients undergoing routine haemodialysis, an initial dose of 30 mg of Tamiflu can be administered prior to the start of dialysis if influenza symptoms develop during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session. For peritoneal dialysis, a dose of 30 mg of Tamiflu administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations). The pharmacokinetics of oseltamivir have not been studied in patients with end stage renal disease (i.e. creatinine clearance of < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

Prophylaxis of influenza

In adults, no dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of > 30 – 60 mL/min, it is recommended that the dose be reduced to 30 mg of Tamiflu once daily. In patients with creatinine clearance between 10 - 30 mL/min receiving Tamiflu, it is recommended that the dose be reduced to 30 mg every other day. In patients undergoing routine haemodialysis, an initial dose of 30 mg of Tamiflu can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis, an initial dose of 30 mg of Tamiflu administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see section 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations). 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.

Children with renal impairment

There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation.

Patients with hepatic impairment

No dose adjustment is required for patients with hepatic dysfunction in the treatment or prophylaxis of influenza (see section 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations). No studies have been carried out in paediatric patients with hepatic impairment.

Immunocompromised patients

Treatment of Influenza

The recommended duration for immunocompromised patients is 10 days.

No dose adjustment is necessary (see Section 4.8 and 5.1).

Prophylaxis of Influenza

Seasonal prophylaxis in immunocompromised patients ≥ 1 year of age is recommended for 12 weeks. No dose adjustment is necessary (see "Prophylaxis of Influenza" in Section 4.2 Dose and Method of Administration).

Use in the elderly
No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see section 5.2 Pharmacokinetic properties).

Paediatric use
The efficacy of Tamiflu in infants less than 2 weeks of age has not been established (see section 5.2 Pharmacokinetic properties). Pharmacokinetic data indicates that a dosage of 3 mg/kg twice daily in infants 2 weeks to less than 1 year of age provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults.

4.3 CONTRAINDICATIONS

Tamiflu is contraindicated in patients with known hypersensitivity to oseltamivir phosphate or any component of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Convulsion and delirium like neuropsychiatric events have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. The contribution of Tamiflu to those events is unknown and these have also been reported in patients with influenza who were not taking Tamiflu (see section 4.8 Undesirable effects).

Patients, especially children and adolescents, should be closely monitored for signs of abnormal behaviour.

There is no evidence for efficacy of Tamiflu in any illness caused by agents other than influenza viruses types A and B.

Sorbitol

Tamiflu powder for oral suspension contains sorbitol. For subjects with hereditary fructose intolerance, Tamiflu powder for oral suspension is not recommended. Sorbitol may have a laxative effect or cause diarrhoea.

A bottle of 13 g Tamiflu 6 mg/mL powder for oral suspension contains 11.142 g of sorbitol.
30 mg oseltamivir suspension delivers 0.9 g of sorbitol.
45 mg oseltamivir suspension delivers 1.3 g of sorbitol.
60 mg oseltamivir suspension delivers 1.7 g of sorbitol.
75 mg oseltamivir suspension delivers 2.1 g of sorbitol.

Use in Renal Impairment
For dose adjustments in patients with renal impairment, refer to the Special dosage instructions and Pharmacokinetics in special populations sections.

Paediatric use
See sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties.

Effects on Laboratory Tests
Elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir (see section 4.8 Undesirable Effects, Post-marketing experience).

Pharmaceutical Precautions
Direct contact of oseltamivir phosphate with the skin and eyes should be avoided, as it is a potential skin sensitiser and eye irritant.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Information derived from pharmacology and pharmacokinetic studies of oseltamivir phosphate suggest that clinically significant interactions with other medicines are unlikely.

Oseltamivir phosphate is extensively converted to the active compound by esterases, located predominantly in the liver. Interactions involving competition for esterases have not been extensively reported in the literature. Low protein binding of oseltamivir and the active metabolite do not suggest the probability of displacement interactions.

In vitro studies demonstrated that neither oseltamivir phosphate nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases (see section 5.2 Pharmacokinetic properties). There is no mechanistic basis for an interaction with oral contraceptives.

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

Clinically important interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these medicines, 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 approximate 2-fold increase in exposure to the active metabolite due to a decrease in active 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.

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

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,

cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), warfarin, rimantadine or amantadine.

In phase III treatment and prophylaxis clinical studies, Tamiflu has been administered with commonly used medicines such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide) antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H_2-receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators and analgesic agents (aspirin, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of Tamiflu with these compounds.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category B1

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Foetal exposure in rats and rabbits was approximately 15 - 20% of that of the mother.

Because animal reproductive studies may not be predictive of human response, and there are no adequate and well-controlled studies in pregnant women, Tamiflu should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

No controlled clinical trials have been conducted on the use of Tamiflu in pregnant women; however, there is evidence from post-marketing and observational studies showing benefit of the current dosing regimen in this patient population. Results from pharmacokinetic analyses indicate lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations). A large amount of data from pregnant women exposed to oseltamivir (more than 1000 exposed outcomes during the first trimester) from post-marketing reports and observational studies in conjunction with animal studies indicate no direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development.

Labour and Delivery

The safe use of oseltamivir during labour and delivery has not been established.

Breast-feeding

In lactating rats, oseltamivir and the active metabolite are secreted in milk. Very limited information is available on children breast-fed by mothers taking Tamiflu and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk; however, the levels were low, which would result in a sub-therapeutic dose to the infant. Based on this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the lactating woman, administration of oseltamivir may be considered if the potential benefit for the lactating mother justifies the potential risk of exposure of the medicine to the nursing infant.

Fertility

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Experience from clinical trials

The overall safety profile of Tamiflu is based on data from 2646 adults/adolescents and 859 paediatric patients with influenza, and on data from 1943 adult/adolescent and 148 paediatric patients receiving Tamiflu for the prophylaxis of influenza in clinical trials. In adult/adolescent treatment studies, the most frequently reported adverse drug reactions (ADRs) were nausea, vomiting and headache. The majority of these ADRs were reported on a single occasion, occurred on either the first or second treatment day and resolved spontaneously within 1 – 2 days. In adult/adolescent prophylaxis studies, the most frequently reported ADRs were nausea, vomiting, headache and pain. In children, the most commonly reported ADR was vomiting. In the majority of patients, these events did not lead to discontinuation of Tamiflu.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed according to the MedDRA system organ class. The corresponding frequency category for each adverse drug reaction (Table 1) is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Treatment and Prophylaxis of Influenza in Adults and Adolescents

In adult/adolescent treatment and prophylaxis studies, ADRs that occurred the most frequently (≥ 1%) at the recommended dose (75 mg twice daily for 5 days for treatment and 75 mg once daily for up to 6 weeks for prophylaxis), and whose incidence is at least 1% higher on Tamiflu compared to placebo, are shown in Table 1.

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

The safety profile reported in the subjects that received the recommended dose of Tamiflu for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in the treatment studies (see Table 1), despite a longer duration of dosing in the prophylaxis studies.

Table 1: Summary of Adverse Reactions in ≥ 1% of adult and adolescent patients that received oseltamivir for treatment or prophylaxis of influenza, in clinical studies (difference to placebo ≥ 1%)

System Organ Class **Adverse Drug Reaction**	**Treatment Studies** **Tamiflu (75 mg twice daily)** ***n* = 2646**	**Prophylaxis** **Tamiflu (75 mg twice daily)** ***n* = 1943**	**Frequency category[a]**
Gastrointestinal Disorders			

System Organ Class Adverse Drug Reaction	Treatment Studies Tamiflu (75 mg twice daily) *n* = 2646	Prophylaxis Tamiflu (75 mg twice daily) *n* = 1943	Frequency category[a]
Nausea	10%	8%	very common
Vomiting	8%	2%	common
Neurological and Nervous System Disorders			
Headache	2%	17%	very common
General Disorders			
Pain	< 1%	4%	common

[a] *Frequency category is reported only for the Tamiflu group.*

Treatment and Prophylaxis of Influenza in Elderly

There were no clinically relevant differences in the safety profile of the 942 subjects, 65 years of age and older who received Tamiflu or placebo, compared with the younger population (aged up to 65 years).

Treatment and Prophylaxis of Influenza in Immunocompromised Patients

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

In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 – 12 years old, the safety profile in the 238 subjects receiving Tamiflu was consistent with that previously observed in Tamiflu prophylaxis clinical trials.

Treatment and prophylaxis of influenza in infants and children > 1 year of age

A total of 1481 paediatric patients (including otherwise healthy children aged 1 – 12 years old and asthmatic children aged 6 – 12 years old) participated in clinical studies investigating the use of Tamiflu in the treatment of influenza. A total of 859 paediatric patients received treatment with Tamiflu suspension.

The ADRs that occurred in ≥ 1% of children aged 1 – 12 years receiving Tamiflu in the clinical trials for treatment of naturally acquired influenza (*n* = 859), and whose incidence is at least 1% higher on Tamiflu compared to placebo (*n* = 622), is vomiting (16% on oseltamivir vs. 8% on placebo). Amongst the 148 children who received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (*n* = 99), and in a separate 6-week paediatric prophylaxis study (*n* = 49), vomiting was the most frequent ADR (8% on Tamiflu vs. 2% in the no prophylaxis group). Tamiflu was well tolerated in these studies and the adverse events noted were consistent with those previously observed in paediatric treatment studies.

Treatment of influenza in infants 2 weeks to less than 1 year of age
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 124 influenza infected infants 2 weeks to less than 1 year of age, the safety profile was similar among age cohorts with vomiting, diarrhoea and nappy rash being the most frequently reported adverse events (see section 5.2 Pharmacokinetic properties, Pharmacokinetics in special populations). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on Tamiflu administered fir the treatment of influenza in children less than 1 year of age from prospective and retrospective observational trials (compromising more 2400 children of that age class), epidemiological database research and post-marketing reports suggest that the safety profile in children less than 1 year of age is similar to the established safety profile of children aged 1 year and above.

Post-Marketing Experience
The following adverse events have been identified during post-marketing use of Tamiflu. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency and/or establish a causal relationship to Tamiflu exposure.

Skin and subcutaneous tissue disorders: hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema and urticaria, erythema multiforme, allergy, anaphylactic/anaphylactoid reactions, face oedema, Stevens-Johnson-Syndrome and toxic epidermal necrolysis have been reported.

Hepatobiliary disorders: hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir.

Psychiatric disorders/Nervous system disorders: convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety and nightmares) have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. These events often had an abrupt onset and rapid resolution. In rare cases, these events resulted in accidental injury, and some resulted in a fatal outcome, however, the contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu. Three separate large epidemiological studies confirmed that influenza-infected patients receiving Tamiflu are at no higher risk of developing neuropsychiatric events in comparison to influenza-infected patients not receiving antivirals.

Patients with influenza should be closely monitored for signs of abnormal behaviour throughout the treatment period.

Gastrointestinal disorders: gastrointestinal bleeding was observed after the use of Tamiflu. In particular, haemorrhagic colitis was reported and subsided when the course of influenza abated or treatment with Tamiflu was interrupted.

Blood and lymphatic system disorders: thrombocytopenia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Tamiflu described in Adverse Effects.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Mechanism of Action
Oseltamivir phosphate is a pro-drug of oseltamivir carboxylate, a potent and selective inhibitor of influenza virus neuraminidase enzymes. Viral neuraminidase is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and the further spread of infectious virus.

Oseltamivir carboxylate inhibits the neuraminidases of influenza viruses of both types A and B. Concentrations of oseltamivir carboxylate required to inhibit the enzyme activity by 50% (IC_{50}) are in the low nanomolar range. Oseltamivir carboxylate also inhibits influenza virus infection and replication *in-vitro* and inhibits influenza virus replication and pathogenicity *in-vivo*.

Oseltamivir carboxylate reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

Clinical trials
Clinical efficacy of Tamiflu has been demonstrated in human experimental infection studies and phase III studies in naturally occurring influenza.

In studies in naturally acquired and experimental influenza, treatment with Tamiflu did not impair normal humoral antibody response to infection. Antibody response to inactivated vaccine is not expected to be affected by treatment with Tamiflu.

Trials in naturally occurring influenza
In phase III clinical trials conducted in the 1997 - 1998 Northern Hemisphere influenza season, patients were treated with Tamiflu for up to 40 hours after reported onset of symptoms. In these studies, 97% of patients were infected with influenza A and 3% with influenza B. Tamiflu treatment significantly reduced the duration of clinically relevant signs and symptoms of influenza by 32 hours. Disease severity in patients with confirmed influenza

taking Tamiflu was also reduced by 38% compared to placebo. Moreover, Tamiflu reduced the incidence of complications associated with influenza treated with antibiotic therapy in otherwise healthy young adults by approximately 50%. These complications include bronchitis, pneumonia, sinusitis and otitis media. In these phase III clinical trials there was clear evidence of efficacy in the secondary endpoints related to antiviral activity in terms of both reduction of duration of virus shedding and reduction in the AUC of viral titres.

Data from a treatment study in the elderly population have shown that Tamiflu 75 mg twice daily for five days was associated with a reduction in median duration of illness that was clinically relevant, and similar to that seen in the younger adult treatment studies. In a separate study, patients aged > 13 years with influenza and co-existing chronic cardiac and/or respiratory disease received the same regimen of either Tamiflu or placebo. No difference in the median time to alleviation of all symptoms was seen between patients taking Tamiflu or placebo, however the duration of febrile illness was reduced by approximately one day by receipt of Tamiflu. The proportion of patients shedding virus on days 2 and 4 was also markedly reduced by active treatment. There was no difference in the safety profile of Tamiflu in the at-risk populations compared to the general adult population.

Treatment of influenza in children

One double-blind placebo controlled treatment trial was conducted in otherwise healthy children (65% influenza positive) aged 1 to 12 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. Tamiflu treatment, started within 48 hours of onset of symptoms, significantly reduced the duration of illness by 35.8 hours compared to placebo. Duration of illness was defined as time to alleviation of cough, nasal congestion, resolution of fever, and return to normal health and activity. The proportion of patients developing acute otitis media was reduced by 40% in children receiving Tamiflu (29/183) vs placebo (53/200). Children receiving Tamiflu returned to normal health and activity almost 2 days earlier than those receiving placebo.

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

Treatment of influenza in immunocompromised patients (children, adolescents, and adults):

A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents, and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered).

The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm^3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatement regimens were: standard dose 75 mg twice daily (73 adult patients, 4

adolescent patients, and 4 children) or double dose, 150mg twice daily (78 adult patients, 3 adolescent patients, and 5 children) of oseltamivir, weight adjusted for children.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95% CI 63.9-140.0]). The TTIRS for children was highly variable and interpretation is limited by the small sample size.

The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).

The TTRS in all oseltamivir-treated adult immunocompromised patients (combined from both dose groups) was shorter when compared to matched placebo-treated otherwise healthy (reduced by 14 hours) and "at risk" patients (reduced by 60 hours), from previous studies.

A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤12 years of age, n=30) receiving weight adjusted standard (75 mg twice daily) vs. triple dose (225 mg twice daily) oseltamivir for an adaptive dosing period of 5-20 days (mean treatment duration: 9 days) [150]. No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis).

The PK and PD data generated in the two studies supported the extrapolation of efficacy from immunocompromised adults to immunocompromised paediatric patients (<18 years old) (See Sections 4.2 and 5.2).

Trials for prophylaxis of influenza

Prophylaxis of influenza in adults and adolescents

The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and two post exposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature ≥ 99.0 ºF/37.2 ºC plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a fourfold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 18 to 65 years), Tamiflu 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the Tamiflu group.

In a seasonal prophylaxis study in elderly residents of nursing homes, Tamiflu 75 mg once daily taken for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the Tamiflu group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders. In a post-exposure prophylaxis study, household contacts (aged ≥ 13 years) who had no laboratory evidence of influenza at baseline, and who were living with an index case subsequently shown to have had influenza infection, were randomized to treatment (the ITTIINAB population). In this population Tamiflu 75 mg

administered once daily within 2 days of onset of symptoms in the index case and continued for 7 days, reduced the incidence of laboratory confirmed clinical influenza in the contacts from 12% (24/200) in the placebo group to 1% (2/205) for the Tamiflu group (risk reduction 91.9%, $p < 0.001$). For the study population as a whole (the ITT population), including contacts of index cases in whom influenza infection was not confirmed, the incidence of laboratory confirmed clinical influenza was reduced from 7.4% (34/462) in the placebo group to 0.8% (4/493) for the Tamiflu group (risk reduction 89%, $p < 0.001$). Index cases did not receive Tamiflu in the study. In the ITT population 13.9%of contacts in the placebo group and 11.4% of contacts in the Tamiflu group had been vaccinated.

The efficacy of Tamiflu in preventing naturally occurring influenza illness in adults and children has also been demonstrated in a post exposure prophylaxis study conducted in households in which index cases with rapid onset of fever, cough and/or coryza received twice daily treatment with Tamiflu for 5 days. The primary efficacy parameter for this study was the percentage of households with at least one secondary case of febrile laboratory confirmed influenza illness. A laboratory confirmed case was defined as a febrile illness (oral/otic temperature ≥ 100.0 ºF/37.8 ºC) plus cough and/or coryza, confirmed to be influenza by either detection of viral shedding within 2 days before or after the time that the fever was reported, and/or a fourfold increase in influenza virus antibody titers from baseline to the day 30 sample. Household contacts were randomized (by household) to receive either once daily prophylaxis with oseltamivir for 10 days (Group P) or to receive treatment for 5 days upon the emergence of influenza-like illness (Group T).

In households with an infected index case and where there was no laboratory evidence of influenza among the contacts at baseline (ITTIINAB), there was a 78.8% ($p = 0.0008$) reduction in households with infected contacts in Group T 22% (20/89) versus Group P 5% (4/84). In the population as a whole (ITT), including contacts of index cases in whom influenza infection was not confirmed, the prophylactic efficacy protection was 62.7% ($p = 0.0042$), Group T 20% (27/137) versus Group P 7% (10/137). A significant number of children aged 1 - 12 participated in this study, both as index cases and as contacts. In the ITTIINAB population of paediatric contacts, there was an 80.1% ($p = 0.0206$) reduction in the incidence of laboratory confirmed influenza in Group T 21% (15/70) versus Group P 4% (2/47). A similar reduction in clinical influenza was seen in the subset of paediatric contacts that also had paediatric index cases.

Prophylaxis of influenza in children
The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in a postexposure prophylaxis study in households that included children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza. In this study, Tamiflu oral suspension 30 mg to 75 mg once daily taken for 10 days among children who were not already shedding virus at baseline reduced the incidence of laboratory-confirmed clinical influenza from 21% (15/70) in the group not receiving prophylaxis to 4% (2/47) in the group receiving prophylaxis.

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 children 1 – 12 years old. Laboratory-confirmed clinical influenza, as defined by RT-PCR plus oral temperature ≥ 37.2 °C/99.0 °F plus cough and/or coryza, all recorded within 24 hours, was evaluated. Among subjects who were not already shedding virus at baseline, Tamiflu reduced the incidence of

laboratory-confirmed clinical influenza from 3.0% (7/231) in the group not receiving prophylaxis to 0.4% (1/232) in the group receiving prophylaxis (see Table 2).

Table 2: Incidence of influenza infection in immunocompromised patients

Population	**Placebo *n*/*N* (%)**	**Tamiflu 75 mg once daily *n*/*N* (%)**	**Treatment effect [a]**	**95% CI for difference in proportions between treatments[b]**	***p*-value [c]**
Overall ITT	7/238 (2.9%)	5/237 (2.1%)	28.3%	-2.3% to 4.1%	0.772
ITTII	7/238 (2.9%)	2/237 (0.8%)	71.3%	-0.6% to 5.2%	–
ITTIINAB	7/231 (3.0%)	1/232 (0.4%)	85.8%	0.1% to 5.7%	–

*[a] Treatment effect = (1 – Relative Risk)*100%; [b] Calculated using Newcombe's method of combining Wilson score intervals without continuity correction; [c] Comparison of Placebo versus Tamiflu using Fisher's exact test ITTII = intent-to-treat index-infected ITTIINAB = intent-to-treat index-infected, not infected at baseline.*

Viral resistance

Reduced sensitivity of viral neuraminidase

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or resistance to oseltamivir has been examined during Roche-sponsored clinical studies (see Table 3). Patients who were found to carry oseltamivir-resistant virus generally did so transiently and showed no worsening of the underlying symptoms. In children a higher proportion of resistance was observed compared to adults and adolescents. In some paediatric 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.

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

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

Table 3: Incidence of Oseltamivir Resistance in Clinical Studies

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

** Full genotyping was not performed in all studies.*

Prophylaxis of Influenza
In clinical studies conducted in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prophylaxis of influenza in immunocompetent persons, there was no evidence for emergence of drug resistance associated with the use of Tamiflu. There was no resistance observed during a 12-week seasonal prophylaxis study in immunocompromised 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. For example, in 2008 the oseltamivir 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 Tamiflu (for the latest information, please refer to WHO and/or local government websites).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to the active metabolite. Plasma concentrations of the active metabolite are measurable within 30 minutes, reach near maximal levels in 2 to 3 hours post dose, and substantially exceed (> 20-fold) those of the pro-drug. At least 75% of an oral dose reaches the systemic circulation as

the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are unaffected by co-administration with food (see section 4.2 Dose and Method of Administration).

Distribution
The mean volume of distribution (V_{SS}) of the active metabolite is approximately 23 litres in humans.

The active moiety reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit. In these studies, anti-viral concentrations of the active metabolite were seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea following oral administration of doses of oseltamivir phosphate.

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

Metabolism
Oseltamivir phosphate is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite are substrates for, or inhibitors of, cytochrome P450 isoforms (see section 4.5 Interactions with other Medicines and other Forms of Interactions).

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

The active substance 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 faeces.

Pharmacokinetics in special populations
<u>Patients with renal impairment</u>
Administration of 100 mg of Tamiflu 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.

A population pharmacokinetic model describing the impact of creatinine clearance (CrCL) on oseltamivir and oseltamivir carboxylate pharmacokinetics was developed and qualified for simulation using 80 subjects with varying degrees of renal function. Subjects had dense pharmacokinetic profiles and were identified from three clinical studies; a study in subjects with either normal renal function or mild, moderate or severe renal impairment (WP15648) and two studies in healthy subjects receiving a range of single (WP15517) or multiple doses of oseltamivir (WP15525). Simulations were performed and suitable regimens using available capsule formulations were selected on the basis to provide oseltamivir carboxylate exposures considered safe and efficacious in clinical trials.

Refer to section 4.2 Dose and method of administration for recommended dosing for patients with severe, moderate and mild renal impairment.

Two clinical studies were performed to evaluate the pharmacokinetic, safety and tolerability of oseltamivir and oseltamivir carboxylate in end stage renal disease patients undergoing haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). In study PP15974 patients undergoing either CAPD or HD received a single 75 mg capsule of oseltamivir, whereas in study NP16472 patients received 30 mg oseltamivir oral suspension for 6.5 weeks, with CAPD patients receiving a single dose per week and HD patients a dose after alternate dialysis sessions. In order to assist in determining appropriate dosing recommendations in HD, a population pharmacokinetic model for HD was constructed and qualified for simulation. Suitable regimens using available capsule formulations were selected on their basis to achieve oseltamivir carboxylate plasma trough levels in subjects with normal renal function dosed at 75 mg twice daily for treatment, or 75 mg oseltamivir given orally once daily for prophylaxis.

Refer to section 4.2 Dose and method of administration for recommended dosing for patients with end stage renal disease undergoing haemodialysis and continuous ambulatory peritoneal dialysis.

Patients with hepatic impairment

In-vitro studies have shown that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite significantly decreased in patients with hepatic impairment (see section 4.2 Dose and method of administration).

Elderly

Exposure to the active metabolite at steady state was 25 to 35% higher in elderly (age range 65 to 78) compared to young adults who were given comparable doses of Tamiflu. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza (see section 4.2 Dose and method of administration).

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in Dosage and Administration results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see sections 4.4 Special warnings and precautions for use and 4.6 Fertility, pregnancy and lactation).

Immunocompromised Patients

Population pharmacokinetic analyses indicate that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 2.2. Dosage and Administration) results in an increased exposure (of up to 50%) to the active metabolite when compared to non-immunocompromised patients. However, due to the wide safety margin of the active metabolite, no dose adjustments are required in immunocompromised patients.

Pharmacokinetic and pharmacodynamic analyses from two studies in IC patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose (see Section 5.1)

Infants and Children ≥ 1 year of age
The pharmacokinetics of Tamiflu have been evaluated in a single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics were studied in a small number of children aged 3 to 12 enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in younger children, than in adults, resulting in lower exposure in these children for a given mg/kg dose. Doses of 2 mg/kg and unit doses of 30 and 45 mg, administered to children in the appropriate categories according to the recommendation in section 4.2 yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

Infants 2 weeks to less than 1 year of age
The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two open-label studies including influenza infected infants 2 weeks to less than 1 year of age (n=124). The rate of clearance of the active metabolite, corrected for body weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in infants 2 weeks to less than 1 year of age provided pro-drug and metabolite exposures anticipates to be efficacious with a safety profile comparable to that seen in older children and adults using the approved dose. The reported adverse events were consistent with the established safety profile in older children.

5.3 PRECLINICAL SAFETY DATA
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenicity
Three studies for carcinogenic potential (2-year rat and mouse studies with oseltamivir, and a 6 month transgenic Tg:AC mouse assay performed with the active metabolite) were negative.

Teratology studies have been conducted in rats and rabbits at doses up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on embryo-foetal development were observed.

Genotoxicity
Oseltamivir and the active metabolite were negative in the standard battery of genotoxicity assays

Impairment of Fertility
A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex.

Reproductive Toxicity
In pre-/post-natal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20% of that of the mother.

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

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

Very high oral single doses of oseltamivir phosphate had no effect in adult rats, however, such doses resulted in toxicity in juvenile seven-day-old rat pups, including death. These effects were seen at doses of 657 mg/kg/day and higher. No adverse effects were seen following a single dose of 500 mg/kg, nor with chronic dosing of 500 mg/kg/day from day 7 to day 21 post-partum.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tamiflu 30 mg hard capsules

Capsule core
Starch
Purified talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin (animal origin)
Yellow iron oxide
Red iron oxide
Titanium dioxide

Printing ink
Opacode blue S-1-4118

Tamiflu 45 mg hard capsules

Capsule core
Starch
Purified talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Black iron oxide
Titanium dioxide

Printing ink

Opacode S-1-4118

Tamiflu 75 mg hard capsules
Capsule core
Starch
Purified talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide
Red iron oxide
Titanium dioxide

Printing ink
Opacode S-1-4118

Tamiflu 6mg/mL powder for oral suspension
Sorbitol
Monosodium citrate
Xanthan gum
Sodium benzoate
Saccharin sodium
Titanium dioxide

Tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
Tamiflu 30mg, 45mg and 75 mg capsules
10 years

Tamiflu 6mg/mL powder for oral suspension
4 years

Reconstituted solution
Not refrigerated - 10 days stored at or below 25°C.
Refrigerated - 17 days stored at 2° to 8°C (Refrigerate, do not freeze).

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Tamiflu 30mg, 45mg and 75 mg capsules
Store at or below 25°C

Tamiflu 6mg/mL powder for oral suspension
Store at or below 25°C
For storage conditions after reconstitution of the medicine, see section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER >

Tamiflu 30mg*, 45mg* and 75 mg capsules
Available in blister packages of 10 capsules.

**Tamiflu 30 mg and 45 mg capsules are currently not available.*

Tamiflu 6mg/mL powder for oral suspension
Available in 100 mL bottle pack with 13 g of white to yellow white powder, a bottle adaptor, a plastic oral dispenser and a measuring plastic cup. After reconstitution with 55 mL of water, the usable volume of oral suspension allows the retrieval of 10 doses of 30 mg oseltamivir.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Handling

Preparation of Tamiflu 6 mg/mL powder for oral suspension
It is recommended that Tamiflu powder for oral suspension be constituted by the pharmacist prior to dispensing to the patient (see section 4.2 Dose and method of administration):

1. Tap the closed bottle several times to loosen the powder.
2. Measure 55 mL of water. Use the measuring cup (where provided) and fill it to the indicated level.
3. Add all 55 mL of water for constitution to the bottle and shake the closed bottle well for 15 seconds. The final constituted volume is 65 mL
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.

7. MEDICINE SCHEDULE

Tamiflu 30mg and 45mg capsules; and Tamiflu 6mg/mL powder for oral suspension: Prescription Only Medicine.

Tamiflu 75mg capsules: Pharmacist Only Medicine for the treatment or prophylaxis of influenza in adults and children aged 13 years and older who have been exposed to the influenza virus.

For children 12 years of age and under, Tamiflu 75mg capsules is a Prescription Only Medicine for the treatment or prevention of influenza.

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

Tamiflu 30 mg capsules – 26 November 2009

Tamiflu 45mg capsules – 26 November 2009
Tamiflu 75 mg capsules 21 January 2000
Tamiflu 6mg/mL powder for oral solution – 1 November 2012

10. DATE OF REVISION OF THE TEXT

21 January 2021

Summary of Changes Table

Section Changed	Summary of new information
4.2	Updated with special dosage instructions for immunocompromised patients for children and adolescents based on new study data.
4.8	Updated with safety profile for immunocompromised children and adolescent patients.
5.1	Addition of immunocompromised information on children and adolescent patients.
5.2	Updated PK-PD analyses based on immunocompromised paediatric patients.
4.7	Updated to align with the company core data sheet global harmonisation wording.