Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Oseltamivir phosphate

Proprietary Product Name: Tamiflu

Sponsor: Roche Products Pty Ltd

July 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (Extension of indications/New Population)
Decision:	Rejected
Date of Decision:	25 March 2011
Active ingredient(s):	Oseltamivir phosphate
Product Name(s):	Tamiflu
Sponsor's Name and Address:	Roche Products Pty Ltd
	4-10 Inman Rd, Dee Why NSW 2099
Dose form(s):	Hard capsules and Powder oral suspension
Strength(s):	30, 45 and 75 mg hard capsules; 12 mg/mL powder oral suspension and 7 kg bulk powder for oral solution
Container(s):	Blister pack, Glass bottle and Drum
Route(s) of administration:	Oral (PO)
Dosage:	The recommended oral dose of Tamiflu capsules in adults and adolescents 13 years of age and older is 75 mg twice daily for five days. Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive the appropriate dose of Tamiflu suspension. *Paediatric patients.* The recommended oral dose of Tamiflu for paediatric patients 1 year and older who cannot swallow a 75 mg capsule may also receive the appropriate dose of Tamiflu suspension.

Published references referred to in this AusPAR are listed at the end of this document.

Product Background

Tamiflu (oseltamivir) is a selective inhibitor of influenza virus neuraminidase enzymes which are essential for the release and spread of recently formed virus particles from infected cells in the body. In addition, oseltamivir may also suppress virus entry into healthy cells. Oseltamivir reduces the duration of symptoms from the influenza A and B virus by 1.3-1.5 days in children and adults 1 year and older.

This AusPAR describes the evaluation of a submission by Roche Products Pty Ltd (the sponsor) which proposes to extend the indication and dosage regime of Tamiflu for the treatment of influenza in 6-12 month olds and the dosage regime for immunocompromised hosts.

The World Health Organization (WHO) states that influenza is a major global cause of morbidity and mortality, especially amongst children, older adults and other at risk individuals, who are chronically ill or who have other serious medical conditions (WHO, 2003). Around 5-15% of the population is affected by annual influenza epidemics, which results in between 250,000 and 500,000 deaths per year (WHO, 2003). Influenza virus is highly contagious, affecting people of all ages and all socioeconomic back-grounds and has

a particularly profound effect on children (Jamieson *et al*., 2009). Amongst children, mortality is highest amongst children aged 0-12 months (Bhat *et al*, 2005). Vaccination has been the mainstay of prevention of morbidity and mortality due to influenza and annual influenza vaccination is recommended for any person ≥ 6 months of age, especially amongst those at risk of complications from influenza infection, such as various cardiac, chronic respiratory conditions and other chronic conditions discussed elsewhere (NHMRC, 2008). However, amongst immunocompromised subjects, in particular, there can be a variable response to and protection from vaccination.

Neuraminidase inhibitors (NAIs), oseltamivir and zanamivir, are effective for the prophylaxis and treatment of both influenza A and B infections (Cochrane, 2006). Oseltamivir (Tamiflu) is also effective for prevention of complications associated with influenza A (including H1N1) in children. Oseltamivir also reduces the duration of influenza by a median of 36 hours, with nausea and vomiting as the primary reported adverse effects (Jamieson *et al*., 2009). Infection with oseltamivir resistant viruses significantly reduced the effectiveness of oseltamivir and reduced effectiveness of oseltamivir has been found to be more prominent in children aged 0 to 6 years than in those aged 7 to 15 years (Saito *et al*., 2010). It was reported that the appearance of NAI-resistant strains was as high as 30% in both H1N1 and H3N2 influenza A subtypes but such viruses were less transmissible (Moscona, 2009).

During the recent Pandemic (H1N1) in 2009, the WHO recommended oseltamivir as first line treatment for H1N1, with the use of zanamivir only for suspected or confirmed oseltamivir resistance (WHO, 2009). In preparation for the Pandemic (H1N1) in 2009, several countries, including the United States, Canada, United Kingdom and the European Union (EU), published interim orders permitting the expanded use of oseltamivir for treatment or prophylaxis for children younger than one year of age (Department of Health, United Kingdom, 2009; Royal College of Paediatrics and Child Health, 2009; American Society of Transplantation Infectious Disease Community of Practice, 2009). This action has provided additional experience and data on this younger age group.

There has been a move towards general widening of the indication for oseltamivir in the treatment of children aged 6-12 months, as well as clarifying the indication for the prophylaxis of immunocompromised children and adults with oseltamivir. An application for registration of Tamiflu (oseltamivir) in children aged one year and over has been previously approved in Australia. The clinical evaluation report submitted with the previous application was not resubmitted with the current submission. The current Australian submission presents additional data in support of an extension of indication for oseltamivir for the treatment of children to those aged 6 months and older and prophylaxis of immunocompromised children aged one year and older, as well as seasonal prophylaxis of children aged 1-12 years. There were also changes to the product information (PI) proposed, especially in terms of compounding of Tamiflu capsules into a solution, directed at pharmacists.

Two EU guidance documents, namely *Guideline on the Role of Pharmacokinetic in the Development of Medicinal Products in the Paediatric Population* (EMA, 2006) and *Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population* (EMA, 2001) have been referred to when compiling this report.

Regulatory Status

Table 1

Country	Relevant change	Submission/Approval Date
European Union	Treatment of children 6-12months old*; immunocompromised patient information; updated pregnancy and lactation precautions	Submitted: August 2009
European Union	Pharmacy compounding; updated pregnancy and lactation precautions**	Approved 9 September 2009

*Note: the EU Summary of Product Characteristics (SPC) contains the text previously approved for treatment of 6-12 month olds in a pandemic setting only. The current application seeks to register influenza treatment in 6-12 month olds in all situations (not just pandemic). **Note: In this EU application an indication for treatment and prophylaxis of 0-12 month olds in a pandemic setting only was approved. The current application does not seek to register an indication for influenza treatment in 0-6 month olds.

Tamiflu was registered in Australia in 2003.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The two main studies, NV20235 and NV20236, were of good quality with moderate to low numbers of subjects respectively and the presentation of the submission was fair. The clinical data presented came from (matching with aspects of the application to which they apply):

Proposed extension of indication to children aged 6 months and older for treatment of influenza A and B

- National Institutes of Health (NIH)/ National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) for

the treatment of children less than 24 months of age with confirmed influenza infection (CASG 114). CASG 114 Bi-Monthly Data Safety and Monitoring Board (DSMB);

Proposed changes to Pharmacology, Clinical Trials, Adverse Events and Dosage and Administration sections to include information on prophylaxis of immunocompromised patients and safety information on the seasonal prophylaxis of children from 1-12 years of age

- A Phase III, prospective, randomised, double blind, stratified (by transplant type, vaccination status and age), multicentre trial of oseltamivir verses placebo for seasonal influenza prophylaxis for 12 weeks in immunocompromised adults and children of 1 year and older (Study NV20235); and,
- A Phase III, prospective, non-randomised, open label, multicentre study to evaluate the safety of oseltamivir for seasonal influenza prophylaxis for 6 weeks in children 1 - 12 years of age, considered at risk of infection or exposure to susceptible individuals in their household (Study NV20236).

Proposed changes to the Dosage and Administration Section to include instructions for pharmacists on how to compound Tamiflu *capsules into a solution*

- The sponsor's *Clinical Overview* and the approved EU Summary of Product Characteristics (SPC; Product Information document)
- Mixing and dosing study-interim results (as sponsored by Hoffman-La Roche).

Proposed changes to the Precautions section dealing with Pregnancy and Lactation, as well as general editing of Tamiflu *documents*

- Various reports, including Drug Safety Report No. 1032998 (April 2009) on Pregnancy Outcomes: Safety review; Drug Safety Report No. 1034695 (July 2009) on oseltamivir use in children >1 year: Safety review; and an oseltamivir and breast feeding literature reference.

CASG 114 is a prospective, ongoing age stratified pharmacokinetic (PK)/pharmacodynamic (PD) and safety evaluation of oseltamivir therapy in children less than 24 months of age with confirmed influenza infection. In this study, based on their age, children have been/will be enrolled into any of five cohorts: Cohort I (12-23 months), Cohort II (9-11 months), Cohort III (6-8 months), Cohort IV (3-5 months) and Cohort V (0-2 months). The dose for Cohort II was increased to 3.5 mg/kg/dose on March 26, 2008 as three subjects in Cohort II had oseltamivir carboxylate (OC) exposures less than the lower limit of the target range. Nine new subjects were to be enrolled into Cohort II at this new dose in subsequent influenza seasons. In addition to PK and PD, this study assesses all adverse events (AEs) and serious adverse events (SAEs) including neurologic AEs, and the general physical condition of the subject. Sequential specimens are obtained for virologic assessments [viral cultures, polymerase chain reaction (PCR) for viral ribonucleic acid (RNA) (quantitative)] and analysis of oseltamivir resistance. A total of 40 subjects have been enrolled in this study as of April 23, 2009 (plus 9 infants enrolled after the cut off for safety data). Among these 40 patients, there were higher number of male patients (25/40; 63%) and Caucasians (23/40; 58%). The Roche claims database has about 1970 (including 967 patients with the diagnosis of influenza) and the Roche Safety database has 78 case reports.

Studies NV20235 is considered to be a **pivotal study** in respect of the current submission and proposed changes to the PI and the extension to the present indications for use of Tamiflu in immunocompromised patients.

The clinical evaluator concurred with the sponsor and the sponsor's Clinical Expert that relevant studies appeared to conform to the principles of Good Clinical Research Practice (GCP). It also appeared that appropriate ethical standards were applied in the studies presented.

Pharmacokinetics

The PK profile of Tamiflu was stated to have been presented in the previous submission for registration of Tamiflu. As it was not resubmitted with this application, the evaluator noted that it would have been useful to have more information on the PK of Tamiflu in the sponsor's *Clinical Overview*. A brief overview of PK is provided here from the literature.

Following administration, the prodrug (oseltamivir phosphate) is readily absorbed from the gastrointestinal tract and rapidly converted into the active metabolite, oseltamivir carboxylate (OC) (Davies, 2010). The active metabolite is detectable in plasma within 30 minutes, with maximum plasma concentrations after 3 to 4 hours (Tullu, 2009). After attaining the plasma concentrations, the concentration of the active metabolite declines with a half-life of 6-10 hours. The plasma protein binding of OC is only 3% (Tullu, 2009). Coadministration with food has no significant effect on the peak plasma concentration of the drug but can enhance the tolerability in some patients.

In all patient groups, OC has high bioavailability and is systemically distributed to infection sites at concentrations sufficient to inhibit a range of influenza virus neuraminidases (Davies, 2010). The OC rate of clearance per kg of body weight in children decreases with advancing age, such that exposure in children ≥13 years is similar to that in adults (Oo *et al*., 2001). Oseltamivir has a predictable linear PK profile and is suitable for a variety of patient populations and age groups. The potential for clinically relevant drug interactions is low (Davies, 2010). These characteristics underpin the use of oseltamivir in the diverse patient populations that are likely to be affected by seasonal and pandemic influenza viruses.

Pharmacodynamics

Similar to the PK data, the PD of Tamiflu were stated to have been presented in the previous submission for Tamiflu registration and the evaluator noted that it would have been helpful if the sponsor's *Clinical Overview* had given more information on what was submitted previously. A brief overview of PD is provided here from the literature.

The neuraminidase (NAI) enzyme is responsible for cleaving sialic acid residues on newly formed virions and this is essential for the release of recently formed viral particles from the infected cell (Tullu, 2009). Thus, the NAI enzyme helps in the spread of the virus to other cells. Tamiflu blocks the ability of the NAI enzyme to cleave sialic acid residues on the surface of the infected cell, thereby inhibiting the release of progeny virions from the infected cells (Tullu, 2009). When exposed to Tamiflu, the influenza virions aggregate on the surface of the host cell, limiting the extent of infection within the mucosal secretions (Tullu, 2009). This also helps in reducing the infectivity.

Efficacy

The clinical data came from several sources as mentioned previously. Study NV20235 was a prospective, parallel group, randomized, double blind, multicentre study of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised subjects as represented by solid organ transplant (SOT) (liver, kidney, liver and kidney) or haematopoietic stem cell transplant (HSCT) recipients. Subjects (≥ 1 year of age) received oseltamivir or placebo for 12 weeks (84 days) when surveillance data indicated that influenza was active in the community. This treatment duration was longer than the current recommendation of 6 weeks in healthy adults and 10 day post-exposure in

children, but was considered necessary to cover the entire period of the influenza season for the more vulnerable immunocompromised population. A follow up visit was conducted 28 days after the conclusion of treatment. The study was conducted over two influenza seasons from January 2007 through to June 2008.

Study NV20236 was a prospective, non-randomised, open label (single arm), multicentre study to collect safety data on the use of oseltamivir for six weeks for the prevention of influenza in children during the influenza season. Children aged between one and twelve years were enrolled in the study if, in the opinion of the investigator, they were at significant risk of morbidity and mortality from influenza or if they had the potential to infect other susceptible household members. The follow up visit, 28 days after last dose, ensured adequate time to detect a rise in antibody titres in subjects who may have become infected towards the end of the treatment period. The study was conducted during the peak of an influenza season from December 2006 through to May 2007.

Study NV20235

A total of 238 placebo subjects and 237 oseltamivir subjects were included in the "intent to treat" (ITT) population. The majority of subjects were White (91%), over half were male (66%). Among female subjects, over half (51% to 64%) of them were postmenopausal. Approximately 80% of all the subjects had solid organ transplant (SOT) and <20% had hematopoietic stem cell transplant (HSCT). Considering that this was a population of immunocompromised subjects who had received either SOT or HSCT, 92% to 95% of subjects had previous diseases that were ongoing at baseline. Concomitant medications were used by 94% to 99% of subjects. Some 94% of subjects received concomitant immunosuppressive treatments.

This study did not meet the primary endpoint (see Table 2). The proportion of subjects with laboratory confirmed (serology/viral culture) clinical influenza was not statistically significantly different in the placebo group (2.9%) compared with the oseltamivir group (2.1%). The treatment effect of oseltamivir was shown to be 28% in this population of immunocompromised SOT/HSCT recipients. When laboratory confirmation of influenza was based solely on reverse transcriptase (RT)-PCR results, seven placebo subjects and two oseltamivir subjects in the ITT population were identified as having laboratory confirmed clinical influenza (treatment effect 71.3%; 95% confidence interval [CI] for the difference in proportions between treatments, –0.6% to 5.2%) (see Table 3). Furthermore, when excluding subjects who were influenza RT-PCR positive at baseline (ITTNAB population), a larger treatment effect was observed with regard to clinical cases (treatment effect, 86%; 95% CI for the difference in proportions between treatments, 0.1% to 5.7%). The viral culture results were in line with the RT-PCR results, which showed that four placebo subjects (1.7%) and one oseltamivir subject (<1.0%) on treatment had laboratory confirmed clinical influenza, for a treatment effect of 74.9% in the ITT population. Similar results were observed for patients in the ITTNAB population.

Table 2: Primary efficacy endpoint for Study NV20235 with comparator studies

Laboratory confirmed[a] clinical influenza (Populations)	Placebo OD n/N (%)	Oseltamivir 75 mg OD n/N (%)	P-value[b]	Treatment effect[c]	95% CI for difference in proportions between treatments
NV20235[d] (ITT)	7/238	5/237			
[9553 5.3.5.1.1/Vol.1/p.54]	(2.9%)	(2.1%)	0.772	28.3%	–2.3% to 4.1%[h]
WV15825[e] (ITT)	12/272	1/276			
[7306 5.4/Vol.20/p.375]	(4.4%)	(0.4%)	0.0015	92%	1.5% to 6.6%[g]
WV15673 and WV15697[e] (ITT)	25/519	6/520			
[7200 5.4/Vol.20/p.166]	(4.8%)	(1.2%)	0.00055	76%	1.6% to 5.7%[g]
WV15799[e] (ITTIINAB)	24/200	2/205			70.6% to
[7305 5.4/Vol.20/p.288]	(12.0%)	(1.0%)	<0.0001	91.9%	98.1%[f]

[a] serology and/or viral culture.
[b] Comparison of placebo versus oseltamivir, using Fisher's exact test.
[c] Treatment effect = (1.0 - Relative Risk)*100%.
[d] Clinical case: fever (>37.2°C) + cough/coryza (score ≥1) occur on the same day on treatment.
[e] Clinical case: fever (≥37.2°C) + one respiratory symptom (cough, sore throat, nasal congestion) + one constitutional symptom (chills/sweats, fatigue, myalgia, headache) all on same day.
[f] 95% confidence interval for treatment effect using the method of Noether.
[g] Calculated using normal approximation to the binomial distribution.
[h] Calculated using Newcombe's method of combining Wilson score intervals without continuity correction.

Table 3: NV20235 Summary of secondary analyses-laboratory confirmed clinical influenza by laboratory confirmation methods and analysis populations

Laboratory confirmed clinical influenza: On Treatment (Population)	Placebo OD n/N (%)	Oseltamivir 75 mg OD n/N (%)	Treatment effect[a]	95% CI[b] for difference in proportions between treatments	P-value[c] (Fisher's exact test)
Serology/viral culture (Per Protocol) [9553 5.3.5.1.1/Vol.1/p.57]	6/208 (2.9%)	4/220 (1.8%)	37.0%	–2.1% to 4.5%	0.534
Serology/viral culture (ITTNAB) [9553 5.3.5.1.1/Vol.1/p.57]	7/231 (3.0%)	4/232 (1.7%)	43.1%	–1.7% to 4.6%	0.381
RT-PCR (ITT) [9553 5.3.5.1.1/Vol.1/p.59]	7/238 (2.9%)	2/237 (<1.0%)	71.3%	–0.6% to 5.2%	—
RT-PCR (ITTNAB) [9553 5.3.5.1.1/Vol.1/p.59]	7/231 (3.0%)	1/232 (<1.0%)	85.8%	0.1% to 5.7%	—
Serology/viral culture/ RT-PCR (ITT) [9553 5.3.5.1.1/Vol.1/p.60]	8/238 (3.4%)	5/237 (2.1%)	37.2%	–1.9% to 4.6%	—
Serology/viral culture/ RT-PCR (ITTNAB) [9553 5.3.5.1.1/Vol.1/p.60]	8/231 (3.5%)	4/232 (1.7%)	50.2%	–1.4% to 5.1%	—

Clinical case: fever (>37.2 °C) and cough/coryza (score ≥1) occur on the same day on treatment.
[a] Treatment effect = (1.0 - Relative Risk)*100%.
[b] Calculated using Newcombe's method of combining Wilson score intervals without continuity correction.
[c] Comparison of Placebo versus Oseltamivir, using Fisher's exact test.

A cross tabulation analysis of RT-PCR and serology results showed that among 49 subjects from both treatment groups in the ITT population who were serology positive, seven subjects were also RT-PCR positive and 42 subjects remained RT-PCR negative throughout this study. Among 381 subjects who were serology negative, 366 subjects were RT-PCR negative and 15 subjects were RT-PCR positive. Assuming RT-PCR is considered the true standard, serology would have a low sensitivity (7/22; 32%) in addition to a low positive predictive value (7/49; 14%) in this population of immunocompromised subjects. Similar results were obtained when subjects were analyzed by baseline vaccination status (vaccinated versus non-vaccinated). No resistance was observed during this 12 month seasonal prophylaxis study in immunocompromised patients.

Study NV20236

A total of 52 subjects from four centres were enrolled into this study. All subjects screened for this study were enrolled and all 52 subjects enrolled for the trial are included in the ITT population. All 52 subjects received at least one dose of oseltamivir but three subjects failed to return for the post-baseline safety assessment. Forty one subjects completed treatment. A summary of the efficacy results for the ITT group is given in Table 4.

There were no cases of laboratory confirmed clinical influenza which is defined as a positive viral culture or a ≥ 4-fold increase in antibody titre, accompanied by fever, cough and coryza or by fever and cough or coryza. Three subjects had laboratory influenza

confirmed by a ≥ 4-fold increase in antibody titre at the end of treatment assessment. A further three subjects had laboratory influenza confirmed by a ≥ 4-fold increase in antibody titre at the follow up visit.

Table 4: Summary of Efficacy Results (ITT Population)

Efficacy Parameter (as defined in Section 2.8.3)	YES (%)	NO (%)
Laboratory Confirmed Clinical Influenza (Fever, cough and coryza)	0	52
Laboratory Confirmed Clinical Influenza (Fever, cough and/or coryza)	0	52
Laboratory Confirmed Influenza	6 (12%)	46 (88%)
Asymptomatic Influenza	4 (8%)	48 (92%)
Influenza-like illness not caused by influenza virus (fever, cough and coryza)	3 (6%)	49 (94%)
Influenza-like illness not caused by influenza virus (fever, cough and/or coryza)	6 (12%)	46 (88%)

Four of these subjects remained asymptomatic (see Table 5), including two subjects who exhibited an increase in antibody titre both at the end of treatment assessment and at the follow up visit, and two subjects who had an increase in antibody titre only at the follow up visit. One subject received only 80% of the prescribed dose. Two subjects with increased antibody titre did experience influenza symptoms (see Table 5), one of whom had an increased antibody titre at the end of treatment assessment. In addition, both subjects had symptom scores for cough and coryza of≥ 1 on several occasions throughout the study but neither reported symptoms meeting the definition of clinical influenza. Three subjects experienced cough and coryza and a further three subjects experienced cough or coryza but there was no laboratory evidence of influenza.

Table 5: Summary of subjects with laboratory confirmed influenza

Subject	Study Day of Increased Antibody Titer Detection	Asymptomatic or Symptomatic Influenza	% Expected Dose
87731/0507	71	asymptomatic	80%
87731/0528	70	asymptomatic	100%
87731/0529	43,71	asymptomatic	100%
87732/0110	41,77	asymptomatic	97.6%
87732/0113	69	symptomatic	97.6%
87735/0702	43	symptomatic	100%

Summary of efficacy

Adults

In this population of immunocompromised SOT/HSCT recipients, the primary endpoint based on standard laboratory confirmation methods (serology/viral culture) was not met in the study. However, a treatment effect of 86% was observed when the laboratory confirmation method was limited to RT-PCR and when only those subjects who were RT-PCR negative at baseline were included in the analysis. In an immunocompromised patient population, diagnostic assessments of influenza infection based on immune function (serology) may not be as predictive as direct measures of influenza virus (viral culture and RT-PCR). Among subjects who were evaluated for the primary endpoint in NV20235, a large proportion met the definition of having laboratory confirmed influenza based upon a

serological response of a ≥ 4-fold increase in antibody titres from baseline up to the end of the follow up period (28 days after oseltamivir dosing had been completed). The serologic results of this study may represent a non-specific immune response to influenza virus, a delayed response to vaccination or other unknown factors related to immune dysfunction. Since numerous studies have documented prolonged shedding in immunocompromised patients, nasal sampling every two weeks in this study makes it unlikely that infection would go undetected in a large number of subjects.

In the elderly population, plasma exposure to the active metabolite at steady state is about 25% higher than in young individuals; but this difference does not necessitate dosage adjustments (Tullu, 2009).

Children

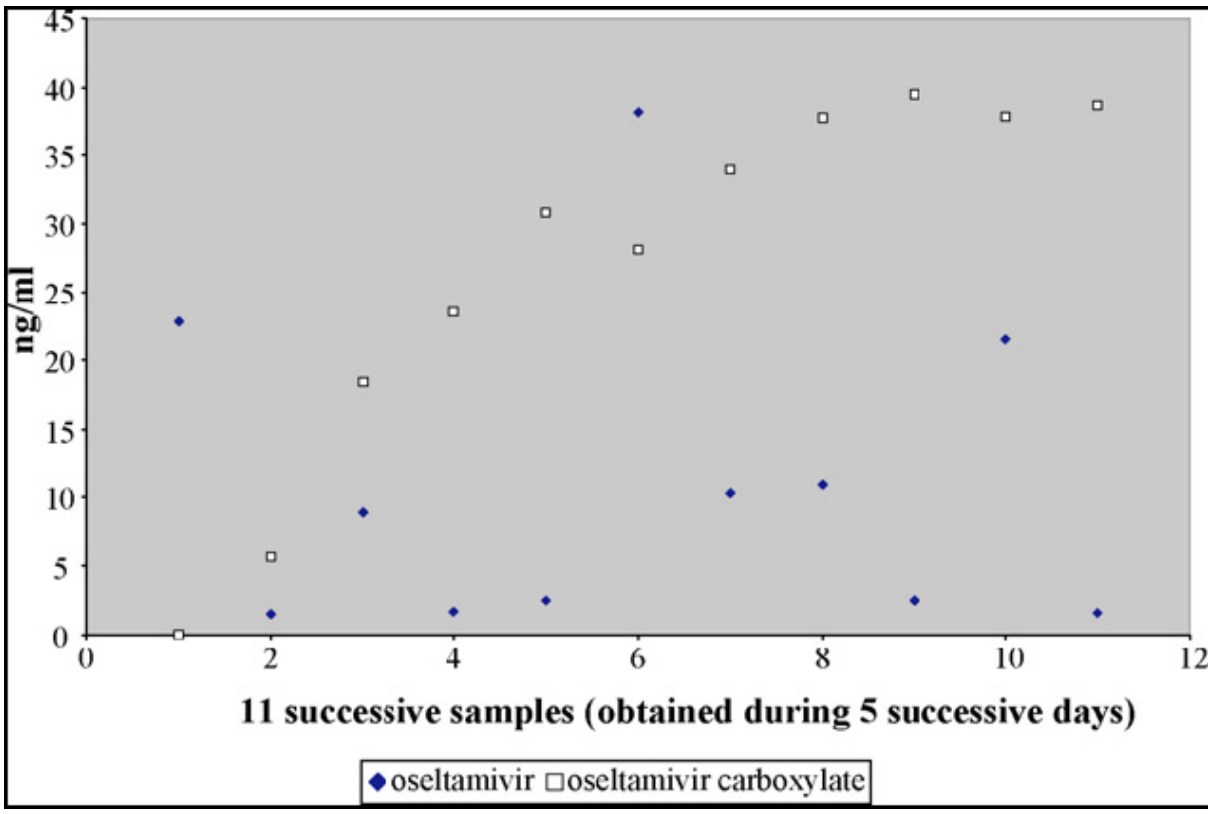
Young children (1 to 12 years of age) clear the active metabolite OC at a faster rate than older children and adults. In fact, infants as young as one year old can metabolize and excrete oseltamivir efficiently (Tullu, 2009). The mixing and dosing studies described in the current Australian submission appear to indicate that compounding of Tamiflu capsules into a solution can be done satisfactorily, which can then be given to children in a sweet drink or similar.

Use in pregnancy and lactation

Oseltamivir is a Pregnancy Category C drug and sufficient data is not available to assess the risk to the pregnant woman or developing fetus. Hence, it should be used during pregnancy, only if the potential benefits justify the potential risks to the fetus (Tullu, 2009). However, if treatment or chemoprophylaxis is required for pregnant women during the current pandemic, oseltamivir could be preferred over zanamivir because more information is available on the safety profile of oseltamivir in pregnancy.

In the Roche Drug Safety Report No. 1034695, the safety of Tamiflu in breastfeeding infants of lactating women taking Tamiflu was discussed based on oseltamivir levels in breast milk. A letter to the editor detailing concentration profiles of oseltamivir and OC in breast milk over five consecutive days of sampling (see Figure 1) suggests that oseltamivir is not expected to cause significant concentrations in the suckling infant (Wentges-van Holthe *et al*., 2008). The dose of oseltamivir that a 3 kg nursing infant would be exposed to is 0.012 mg/kg/day (Wentges-van Holthe *et al*., 2008). Otherwise, little information is available in lactation. It should, therefore be used in lactating mothers only if the benefit for the mother justifies the potential risk of exposure of the drug to the nursing infant (Tullu, 2009).

Figure 1: Concentration profiles of oseltamivir and oseltamivir carboxylate in breast milk over the five consecutive days of sampling



Impaired hepatic function and renal failure

As the metabolism of oseltamivir is not compromised in those with liver impairment, dose adjustment is not required in these cases (Tullu, 2009). The drug and its active metabolite are excreted by glomerular filtration and active tubular secretion. In patients with renal impairment, the metabolite clearance decreases linearly with creatinine clearance and averages about 23 hours after oral administration in individuals with a decreased creatinine clearance (< 30 mL/min). Hence a dosage reduction to 75 mg once daily is recommended for patients with a creatinine clearance < 30 mL/min (Tullu, 2009).

Cardiac disease and reactive airways disease

In the data given, which was not specifically directed to patients with these conditions, oseltamivir did not appear to have any major effect on blood pressure or heart rate. In addition, oseltamivir did not appear to have any major effect on patients with reactive airways disease, including bronchial asthma, or a history thereof, and severe chronic obstructive pulmonary disease. Oseltamivir should be used with caution in these patients. However, these diseases alone would not seem to be absolute contraindications to treatment or prophylaxis with oseltamivir.

Diabetes, malignancy, immunosuppression

These patient populations were not specifically examined for these conditions, except in Study NV 20235, which examined seasonal prophylaxis in 475 immunocompromised subjects, including 18 children 1-12 years old. Oseltamivir should therefore be used with caution in these groups. However, these diseases alone would not seem to be absolute contraindications to treatment with oseltamivir.

Safety

Most of the AEs reported were largely expected, as the AE profile of oseltamivir has been described previously. AEs were predominantly mild to moderate in severity. The side effect profile of oseltamivir includes diarrhea, headache and nausea as the most common AEs.

In the past few years, there have been concerns regarding two studies of oseltamivir conducted in Japan and funded by the Japanese Government. The first study was in 2846 children during the winter of 2005 to 2006. This study found evidence of unusual behaviour in recipient children within the first day of infection (Maxwell, 2007; Yorifuji *et al*., 2009). The second larger (>10 000 children) cohort study done the following winter failed to find any positive association. However, the analysis was criticized in this latter study (Maxwell, 2007; Yorifuji *et al*., 2009).

A detailed independent review of eight serious cases concluded that three sudden deaths during sleep and two near deaths, as well as two deaths from accidents resulting from abnormal behaviour in older children and adolescents shortly after taking oseltamivir, were probably related to the central depressant action of oseltamivir (Hama, 2008). In an industry sponsored review, no plausible genetic explanations for neuropsychiatric AEs were found (Toovey *et al*., 2008). One retrospective study reported no increase in the incidence of insurance claims for neuropsychiatric events in patients receiving oseltamivir compared with those with no antiviral prescribed (Smith and Sacks, 2009). It has been suggested that the neuropsychiatric events reported were actually a result of viral illness (Jamieson *et al*., 2009). Since the Japanese experience has not been replicated, the neuropsychiatric AEs from this earlier study have been largely put to one side.

Study CASG 114

Safety data are available for the 40 patients enrolled as of April 23 2009. Of the 40 patients, 26 reported an AE. There were a total of 57 non-SAEs and six SAEs. The most frequently reported AE was vomiting (n=8), followed by otitis media (n=5). A list of AEs and SAEs reported in CASG 114 is provided in Table 6. One event of neutropenia was considered life threatening (but not reported as serious) because the absolute neutrophil count (ANC) level fell in the range of the Division of AIDS (DAIDS) paediatric toxicity table for a Grade IV 'potentially life-threatening' event. The event was subsequently assessed to be related to influenza and resolved without any intervention. Of the six SAEs, one was a SAE of hypersensitivity which resulted in the withdrawal of the patient. The remaining events were influenza (two events) and one event each of pyrexia, pneumonia and decreased oxygen saturation. These events were not considered to be associated with oseltamivir. With the exception of pneumonia, all other events (four events) resolved without sequelae. Follow up information on the final disposition of the pneumonia patient was still pending. There were no deaths.

Table 6: Safety Results of Study CASG 114. Adverse Events (Cut off date April 23, 2009)

Adverse Event	COHORT I	COHORT II-A	COHORT II-B	COHORT III
Blood and Lymphatic system disorders				
Neutropenia	--	--	--	1 (6.7%)
Ear and labyrinth disorders				
Tympanic membrane perforation	--	1 (14.3%)	--	--
Eye disorders				
Conjunctivitis	--	--	--	1 (6.7%)
Gastrointestinal disorders				
Diarrhoea	1 (9.1%)	1 (14.3%)	--	1 (6.7%)
Flatulence	--	--	--	1 (6.7%)
Teething	--	--	--	1 (6.7%)
Vomiting	4 (36.4%)	--	--	4 (26.7%)
General disorders and administration site conditions				
Pyrexia	1 (9.1%)	1 (14.3%)	--	2 (13.3%)
Infections and infestations				
Conjunctivitis bacterial	--	--	--	1 (6.7%)
Croup infectious	--	--	--	1 (6.7%)
Nasopharyngitis	--	--	--	1 (6.7%)
Otitis media	--	1 (14.3%)	--	4 (26.7%)
Pharyngitis streptococcal	1 (9.1%)	--	--	--
Pneumonia	1 (9.1%)	--	--	--
Roseola	--	--	--	1 (6.7%)
Sinusitis	--	1 (14.3%)	--	--
Skin infection	1 (9.1%)	--	--	--
Upper respiratory tract infection	1 (9.1%)	1 (14.3%)	--	2 (13.3%)
Investigations				
Oxygen saturation decreased	--	--	1 (33.3%)	--
Metabolism and nutrition disorders				
Dehydration	--	--	--	1 (6.7%)
Psychiatric disorders				
Staring	--	--	--	1 (6.7%)
Renal and urinary disorders				
Urine odour abnormal	--	--	--	1 (6.7%)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (9.1%)	--	--	1 (6.7%)
Dyspnoea	--	--	--	1 (6.7%)
Wheezing	--	--	--	1 (6.7%)
Skin and subcutaneous tissue disorders				
Dermatitis contact	--	1 (14.3%)	--	--
Dermatitis diaper	3 (27.3%)	1 (14.3%)	--	1 (6.7%)
Erythema	--	--	--	3 (20.0%)
Rash	--	--	--	1 (6.7%)
Rash macular	--	--	--	1 (6.7%)
Urticaria	1 (9.1%)	--	--	--

Study NV20235

The safety population was identical to the efficacy group. However, one patient randomized to placebo received oseltamivir and was therefore assessed in the oseltamivir group for the safety population, which had 237 subjects in the placebo group and 238 subjects in the oseltamivir group. The safety population included a broad age range of subjects (1 to 76 years) with a mean age of approximately 49 years. The majority of subjects were White (91%), over half were male (66%) and among female subjects, over half (51% to 64%) were postmenopausal. Approximately 80% of all the subjects had SOT and <20% had HSCT. Considering that this was a population of immunocompromised subjects who had received either SOT or HSCT, 92% to 95% of subjects had previous diseases that were ongoing at baseline. Concomitant medications were used by 94% to 99% of subjects and 94% of all subjects received concomitant immunosuppressive treatments.

Overall, the outcomes of oseltamivir seasonal prophylaxis safety studies were consistent with the known safety profile of oseltamivir. The incidence of 'on-treatment' AEs reported during the 12 week period of oseltamivir administration was similar for subjects on placebo (58%) and oseltamivir (55%), the majority of which were mild or moderate in intensity. The AEs most commonly reported were diarrhoea, headache and nausea (see Table 7). Two placebo subjects died after being withdrawn from the study. Neither death was considered related to study medication by the investigator. SAEs were reported in 10% of placebo and 8% of oseltamivir subjects, the most common of which were infections (placebo, 4%; oseltamivir, 3%). AEs that led to treatment withdrawal were reported in 6% of placebo and 3% of oseltamivir subjects, the most common of which were gastrointestinal disorders in the placebo group (placebo 2%; oseltamivir <1%) and nervous system disorders in the oseltamivir group (placebo 0; oseltamivir 1%).

There were no consistent patterns with regard to laboratory parameter abnormalities. Five subjects (two placebo; three oseltamivir) had either a Grade 3 or 4 shift from baseline through the end of treatment in a laboratory tested variable: one oseltamivir subject with Grade 3 hemoglobin concentration; two oseltamivir subjects with Grade 3/4 alanine transaminase (ALT)/ aspartate transaminase (AST); and two placebo subjects with Grade 3/4 ALT. No clinically significant changes in vital signs were reported.

Table 7: Summary of on-treatment adverse events with an incidence rate of at least 2% by trial treatment (safety population) (Study NV20235)

Adverse Event	Placebo OD N = 237 No. (%)	Oseltamivir 75 mg OD N = 238 No. (%)
DIARRHOEA	18 (8)	15 (6)
HEADACHE	12 (5)	11 (5)
NAUSEA	9 (4)	13 (5)
FATIGUE	7 (3)	12 (5)
HYPERTENSION	10 (4)	9 (4)
UPPER RESPIRATORY TRACT INFECTION	10 (4)	8 (3)
VOMITING	7 (3)	9 (4)
NASOPHARYNGITIS	5 (2)	10 (4)
OEDEMA PERIPHERAL	7 (3)	6 (3)
ABDOMINAL PAIN	5 (2)	7 (3)
DIZZINESS	6 (3)	5 (2)
COUGH	8 (3)	2 (<1)
DYSPNOEA	5 (2)	3 (1)
PYREXIA	5 (2)	3 (1)
BRONCHITIS	6 (3)	1 (<1)
GASTROENTERITIS	2 (<1)	5 (2)
OROPHARYNGEAL PAIN	5 (2)	1 (<1)

Investigator text for Adverse Events encoded using MedDRA version 12.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
On-treatment adverse events are defined as those occurring within a time window of up to and including two days after the last day of
study treatment.
AE13 12MAY2009:16:08:06

Study NV20236

The safety population comprised 49 subjects. Three subjects did not return for a post-baseline safety assessment and were excluded from the safety population. During the "on-treatment period", up to and including two days after the last day of oseltamivir administration, 17/49 (35%) subjects reported a total of 22 AEs (see Table 8), which

erroneously does not capture one incident of on-treatment tonsillitis as it was captured as being off-treatment.

The most common events were in the System Organ Classes of *Gastrointestinal Disorders* (6 subjects) and *Infections and Infestations* (6 subjects). Twelve of the AEs were mild in nature, eight events were of moderate intensity and two events, toothache and otitis media, were rated as severe by the investigator. The investigator considered three AEs (moderate nausea, mild nausea and vomiting) as probably related to treatment. The investigator considered all other AEs as unrelated to treatment. Of the three subjects who received more than the prescribed dose, one subject had several AEs during treatment (mild ear pain on Day 39 and mild tendonitis on Day 43) and during the follow up period (moderate otitis media and moderate sinusitis on Day 63). All events were considered by the investigator as unrelated to treatment.

AEs occurring "off-treatment" (more than two days after stopping treatment up until the Day 70 follow up visit) were also collected. Five (10%) subjects reported a further six AEs as detailed in Table 9, which erroneously includes one subject who had on-treatment tonsillitis referred to above. Of these six post-treatment AEs, three were infections (otitis media, tonsillitis and sinusitis) and there were single occurrences of joint injury, headache and wheezing. There were no deaths or SAEs during the course of this study.

Table 8: Summary of on-treatment adverse events by body system (safety population) (Study NV20236)

Body System/ Adverse Event	OSELTAMIVIR N = 49 No. (%)
ALL BODY SYSTEMS	
Total Pts with at Least one AE	16* (33)
Total Number of AEs	21*
GASTROINTESTINAL DISORDERS	
Total Pts With at Least one AE	6 (12)
NAUSEA	2 (4)
VOMITING	2 (4)
DENTAL CARIES	1 (2)
ORAL MUCOSAL BLISTERING	1 (2)
Total Number of AEs	6
INFECTIONS AND INFESTATIONS	
Total Pts With at Least one AE	5* (10)
NASOPHARYNGITIS	1 (2)
OTITIS MEDIA	1 (2)
OTITIS MEDIA ACUTE	1 (2)
SINUSITIS	1 (2)
TONSILLITIS[a]	1 (2)*
UPPER RESPIRATORY TRACT INFECTION	1 (2)
Total Number of AEs	6*
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total Pts With at Least one AE	3 (6)
ASTHMA	1 (2)
TONSILLAR HYPERTROPHY	1 (2)
WHEEZING	1 (2)
Total Number of AEs	3
EYE DISORDERS	
Total Pts With at Least one AE	2 (4)
EYE SWELLING	1 (2)
EYELID IRRITATION	1 (2)
Total Number of AEs	2
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total Pts With at Least one AE	2 (4)
CONTUSION	1 (2)
JOINT SPRAIN	1 (2)
Total Number of AEs	2
EAR AND LABYRINTH DISORDERS	
Total Pts With at Least one AE	1 (2)
EAR PAIN	1 (2)
Total Number of AEs	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total Pts With at Least one AE	1 (2)
TENDONITIS	1 (2)
Total Number of AEs	1

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
On-treatment adverse event are defined as those occurring within time window of up to and including 2 days after the last day ofstudy treatment.
AE11_1 26JAN2008:23:52:15 (modified by PDRD)

[a]One additional subject (subject 87732/115) reported an adverse event of "tonsillitis" whilst on treatment that was erroneously not captured in this summary. Data points affected are marked *.

Table 9: Summary of Off-Treatment Adverse Events (Those Occurring Later Than 2 Days after End of Study Treatment) (NV20236)

Body System/ Adverse Event	OSELTAMIVIR N = 49 No. (%)
ALL BODY SYSTEMS	
Total Pts with at Least one AE	6[A] (12)
Total Number of AEs	7[A]
INFECTIONS AND INFESTATIONS	
Total Pts With at Least one AE	3[A] (6)
TONSILLITIS[A]	2[A] (4)
OTITIS MEDIA	1 (2)
SINUSITIS	1 (2)
Total Number of AEs	4[A]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total Pts With at Least one AE	1 (2)
JOINT INJURY	1 (2)
Total Number of AEs	1
NERVOUS SYSTEM DISORDERS	
Total Pts With at Least one AE	1 (2)
HEADACHE	1 (2)
Total Number of AEs	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total Pts With at Least one AE	1 (2)
WHEEZING	1 (2)
Total Number of AEs	1

Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Off-treatment adverse event are defined as those occurring more than 2 days after end of study treatment.
AE11_2 28JAN2008:23:52:23 modified by PDRD
[A]One subject (67732/115) who reported an adverse event of "tonsillitis" on-treatment is erroneously included in this off-treatment summary. Data points affected are marked *.

Drug Safety Reports

The clinical safety of oseltamivir was evaluated in 2477 infants in US, German and Japanese retrospective and prospective observational and clinical studies. Most studies used a dose of 2 mg/kg dose twice a day (bid). As described earlier, in CASG 114 (an ongoing NM study), safety and PK were evaluated in 40 infants treated with oseltamivir (3 to 3.5 mg/kg/dose bid). In all of these studies oseltamivir was found to be generally safe and well tolerated. In another analysis, infants with influenza were identified in an insurance claims database. There were 967 infants treated with oseltamivir compared with 16594 with no treatment. There were no AEs with a significantly [mutually exclusive confidence intervals (CI)] higher incidence in the oseltamivir group compared to no treatment. As of 29 April 2009, a total of 118 events were distributed among 78 infants less than one year old taking oseltamivir in the Roche safety database. As would be expected for the infant population, a majority of the events (50) were serious. There was one fatality in a high risk infant (Down's syndrome with large ventricular septal defect (VSD)). The 118 events were distributed among 63 preferred terms (PTs). Of the 63 PTs, 43 were considered unexpected and 20 as expected for oseltamivir. There were a total of 59 events (24 serious, 33 non-serious and two co-manifestations) distributed amongst 43 different PTs considered unexpected. The unexpected events did not appear to be causally related with the use of oseltamivir. Most events were expected for influenza in infants or other illnesses/seasonal infections common in infants. A total of 59 events (26 serious and 33 non-serious) were reported for the 20 PTs considered expected for oseltamivir.

Summary of safety

The overall safety results of the various studies were consistent with the known safety profile of oseltamivir. From Study NV20235, oseltamivir was safe and well tolerated in an immunocompromised patient population. The proportion of patients experiencing an AE was similar in the two treatment groups and there were no clinically meaningful differences in laboratory parameters observed between the two treatment groups. The immunocompromised status of these subjects may have confounded the serologic findings. Thus, the more sensitive RT-PCR laboratory confirmation method, which showed a similar treatment effect to that observed using viral culture, may be a more clinically relevant diagnostic tool for use in an immunocompromised population. From Study NV20236, once daily administration with oseltamivir (dose dependent on weight) for 6 weeks to children between the ages of 1 and 12 years old is well tolerated. The drug safety reviews, including CASG 114, appear to support the safety profile of oseltamivir and there was no suggestion of the neuropsychiatric issues found in the earlier Japanese study.

Clinical Summary and Conclusions

- Influenza is a major cause of morbidity and mortality worldwide. Mortality is particularly high in young infants. Apart from immunization (which has some limitations, in particular in groups like the immunocompromised), antiviral agents such as oseltamivir are being increasingly used in treatment and prophylaxis for influenza.
- Oseltamivir has been approved in Australia and other jurisdictions for the treatment of infections due to influenza A and B viruses in adults and children aged one year and older. Twice daily dosing is recommended.
- A number of special approvals have seen Tamiflu fast tracked to combat diseases such as avian influenza as well as pandemic influenza, especially in younger children (including children aged 6-12 months).
- PK studies appear to support the use of once a day oseltamivir dosing for prophylaxis in children. In particular, the safety of once a day dosing was supported by Study NV20236, although this was a relatively small, uncontrolled study of 52 patients.
- In the pivotal clinical Study NV20235, which involved approximately 238 placebo subjects and 237 oseltamivir subjects, there was reasonable support for the safety of prophylaxis in immunocompromised patients. The efficacy results were however less convincing.
- The AE and SAE profile was substantially known from previous studies of oseltamivir and were primarily gastrointestinal in nature, which tended to decrease with time. The most frequently reported treatment related AE in the various studies was diarrhoea.

Conclusions and recommendations

In general, the additional data presented provides support for the safety of the proposed changes to the PI and CMI for Tamiflu (Study CASG114), as well as the extensions to treatment of infants < 12 months of age and use in seasonal prophylaxis (Study NV 20236). Efficacy and safety data from Study NV20235 appears to be sufficient to support the safety of the extension of indication to immunocompromised patients. There is additional data presented for use of oseltamivir during pregnancy and lactation, which provides some additional evidence for safety in these groups. However, further research is needed. The regimen should be used with caution in patients with existing renal disease. It may require reduction in the dosage of oseltamivir. Because of the complexity of the

number and scope of the proposed changes to indications and other PI modifications, the general recommendations are summarized in Table 10.

- Overall, the risk-benefit profile of Tamiflu seems to be favorable. It is recommended that:
    - The use of Tamiflu continues to be closely monitored in respect of resistance to this product.
    - Treatment and prophylaxis using Tamiflu should preferably be initiated in recognised hospitals and medical centres under the direction of an appropriately trained general practitioner or specialist in infectious disease.
- The changes in indications for Tamiflu will need to be reflected in relevant clinical guidelines in Australia. The guideline will need to be updated to include this new dosing regimen and extension of indication, as well as provide advice to clinicians on best practice for its implementation.
- Gastrointestinal issues appear to be the major AE seen in studies involving oseltamivir and it has been mentioned in the re-drafted PI and CMI. However, postmarketing surveillance is needed to monitor for other AEs or SAEs, in particular to ensure that neuropsychiatric problems are not re-encountered.

Table 10: Summary of Recommendations

Proposed modification/extension of indication.	Recommendation
Proposed extension of indication to children aged 6 months and older for treatment of influenza A and B.	Safety supported
Proposed changes to *Pharmacology*, *Clinical Trials*, *Adverse Events* and *Dosage and Administration* sections to include information on prophylaxis of immunocompromised patients and safety information on the seasonal prophylaxis of children from 1-12 years of age.	Safety Supported
Proposed changes to the *Dosage and Administration* Section to include instructions for pharmacists on how to compound Tamiflu capsules into a solution.	Supported
Proposed changes to the *Precautions* section dealing with *Pregnancy* and *Lactation*, as well as general editing of Tamiflu documents.	Data can be incorporated; more research needed in relation to pregnancy and lactation

V. Pharmacovigilance Findings

Risk Management Plan

Safety Specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the nonclinical evaluator and the clinical aspects by the clinical evaluator, the summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 11.

Office of Product Review (OPR) reviewer comment

Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the ongoing safety concerns is considered satisfactory, except under

'Important missing information – Children < 6 months of age' needs to be updated to reflect the text in both the Pharmacovigilance (PhV) Plan and the risk minimisation actions to be 'Important missing information – Children < 1 year of age'.

Table 11: Ongoing Safety Concerns

Important identified risks	• Neuropsychiatric events • Skin disorders (skin rash, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis) • Gastrointestinal bleeding and haemorrhagic colitis • Liver and biliary system disorders (fulminant hepatitis) • Fructose intolerance (children) • Cardiac arrhythmia • Visual disturbance • Development of oseltamivir-induced viral resistance
Important potential risks	• Exposure during pregnancy • Exposure of infants through lactation • Potential drug-drug interactions (probenecid, chlorpropamide, methotrexate, phenylbutazone, clopidogrel)
Important missing information	• Hepatic and renal impairment in children • Treatment of influenza in immunocompromised patients (study NV20234 is still ongoing) • Children <6 months of age
Areas of special interest under influenza pandemic situation	• Use in pregnant women (see section 1.4.2, Table 25) • Use in breastfeeding women (see section 1.4.2, Table 26) • Use in young children (see sections 1.8.4 and 1.8.5) • Lack of efficacy/development of resistance (see section 1.8.6, Table 24 and Table 46) • Medication errors • Neuropsychiatric ADRs (see Table 33 and Table 45) • Fatal ADRs

Pharmacovigilance Plan and Risk Minimisation Activities

The Pharmacovigilance Plan and Risk Minimisation Activities are shown in Table 12.[1]

[1] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 12: Sponsor's summary of the Risk Management Plan (RMP)

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Neuropsychiatric events	Close observation through routine pharmacovigilance system	The MAH has updated its Core Data Sheet (CDS) to ensure adequate risk minimisation, by updating the warnings and precautions with information already provided in the EU, US and Japanese labels. Additionally, the post-marketing section of the CDS has been updated with terms clarifying the clinical features occurring with delirium. Both of these changes enable healthcare providers to communicate this information to patients and to the parents of infected children. A Type II variation was submitted following the EMEA assessment of the Comprehensive Report on neuropsychiatric events [4]. On 25 September 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the EU summary of product characteristics and package leaflet. These amendments have been described in Section 4.8 of the SmPC 'Undesirable Effects'
Skin disorder (skin rash, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis)	Close observation through routine pharmacovigilance system	Described in Section 4.8 of the SmPC 'Undesirable Effects'
Gastrointestinal bleeding and haemorrhagic colitis	Close observation through routine pharmacovigilance system	Described in Section 4.8 of the SmPC 'Undesirable Effects'
Liver and biliary system disorders (hepatitis, elevated liver enzymes)	Close observation through routine pharmacovigilance system	Described in Section 4.8 of the SmPC 'Undesirable Effects' The guided questionnaire to procure more detailed information on liver and biliary disorders has been instituted.
Fructose intolerance (children)	Close observation through routine pharmacovigilance system	Described in Section 4.4 of the SmPC ' Special Warnings and Precautions for Use'
Cardiac arrhythmias	Close observation through routine pharmacovigilance system	Described in Section 4.8 of the SmPC 'Undesirable Effects'
Visual disturbances	Close observation through routine pharmacovigilance system	Described in Section 4.8 of the SmPC 'Undesirable Effects'
Development of oseltamivir-induced viral resistance	Regular monitoring of the potential for the emergence of Tamiflu resistance in the circulating influenza virus populations.	Described in Section 5.1 of the SmPC, 'Pharmacodynamic Properties'

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Pregnancy	Close observation through routine pharmacovigilance system	Precaution included in Section 4.6 of the SmPC 'Pregnancy and Lactation'
Exposure of infants through lactation	Close observation through routine pharmacovigilance system	Precaution included in Section 4.6 of the SmPC 'Pregnancy and Lactation'
Potential Interaction with, probenecid, chlorpropamide, methotrexate, phenylbutazone, clopidogrel	Close observation of reported cases through routine pharmacovigilance system	Included in SmPC under section 4.5
Additional pharmacovigilance activities according to CHMP July 2009 strategy paper for monitoring of Tamiflu use during pandemic	- Working with existing pregnancy registries - Prospective, observational, non-interventional safety study in young children in EU - Pandemic periodic safety report addressing the areas of interest raised in strategy paper (see section 1.8.9)	- Swift signal detection for use of Tamiflu during pandemic and communication to health authorities, physician, prescribers, policy makers (see section 1.8.9) - Instructions for use in special populations such as pregnancy, lactation, children aged 6 months to 1 year have been mentioned in the EU SmPC

Summary of Recommendations

The OPR provided these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

The RMP provided by the sponsor is Version 5.0, August 2009. It was recommended to the Delegate that an updated post-H1N1 pandemic RMP be provided. Information pertaining to studies that were proposed by the sponsor during the H1N1 pandemic (NV22155" and Working with existing pregnancy registries to monitor pregnancy outcomes during H1N1 pandemic") needs to be updated. In addition, any other post-pandemic changes to the RMP should also be updated in the new version.

Recommendations to the Delegate in regards to the current RMP:

Pharmacovigilance activities

- Provide details of the Australian pharmacovigilance unit and Roche Pharmacovigilance system version 3.2
- Guided questionnaire for neuropsychiatric events needs to be provided
- Protocols for the planned studies need to be provided.

Risk minimisation activities

- Include the three safety concerns, 'Hepatic and renal impairment in children', 'Treatment of influenza in immunocompromised patients' and 'children < 1 year of age', into the Summary of the EU Risk Management Plan
- The PI should include the statement "no studies have been carried out in paediatric patients with hepatic disorder or renal impairment" or similar.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Tamiflu is currently approved for use in the treatment and (post-exposure) prophylaxis of influenza from one year of age and older. The seasonal influenza vaccines are approved for use from 6 months of age onwards.

The publicly available information indicates that this product has been approved for use in children below 12 months of age during a pandemic influenza. In EU the approved dosing is as shown in Table 13.

Table 13: Approved dosing in the EU

➢ For infants below 12 months of age: The recommended treatment dose for infants less than 12 months is between 2 mg/kg twice daily and 3 mg/kg twice daily during a pandemic influenza outbreak. This is based upon limited pharmacokinetic data indicating that these doses provide plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in older children and adults (see section 5.2). The following weight-adjusted dosing regimens are recommended for treatment of infants below 1 year of age:

Age	Recommended dose for 5 days
> 3 months to 12 months	3 mg/kg twice daily
> 1 month to 3 months	2.5 mg/kg twice daily
0 to 1 month*	2 mg/kg twice daily

* There is no data available regarding the administration of Tamiflu to infants less than one month of age.

Administration of Tamiflu to infants less than one year of age should be based upon the judgment of the physician after considering the potential benefit of treatment versus any potential risk to the infant.

These age-based dosing recommendations are not intended for premature infants, i.e. those with a postmenstrual age less than 37 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions

➢ For infants below 12 months of age: The recommended prophylaxis dose for infants less than 12 months during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in children > 1 year of age and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following weight-adjusted dosing prophylaxis regimens are recommended for infants below 1 year of age:

Age	Recommended dose for 10 days
> 3 months to 12 months	3 mg/kg once daily
> 1 month to 3 months	2.5 mg/kg once daily
0 to 1 month*	2 mg/kg once daily

* There is no data available regarding the administration of Tamiflu to infants less than one month of age.

Administration of Tamiflu to infants less than one year of age should be based upon the judgment of the physician after considering the potential benefit of prophylaxis versus any potential risk to the infant.

These age-based dosing recommendations are not intended for premature infants, i.e. those with a postmenstrual age less than 37 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions

In the US, the approved use is still restricted to one year and above ages. The FDA, however, approved the dosing instructions in Table 14 as an emergency procedure during the H1N1 pandemic in 2009:

Table 14: Emergency dosing instructions in the US

Tamiflu® EUA, Fact Sheet for Health Care Providers: Authorized by FDA on April 27, 2009

Recommended Treatment Dosage

Pediatric Patients Less than 1 year old.

Body Weight (kg)	Dose by Age	Recommended Treatment Dose for 5 Days
Dosing for infants younger than 1 year not based on weight	6-11 months	25 mg twice daily
	3-5 months	20 mg twice daily
	<3 months	12 mg twice daily

For infants less than 1 year old, a different measuring device (such as a 5-ml oral syringe) must be used that will dispense 2 ml (about 25 mg), 1.6 ml (about 20 mg) or 1 ml (12 mg).

Recommended Prophylaxis Dosage

Pediatric patients less than 1 year old

Body Weight (kg)	Dose by Age	Recommended Prophylaxis Dose for 10 Days
Dosing for infants younger than 1 year not based on weight	6-11 months	25 mg once daily
	3-5 months	20 mg once daily
	<3 months	Not recommended unless situation judged critical

In Australia, the paediatric dosing was considered during this pandemic but no recommendations followed. The sponsor is seeking approval of 3 mg/kg twice daily dosing in 6-12 months old children for treatment of influenza.

The current Australian submission consists of clinical data only. The clinical evaluator supported the changes proposed by the sponsor in their application. Based on known adult pharmacokinetic data and the approved PI, the prodrug oseltamivir phosphate is well absorbed from the gastrointestinal tract. The active metabolite oseltamivir carboxylate is predominantly responsible for therapeutic effect. The metabolite is detectable in plasma at 30 minutes and has maximum plasma concentration (C_{max}) of 350-400 ng/mL at 2-3 hours. The apparent clearance (CL/F) is 0.438 ± 0.092 L/min mostly via renal route (CL/r 18.8 L/h). No cytochrome P450 (CYP450) enzyme interactions have been found.

According to the information provided in the sponsor's current submission, the plasma levels (area under the plasma concentration time curve (AUC)) of active metabolite in the range 2660-5500 hr.ng/mL are considered efficacious and safe based on adult studies (75mg bid) in the treatment of influenza.

The kinetics are linear. However, the therapeutic index is considered poorly defined.[2]

Treatment of influenza in 6-12 months old children

There is an ongoing PK/PD study (CASG 114) in the US, sponsored by NIH[3] & NIAID[4], for profiling the use of oseltamivir in children less than 24 months of age in the treatment of confirmed influenza.

Five groups are included based on age categories (Cohorts III [6-8 months] and II [9-11 months] are the subject of this application; Cohort I (12-23 months) is already approved whereas Cohorts V [0-2 months] and IV [3-5 months] are not sought at this stage).

[2] Widmer *et al*. Oseltamivir in Seasonal, Avian H5N1 and Pandemic 2009 A/H1N1 Influenza – Pharmacokinetic and Pharmacodynamic Characteristics. *Clin Pharmacokinet* 2010:49 (11):741-765.
[3] National Institute of Health
[4] National Institute of Allergy and Infectious Diseases

All groups are reported to receive 3 mg/kg oseltamivir twice daily oral dose for 5 days (increased to 3.5mg/kg in Cohort IIb).

The reported results for active metabolite, at the cut-off date of 23 April 2009 are tabulated in Table 15.

Based on these results, it can be seen that 3 mg/kg twice dosing in the 6-11 months age group (Cohorts II & III) resulted in AUC levels well above those considered therapeutic in adults.

The higher AUCs were consistent with the relatively lower clearances and longer half-lives in this age group compared with the 12-23 months old age group.

The results are consistent with the known physiology of renal function whereby children attain adult levels of renal function by 12 months (Table 16).

Table 15: Pharmacokinetic data for Study CASG 114

Study CASG 114		Active metabolite (oseltamivir carboxylate)				
		Cohort				
		I (12-23 months)	IIa (9-11 months)	IIb (3.5mg) (9-11 months)	III (6-8 months)	IV (3-5 months)
AUC(inf) (hr.ng/mL)	N	8	6	1	13	2
	mean [se]	4756.42 [694.91]	9669.32 [1731.18]	8026.27 [NA]	13131.59 [2432.85]	7906.79 [1933.70]
	median	3850.38	10379.62	8026.27	12614.38	7906.79
	min-max	2573.06, 7807.19	4054.96, 15959.87	8026.27	3226.89, 32540.81	5973.09, 9840.49
Cmax (ng/mL)	N	8	6	3	14	2
	mean [se]	305.50 [46.95]	384.00 [77.37]	474.67 [73.31]	445.07 [40.53]	394.00 [30.00]
	median	294.5	347.5	497	417.5	394
	min-max	101, 526	200, 705	338, 589	239, 864	364, 424
CL/F (L/hr/kg)	N	8	6	1	13	2
	mean [se]	0.64 [0.08]	0.38 [0.09]	0.42 [NA]	0.34 [0.07]	0.40 [0.10]
	median	0.65	0.29	0.42	0.24	0.4
	min-max	0.38, 1.05	0.18, 0.74	0.42	0.09, 0.93	0.30, 0.50
t1/2 (hr)	N	8	6	1	13	2
	mean [se]	8.55 [1.35]	19.30 [7.23]	7.41 [NA]	21.12 [5.98]	10.20 [1.88]
	median	6.53	11.13	7.41	17.19	10.2
	min-max	4.49, 14.69	5.40, 51.86	7.41	1.02, 78.26	8.32, 12.07
Tmax (hr)	N	8	6	3	14	2
	mean [se]	3.71 [0.62]	4.41 [0.60]	6.14 [2.42]	3.98 [0.48]	5.68 [0.50]
	median	3.93	5.14	5.72	2.98	5.68
	min-max	0.90, 5.40	2.22, 5.73	2.17, 10.52	2.17, 8.67	5.18, 6.18
V/F (L/kg)	N	8	6	1	13	2
	mean [se]	8.10 [2.13]	7.93 [1.71]	4.53 [NA]	6.02 [0.85]	5.67 [0.36]
	median	6.56	7.83	4.53	5.48	5.67
	min-max	3.85, 22.24	3.37, 13.60	4.53	1.36, 12.43	5.31, 6.03

se = standard error

Table 16: Normal renal function in children and adults

Age	Glomerular filtration rate (mL/min/1.73m^2)	Renal blood flow (mL/min/1.73m^2)	Maximal urine osmolality (mOsm/kg)	Serum creatinine
Newborn				
32-34 week gestation	14 ± 3	40 ± 6	480	1.3
Full term	21 ± 4	88 ± 4	800	1.1
1-2 week	50 ± 10	220 ± 40	900	0.4
6 months-1year	77 ± 14	352 ± 73	1200	0.2
1-3 year	96 ± 22	540 ± 118	1400	0.4
Adult	118 ± 18	620 ± 92	1400	0.8- 1.5

The validity of the pharmacokinetic results within Study CASG 114 is also supported by their relative consistency with the previously reported results in the 1-2 year age group (Table 17).

Table 17: Pharmacokinetics of oseltamivir and oseltamivir carboxylate in children and adults

Parameters	Oseltamivir			Metabolite (OC)		
	30 mg (1-2 yrs)	45 mg* (3-5 yrs)	75 mg** (adult)	30 mg (1-2 yrs)	45 mg* (3-5 yrs)	75 mg** (adult)
Cmax (ng/mL)	42.9 (54)	65.5 (41)	65.2 (26)	146 (42)	236 (41)	348 (18)
AUC (ng.h/mL)	183 (33)	268 (32)	112 (25)	3405 (31)	4408 (20)	2719 (20)

* PP16351 [1] ** NP15717 [2]; AUC = area under the curve

The pharmacokinetic results for the prodrug (oseltamivir phosphate) and oseltamivir:carboxylate ratios were provided.

Prophylaxis of influenza in immunocompromised patients

Studies NV20235 and 236 were presented in support of these changes.

Study 235 was randomised, double blind, placebo controlled, multicentre trial seeking to compare oseltamivir with placebo for prophylaxis of influenza in immunocompromised (solid organ or allogenic haematopoietic stem cell transplant) patients who were one year of age and older. At baseline, influenza was excluded by negative influenza rapid test[5] and absence of clinical symptoms.

The primary efficacy outcome was the incidence of laboratory confirmed (serology/culture) influenza. The dosing was consistent with the currently approved regimens (30-75 mg once daily on body weight basis). The duration of treatment was 12 weeks with a follow up period of 28 days.

The exclusion criteria included (among others) patients who had received influenza vaccination in the four weeks prior to randomisation. A total of 239 and 238 patients were randomised to the oseltamivir and placebo groups respectively. The mean age of participants was 49 ± 16 years (median 51-52 years; range 1-76 years including 18 children in the 1-12 year age range).

The efficacy outcomes are shown in Table 18.

[5] Commercially available rapid diagnostic tests are screening tests for influenza A and B virus infections, which can provide results within 30 minutes. These tests are largely immunoassays which detect influenza viral antigen, while one test detects viral neuraminidase activity (WHO recommendations on the use of rapid testing for influenza diagnosis July 2005).

Table 18: Summary of Laboratory Confirmed Clinical Influenza by Laboratory Confirmation Methods and Analysis Population

Laboratory confirmed clinical influenza: On Treatment (Population)	Placebo OD n/N (%)	Oseltamivir 75 mg OD n/N (%)	Treatment effect[a]	95% CI[b] for difference in proportions between treatments	P=value[c] (Fisher's exact test)
Primary Analysis					
Serology/viral culture (ITT)	7/238 (2.9%)	5/327 (2.1%)	28.3%	–2.3% to 4.1%	0.772
Secondary Analyses					
Serology/viral culture (Per Protocol)	6/208 (2.9%)	4/220 (1.8%)	37.0%	–2.1% to 4.5%	0.534
Serology/viral culture (ITTNAB)	7/231 (3.0%)	4/232 (1.7%)	43.1%	–1.7% to 4.6%	0.381
RT-PCR (ITT)	7/238 (2.9%)	2/237 (<1.0%)	71.3%	–0.6% to 5.2%	—
RT-PCR (ITTNAB)	7/231 (3.0%)	1/232 (<1.0%)	85.8%	0.1% to 5.7%	—
Serology/viral culture/ RT-PCR (ITT)	8/238 (3.4%)	5/237 (2.1%)	37.2%	–1.9% to 4.6%	—
Serology/viral culture/ RT-PCR (ITTNAB)	8/231 (3.5%)	4/232 (1.7%)	50.2%	–1.4% to 5.1%	—
Exploratory Analyses					
Viral Culture (ITT)	4/238 (1.7%)	1/237 (<1.0%)	74.9%	–0.9% to 3.8%	—
Viral Culture (ITTNAB)	4/231 (1.7%)	1/232 (<1.0%)	75.1%	–0.9% to 4.0%	—
Serology (ITT)	3/238 (1.3%)	5/237 (2.1%)	—	–3.7% to 1.8%	—
Serology (ITTNAB)	3/231 (1.3%)	4/232 (1.7%)	—	–3.2% to 2.2%	—

Clinical case: fever (>37.2 °C) and cough/coryza (score ≥1) occur on the same day on treatment.
[a] Treatment effect = (1.0 - Relative Risk)*100%.
[b] Calculated using Newcombe's method of combining Wilson score intervals without continuity correction.
[c] Comparison of Placebo versus Oseltamivir, using Fisher's exact test.

NAB = negative at baseline

As can be seen, the treatment differences between the two groups were not statistically significant except when influenza is confirmed by RT-PCR. This is clearly indicative of its higher diagnostic value in immunocompromised population and the need to initiate antiviral treatment as soon as possible.

However, it should be noted that the absolute effect was small in all cases; for RT-PCR (ITTNAB) 7/231 (3%) versus 1/232 (0.4%) indicates an absolute risk reduction of 2.6% (NNT 39) compared to treatment with placebo.

Study 236 was seasonal prophylaxis study involving uncontrolled treatment of 52 children (1-12 years old) who were considered at risk of morbidity or mortality from influenza. The participants had negative rapid test and no influenza like symptoms. All were given fixed once daily dose according to the weight category for a period of six weeks and further follow up until Day 72. No clinical or laboratory confirmed incidences of influenza were reported.

Risk Management Plan

See below (under *Risk Benefit Analysis*).

Risk-Benefit Analysis

Delegate Considerations and Proposed Actions

The Delegate recommended the following:

(1) An extension of indication and dosing (3 mg/kg twice daily) for treatment of influenza in 6-12 month old children cannot be supported based on the Study CASG 144. However, it is desirable to include dosing instructions for this age group in the approved PI and the sponsor was asked to provide comments and indicate whether the study has concluded and the data analysed. These data from can be expected to be very usefully employed in modelling using population pharmacokinetic techniques. This may have been undertaken by the authorities in the US and the sponsor may be able to access and supply this information.

(2) Notwithstanding the outcome of this consultation, an updated RMP should be provided for consideration by the Advisory Committee on Prescription Medicines (ACPM). This is expected to be the Australian version of the v7.0 as indicated in the sponsor's recent communications with TGA's Office of Product Review.

(3) In view of this course of action, an updated PI should be provided.
In addition, the description of Study 235 in the PI should express results in a tabular format and include both relative and absolute effects.

(i) As no change in pregnancy classification is intended, the current text should be retained. The additional new text should be limited to 'while no controlled clinical trials have been conducted in pregnant women, limited data available from post-marketing and retrospective observational surveillance do not indicate direct or indirect harmful effects with respect to pregnancy or embryonic/fetal development.

(ii) For use in lactation, the recommended text is 'very limited information is available in children breast-fed by mothers taking Tamiflu and excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk at very low levels. Tamiflu should be used in lactating mother only if potential benefit for lactating mother justifies the potential risk of exposure of drug to the nursing infant.'

Response from Sponsor

Response to the Delegate's and Clinical Evaluator's Indication and Dosing Recommendations

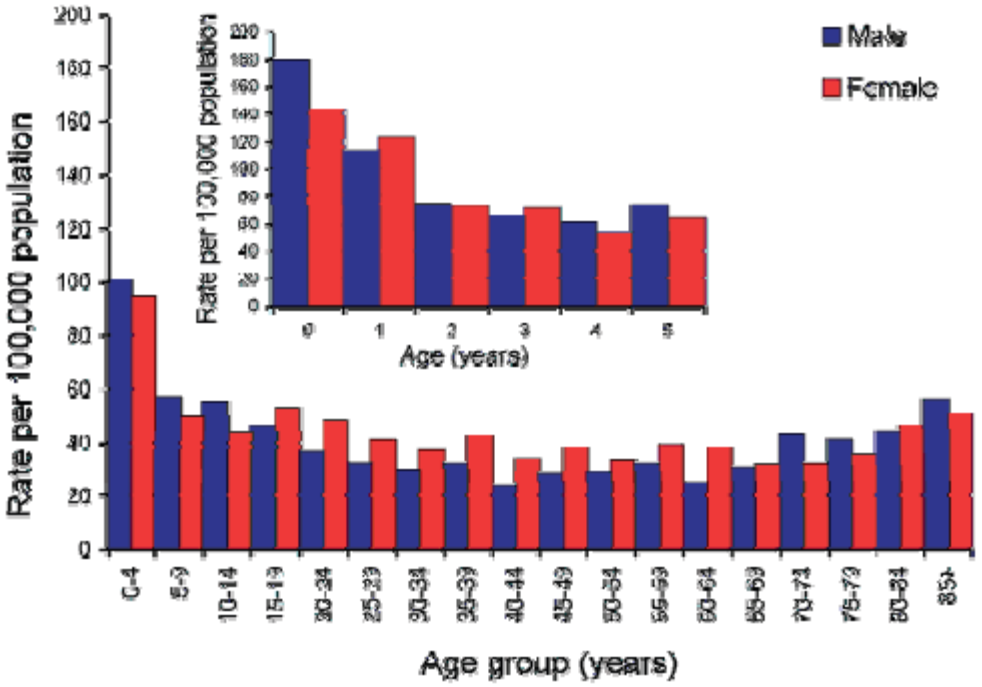
The sponsor concurred with the Clinical Evaluator's recommendation to approve the extension of indication and dosing for infants 6 – 12 months old and for immunocompromised patients. The Delegate also supported the inclusion of the information relating to the treatment of immunocompromised patients.

The Delegate did not support the extension to the indication for treatment of influenza in 6 – 12 month old infants based on the data provided, although the Delegate did acknowledge that it is desirable to include dosing instructions for the treatment of influenza in 6 – 12 month old children in the PI. Given the need for treatment options in this population the sponsor did not concur with the Delegate's recommendation that the extension of indication and dosing for treatment of influenza in 6 – 12 month old infants was not supported.

The sponsor believed that this extension of indication and dosing for the treatment of influenza in 6 – 12 month old infants provides important guidance for physicians treating this susceptible population. At present there are no other treatment options for this population. Zanamivir (Relenza) is indicated for the treatment and prophylaxis of infections due to influenza A and B viruses in adults and children aged 5 years and older. Amantadine (Symmetrel) is indicated for the prophylaxis of respiratory tract illness caused by influenza Type A only. It is also widely acknowledged that viral resistance to the adamantanes can emerge rapidly during treatment (see Hurt *et al*., 2010 for review). Even in Australia where use of adamantine in the influenza setting is very infrequent, viruses resistant to adamantine have been increasing (Hurt *et al*., 2010).

In a typical Australian influenza season notification rates for laboratory confirmed influenza are often 3 - 3.5 times higher in patients aged 0 – 4 years of age than for other age groups (Kaczmarek *et al*., 2010; see Figure 2).

Figure 2: Notification rate of laboratory-confirmed influenza, Australia, 2008, by age group and sex



As detailed by the Clinical evaluator, the data provided in the current submission demonstrates that, based on adult studies, the dosing proposed for children 6-12 months old is efficacious and safe. Study CASG 114 provides important baseline information to establish dosing for this vulnerable population. As noted by the clinical evaluator, a number of agencies fast tracked approval during the 2009 pandemic to allow children aged 6-12 months old to be treated for influenza infection. Although the pandemic is now declared over and Australia has moved from PROTECT phase back to ALERT phase, pandemic H1N1 2009 still accounted for 71% of all notifications in 2010 and 80% of influenza hospitalisations during 2009[6].

6

It is important to note that the supporting Study CASG 114 is ongoing and more data will be provided as the results are made available. This should not preclude clinicians from access to the information that is currently available.

Comment on Study CASG 114

The sponsor indicated that the Clinical Study Report will be finalised in mid 2011. The resistance data will follow at a later date. Dosing recommendations for infants 1-12 months of age will be available for submission towards the end of 2011.

Risk Management Plan

The sponsor submitted the latest version of the Risk Management Plan with the requested amendments.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission to register all presentations of oseltamivir (as phosphate) (Tamiflu) for the proposed extension of indication and dosing (3 mg/kg twice daily) to treat infections due to influenza A and B viruses in 6-12 month old children.

In making this recommendation, the ACPM agreed with the Delegate that the study submitted, CASG 144, provided insufficient evidence of safety and efficacy at the proposed dose in this age group. The committee noted that the pharmacokinetic data demonstrate a significant increase in AUC of the active metabolite, oseltamivir carboxylate, in this population, representing greater exposure. This suggests that a lower dose in this population may be more suitable. Further data are to become available in the near future which may clarify the implications suggested by the current data.

The ACPM agreed that an updated RMP should be submitted.

The sponsor was encouraged, however, to submit a new submission once further pharmacokinetic data are available from the supporting trial which should include a revised dose for this population.

Outcome

Based on a review of quality, safety and efficacy, TGA decided not to approve the proposed extension of indication/patient population to "children aged 6 months and older" and dosing information in this patient population for Tamiflu oseltamivir (as phosphate) 75mg capsule blister pack, Tamiflu oseltamivir (as phosphate) 12mg/ml powder for oral suspension bottle, Tamiflu oseltamivir phosphate bulk powder for oral solution, Tamiflu oseltamivir (as phosphate) 30 mg capsule blister pack, Tamiflu oseltamivir (as phosphate) 45 mg capsule blister pack.

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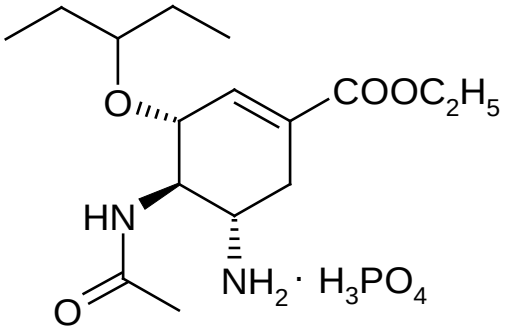
Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

NAME OF THE MEDICINE

TAMIFLU®
oseltamivir phosphate

CAS registry number: 204255-11-8



The chemical name (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.

DESCRIPTION

Oseltamivir phosphate is a white crystalline solid, highly soluble in water (> 500 mg/mL).

TAMIFLU (oseltamivir phosphate) is available as hard capsules for oral use. Each 75 mg hard capsule of TAMIFLU contains 98.5 mg oseltamivir phosphate, equivalent to 75 mg of oseltamivir. Each 45 mg hard capsule of TAMIFLU contains 59.1 mg oseltamivir phosphate, equivalent to 45 mg of oseltamivir. Each 30 mg hard capsule of TAMIFLU contains 39.4 mg of oseltamivir phosphate, equivalent to 30 mg of oseltamivir.

The hard capsules contain the following excipients: starch – pregelatinised maize, talc, povidone K 30, croscarmellose sodium and sodium stearylfumarate. The capsule shell contains gelatin, titanium dioxide, iron oxide red CI77491, iron oxide yellow CI77492, iron oxide black CI77499, shellac and indigo carmine CI73015**.**

TAMIFLU is also available as powder for oral suspension. Each bottle, with 30 g powder for oral suspension, contains 1.182 g of oseltamivir phosphate and when reconstituted with water results in a concentration of 12 mg/mL of oseltamivir. Each bottle contains the following excipients: xanthan gum, sodium dihydrogen citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide and Tutti-Frutti flavouring.

PHARMACOLOGY

Pharmacodynamics
Mechanism of Action

Oseltamivir phosphate is a pro-drug of the active metabolite, oseltamivir carboxylate. The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. A study in cultured tracheobronchial epithelial cells and primary nasal epithelial cells has shown that oseltamivir may also suppress virus entry to cells.

In Vitro Susceptibility Tests

Antiviral susceptibility and development of resistance to oseltamivir is usually discussed in the context of cell culture experiments involving Madin-Darby Canine Kidney (MDCK) virus reduction assay and/or neuraminidase inhibition assay (NA IC_{50}). The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. Oseltamivir carboxylate showed antiviral activity in the low nano-molar range in all these cell assays.

In vitro neuraminidase enzyme IC_{50} (NA IC_{50}) values for oseltamivir-susceptible clinical isolates of influenza A ranged from 0.1 – 1.3 nM and for influenza B from 2.6 – 8.7 nM.

Reduced susceptibility to oseltamivir carboxylate has been recovered *in vitro* by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. *In vitro* NA IC_{50} assays showed that the degree of reduced sensitivity (IC_{50}) differs markedly for different mutations from 2-fold for resistant variant with the I222V mutation in influenza A N1 to 30 000-fold for resistant variant with the R292K mutation in influenza A N2.

The relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Viral Resistance

Resistance to neuraminidase inhibitors *in vitro* can occur by neuraminidase mutations or haemagglutinin mutations. Haemagglutinin mutations generally reduce haemagglutinin binding affinity to sialic acid and thus reduce viral dependence on neuraminidase activity *in vitro*, resulting in neuraminidase inhibitor resistance indirectly. Neuraminidase mutations generally reduce binding affinity of neuraminidase inhibitors to the neuraminidase enzyme and thus confer resistance to neuraminidase inhibitors. To date, haemagglutinin mutations have not been described to confer resistance *in vivo* or in clinical studies, whereas neuraminidase mutations can confer resistance *in vivo* and have been observed to be selected at low frequency in clinical treatment studies.

Neuraminidase mutations have been observed to be selected *in vitro* after several passages in MDCK cells in the presence of increasing concentrations of oseltamivir carboxylate for influenza A virus isolates. Genetic analysis of resistant isolates obtained *in vitro* and in clinical studies, showed that reduced susceptibility to oseltamivir carboxylate is associated with presence of resistance mutations N294S; E119V; R292K and in one instance each

N294S and SASG245-248del in N2 neuraminidase of influenza A virus isolates and resistance mutation H274Y in influenza A N1 (including H5N1). In influenza B neuraminidase one instance of G402S giving a 4-fold decrease in sensitivity has been reported and one instance of D198N (10-fold decrease) in an immunocompromised child has been reported. Also, influenza virus isolated from an 8 month old infant girl (B/Perth/211/2001) carried neuraminidase with approximately 10-fold reduced sensitivity to oseltamivir. Sequencing indicated carrying a D197E mutation (D198E in N2 numbering) was associated with the reduced sensitivity.

Viruses with resistant neuraminidase genotypes have varying degrees of loss of fitness and transmissibility compared to wild-type. Infectivity, pathogenicity and transmission studies in mice and ferrets indicate R292K mutation in N2 was associated with compromised growth and transmissibility, where as the growth and transmissibility of viruses carrying the E119V mutation in N2 or D198N in influenza B were similar to wild-type virus. H274Y in N1 and N294S in N2 appear intermediate, although growth and transmissibility may depend on the genetic background in which these mutations occur.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In clinical studies in naturally acquired infection (irrespective of treatment dose) the incidence of patients found to carry oseltamivir-resistant virus for adults and adolescents was 0.32% (4/1245) by phenotyping alone, 0.4% (5/1245) by genotyping and phenotyping (full genotyping was not performed on all studies) and 4.1% (19/464) or 5.4% (25/464) respectively, for children aged 1 – 12 years old. All these patients were found to carry oseltamivir carboxylate-resistant virus only transiently. The patients cleared the virus normally and showed no clinical deterioration.

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.

Insufficient information is available to date to fully characterise the risk of emergence of resistance to neuraminidase inhibitors in clinical use.

Cross-Resistance

Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed *in vitro*. Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir-resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, two of the three oseltamivir-induced mutations (E119V, H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same amino acid residues as two of the three mutations (E119G/A/D, R152K and R292K) observed in zanamivir-resistant virus.

Pharmacokinetics

Absorption

Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is converted predominantly by hepatic esterases to the active metabolite. In multiple dose studies the peak concentration of the active metabolite occurs 2 – 3 hours after dosing. Following an oral dose of 75 mg twice daily, the peak concentration (C_{max}) of the active metabolite is approximately 350 – 400 ng/mL. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5% relative to the active metabolite. Plasma concentrations of the active metabolite are unaffected by co-administration with food (see DOSAGE AND ADMINISTRATION).

Distribution

The active metabolite 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 oseltamivir phosphate.

The mean volume of distribution (V_{ss}) of the active metabolite is approximately 23 L in humans.

The binding of the active metabolite to human plasma protein 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 is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. Thus, interactions mediated by competition for these enzymes are unlikely.

Elimination

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to the active metabolite. Peak plasma concentrations of the active metabolite decline with a half-life of 6 – 10 hours in most subjects. The active metabolite is not further metabolised and 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 (via the anionic pathway) in addition to glomerular filtration occurs. Less than 20% of an oral radiolabelled dose is eliminated in faeces.

Special Populations

Renal impairment

Administration of 100 mg of TAMIFLU twice daily, for 5 days, to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose is reduced to 75 mg of TAMIFLU once daily for 5 days. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see DOSAGE AND ADMINISTRATION - Special Patient Populations).

Prophylaxis of influenza

In patients with creatinine clearance between 10 – 30 mL/min receiving TAMIFLU it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg of suspension once daily. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see DOSAGE AND ADMINISTRATION - Special Patient Populations).

Hepatic impairment

Based on *in vitro* and animal studies, significant increases in exposure to oseltamivir or its metabolite are not expected and this has been confirmed in clinical studies in patients with mild or moderate hepatic impairment. The pharmacokinetics of a single oral dose of oseltamivir 75 mg have been established in moderately hepatic impaired (Child-Pugh score 7 – 9) patients. Results of the study showed that C_{max} and AUC of active metabolite of oseltamivir in the 12 hepatic impaired patients fell within the therapeutic margin of safety and efficacy. The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied (see DOSAGE AND ADMINISTRATION).

Elderly

Exposure to the active metabolite at steady-state was approximately 25% higher in elderly patients (age range 65 – 78 years old) compared to young adults given comparable doses of TAMIFLU. Half-lives observed in 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 prophylaxis of influenza unless there is co-existent renal impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Paediatrics ≥ 1 year of age

The pharmacokinetics of TAMIFLU have been evaluated in pharmacokinetic studies in children aged 1 – 16 years old. Multiple dose pharmacokinetics were studied in a small number of children aged 3 – 12 years old 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 the DOSAGE AND ADMINISTRATION section yield oseltamivir

carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). With advancing age, the difference in exposure between children and adults (per mg/kg dose) lessened to the extent that the exposure in children over 12 years of age was similar to that in adults (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

TAMIFLU should not be used in children under 1 year of age (see PRECAUTIONS - Toxicology).

CLINICAL TRIALS

Treatment of Influenza in Adults

A total of 1355 patients were included in two phase III multicentre, placebo-controlled trials in naturally acquired influenza which were conducted in the Northern Hemisphere influenza season of 1997 – 1998 (Studies WV15670 & WV15671). An identical trial (Study WV15730) followed in the Southern Hemisphere winter of 1998 where 60 patients were recruited. 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 had laboratory-confirmed influenza. The 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 the two pivotal studies are shown in Tables 1 and 2.

Table 1: Median Time (hours) to Alleviation of All Symptoms in the ITTI and ITT Populations

Study		**Placebo** **(95% CI)**	**TAMIFLU 75 mg bd (95% CI)**	***p*-value***
WV15671	ITTI	*n* = 129 103.3 (92.6 - 118.7)	*n* = 124 71.5 (60.0 - 83.2)	<0.0001
	ITT	*n* = 200 97.0 (86.3 - 113.6)	*n* = 204 76.3 (66.3 - 89.2)	0.004
WV15670	ITTI	*n* = 161 116.5 (101.5 - 137.8)	*n*= 158 87.4 (73.3 - 104.7)	0.0168
	ITT	*n* = 235 116.1 (99.8 - 129.5)	*n* = 240 97.6 (79.1 - 115.3)	0.0506

ITT Intent-to-treat
ITTI Intent-to-treat infected
* Difference between medians

Table 2: Summary of Secondary Efficacy Results (Median and 95% Confidence Interval) from the Studies in the Treatment of Naturally Acquired Influenza

Study (Protocol Number(s)) Treatment group	**AUC of total symptom score (h)**	**Time to become afebrile (h)**	**AUC of virus titer ($log_{10}TCID_{50}$.h/mL)**	**Duration of virus shedding (h)**
Study WV15671				
• Placebo (*n* = 129)	962.6#	64.6 (59.2 - 76.3)	126.7#	70.2 (68.0 - 71.4)
• TAMIFLU 75 mg twice daily (*n* = 124)	597.1#	41.5 (34.0 - 48.0)	111.4#	66.8 (64.6 - 68.8)
p-value*	<0.0001	Not calculated	0.2951	0.0332
Study WV15670				
• Placebo (*n* = 161)	943.0#	73.5 (64.0 - 86.4)	130.8#	71.0 (70.2 - 73.5)
• TAMIFLU 75 mg twice daily (*n* = 158)	773.3#	43.6 (36.0 - 54.4)	78.2#	70.2 (67.5 - 71.4)
p-value*	0.0073	Not calculated	0.0259	0.0917

n = number of subjects in the intent to treat infected population
* Comparison of placebo with TAMIFLU
\# 95% confidence interval not calculated

Studies WV15670 and WV15671

Studies WV15670 and WV15671 were multicentre, double blind, randomised, parallel group studies with the objective of assessing the safety and antiviral efficacy of TAMIFLU. Subjects who enrolled in these studies presented with symptoms of influenza defined as:

- **fever** (defined as body temperature ≥ 38 ºC)
- **plus one respiratory symptom** [cough, sore throat, nasal symptoms (rhinorrhoea/ congestion)]
- **plus one constitutional symptom** [headache, malaise (feeling unwell), myalgia (aches and pains), sweats/chills (feeling feverish), prostration (fatigue)].

Subjects were randomised to receive either 75 mg TAMIFLU twice daily, 150 mg TAMIFLU twice daily or placebo twice daily for a period of 5 days, commencing up to 36 hours, later amended to 48 hours after the reported onset of symptoms.

Primary efficacy parameter: Time to alleviation of all symptoms was significantly reduced by up to 30 hours in both the 75 mg and 150 mg active treatment groups compared with placebo, demonstrating a more rapid recovery for subjects on TAMIFLU. Treatment with TAMIFLU resulted in a reduced median time to alleviation of all of the seven defined influenza symptoms. No increase in efficacy was demonstrated in subjects who received TAMIFLU 150 mg twice daily compared to 75 mg twice daily.

Secondary efficacy parameters: Both doses of TAMIFLU significantly reduced the median total symptom score AUC (measure of extent and severity of illness) by up to 40% compared to placebo. The duration of virus shedding was also reduced in subjects treated with TAMIFLU.

Temperature AUC was reduced in TAMIFLU-treated subjects compared with placebo. Fewer subjects reported fever following dosing with TAMIFLU, despite a lower consumption of symptom relief medication (paracetamol) by the TAMIFLU groups compared to the placebo group. This was in addition to a marked reduction in the time taken for subjects on TAMIFLU to return to an afebrile state during the treatment interval compared with placebo.

The overall incidence of secondary illnesses (such as bronchitis, otitis media, sinusitis and pneumonia) requiring antibiotic medication was reduced by 50% in TAMIFLU-treated subjects when compared with placebo. Subjects treated with TAMIFLU rated their health, activity and quality of sleep to be better than patients on placebo during the dosing period. Moreover, treatment with TAMIFLU was associated with a reduction in time taken to return to normal (pre-influenza) health status and ability to perform daily activity.

Treatment of Influenza in Adolescents, Adults and Elderly – Study M76001

In a recent study which included adolescents, adults and elderly patients (13 – 80 years), time to alleviation of all symptoms was significantly reduced by up to 24.2 hours in patients treated with TAMIFLU. There was a significant reduction of the median total symptom score AUC in the treatment group compared to placebo. Consistent with other studies, temperature AUC, number of patients with fever and the time to afebrile state were reduced in TAMIFLU treated subjects compared with placebo. There was also a reduced need for patients receiving TAMIFLU to take symptom relief medication (paracetamol).

Treatment of Influenza in High Risk Populations – Study WV15758/872

In a separate study, patients aged > 13 years with influenza and co-existing chronic cardiac and/or respiratory disease received TAMIFLU 75 mg or placebo twice daily. 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 in the TAMIFLU treatment group. The number of patients shedding virus on days 2 and 4 was also markedly reduced in those treated with TAMIFLU. There was no difference in the safety profile of TAMIFLU in the at-risk populations compared to the general adult population.

Prevention 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 a 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 ≥ 37.2 ºC /99.0 ºF 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 4-fold increase in virus antibody titres from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 18 – 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 who was subsequently shown to have had influenza infection, were randomised to treatment (the intent-to-treat index-infected, not infected at baseline [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.

Treatment of Influenza in Infants and Children

One double-blind placebo controlled treatment trial was conducted in children, aged 1 – 12 years old (mean age 5.3 years old), who had fever (≥ 37.8 °C) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected with influenza A and 33% with influenza B.

The primary endpoint in this study was the time to freedom from illness, a composite endpoint which required 4 individual conditions to be met. These were: alleviation of cough, alleviation of coryza, resolution of fever, and parental opinion of a return to normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom from illness by 1.5 days compared to placebo. The median time to freedom from illness in the intent-to-treat infected (ITTI) population was 5.7 days in the placebo group and 4.2 days in patients treated with TAMIFLU. In the intent-to-treat population (ITT), the median time to freedom from illness was 5.2 days in the placebo group and 4.4 days in patients treated with TAMIFLU. The median time to freedom from illness was significantly reduced in the subgroup of patients infected with influenza A and treated with TAMIFLU, compared to patients infected with influenza B and treated with TAMIFLU (not statistically significant). The proportion of patients developing acute otitis media was reduced by 40% in children receiving TAMIFLU

compared to placebo. Subgroup analyses of this study by gender showed no differences in the treatment effect of TAMIFLU in males and females.

A second study was conducted in 334 asthmatic children aged 6 – 12 years of age, 53.6% of whom were influenza-positive. The median time to freedom from illness was reduced by 8% in patients treated with TAMIFLU compared to placebo (not statistically significant). By day 6 (the last day of treatment) FEV_1 had increased by 10.8% in the TAMIFLU-treated group compared to 4.7% in the placebo group ($p = 0.0148$) although there was no difference in the use of asthma medication between groups.

Prevention of Influenza in Infants and Children – Study WV16193

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, children and infants aged 1 – 12 years old, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days (prophylactic efficacy in adults and adolescents ≥ 13 years old has previously been demonstrated with a 7 day dosing regimen [see above]).

In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction, [95% CI 26.0 - 81.2]; $p = 0.0042$). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention (58.5% reduction, [95% CI 15.6 - 79.6]; $p = 0.0114$).

According to subgroup analysis in children 1 – 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19% (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving (64.4% reduction, [95% CI 15.8 - 85.0]; $p = 0.01$; ITT). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21% (15/70) in the group not receiving prevention to 4% (2/47) in the group receiving prevention (80.1% reduction, [95% CI 22.0 - 94.9]; $p = 0.0206$; ITTIINAB) (see Table 3).

Table 3: Incidence of Influenza Infection among Paediatric Contacts

Population	Number of Contacts 1-12 years	Influenza-infected Contacts			Index Case Infected	% Protective efficacy of oseltamivir	*p*-value
		P	T	Total			
Overall ITT	215	7 (7%)	21 (19%)	28	24	64.4	0.01
ITTII	129	6 (11%)	18 (24%)	24	24	55.2	0.089
ITTIINAB	117	2 (4%)	15 (24%)	17	24	80.1	0.0206

P = prophylaxis
T = treatment
ITTII = intent-to-treat index-infected
ITTIINAB = intent-to-treat index-infected, not infected at baseline.

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 4).

Table 4: 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.

INDICATIONS

TAMIFLU is indicated for the treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection.

TAMIFLU is indicated for the prevention of influenza in adults and children aged 1 year and older. Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

CONTRAINDICATIONS

TAMIFLU is contraindicated in patients with known hypersensitivity to any of the components of the product.

PRECAUTIONS

TAMIFLU is a specific treatment for infections due to influenza A or B viruses. Use should be limited to patients who have characteristic symptoms of influenza when influenza A or B virus infections have been documented locally. Data on the treatment of influenza B are limited.

There is no current evidence for the safety or efficacy of oseltamivir in persons with complications of an acute influenza episode such as viral or bacterial pneumonia. Such patients may require extensive supportive and adjunctive care. Antiviral therapy has not been shown to reduce the need for such care and monitoring.

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac diseases/or respiratory diseases has not been established.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied. TAMIFLU powder for oral suspension contains sorbitol. One dose of 45 mg TAMIFLU oral suspension administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance, this is above the recommended daily maximum limit of sorbitol.

Use in Renal Impairment

Dose adjustment is recommended for patients with creatinine clearance of 10 – 30 mL/min for the treatment and prevention of influenza. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance < 10 mL/min. Therefore, caution should be taken when administering TAMIFLU to those patients (see PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Effects on Fertility

No effect on male or female fertility was observed in rats exposed to oseltamivir phosphate. The highest dose has approximately 180 times the human systemic exposure (AUC) to the active metabolite.

Use in Pregnancy – Category B1

Studies for effects on embryo-foetal development were conducted in rats (at doses up to 1500 mg/kg/day) and rabbits (at doses up to 500 mg/kg/day) by the oral route. Relative exposures in these studies were 180 times human exposure (AUC_{0-24h} of the active metabolite) in the rat and 50 times human exposure in the rabbit. Foetal exposure in both species was approximately 15 – 20% of that of the mother. 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. The duration of parturition was increased in rats at oral doses of 1500 mg/kg/day of oseltamivir phosphate, 180 times human exposure (AUC_{0-24h}), but it was not affected at 500 mg/kg/day (approximately 40 times human exposure). Oseltamivir phosphate was not teratogenic in these studies.

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.

While no controlled clinical trials have been conducted on the use of TAMIFLU in pregnant women, limited data available from post-marketing and retrospective observational surveillance do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development.

Use in Lactation

In lactating rats, oseltamivir and the active metabolite are excreted 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 at very low levels. TAMIFLU should be used in lactating mothers only if the potential benefit for the lactating mother justifies the potential risk of exposure of the medicine to the nursing infant.

Paediatric Use

The safety and efficacy of TAMIFLU in paediatric patients have not been established in children aged less than 1 year of age. TAMIFLU should not be used in children under 1 year of age (see Toxicology).

No studies have been carried out in paediatric patients with hepatic impairment.

Use in Elderly Patients

Limited numbers of subjects aged ≥ 65 years old have been included in the clinical trials. However, on the basis of drug exposure and tolerability, dose adjustments are not required for elderly patients unless there is co-existent renal impairment (see PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Toxicology

In unweaned rats a single oral dose of oseltamivir phosphate 500 mg/kg (free base equivalent) to 7-day old pups resulted in deaths associated with high exposure to the prodrug. However, at 1520 mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occurred at 300 mg/kg administered to 7-day old rats. This dose level resulted in maximum plasma concentrations of 42.4 μg/mL for the prodrug and 9.4 μg/mL for the active metabolite, and maximum brain concentrations of 10.7 μg/g for the prodrug and 0.54 μg/g for the active metabolite. Based on the correlation between mortality and plasma exposure across the dose-range, the prodrug, but not the active metabolite, appears to underlie the toxicity in 7-day old juvenile rats.

Carcinogenicity

A two-year carcinogenicity study with oseltamivir phosphate in rats was negative at oral doses up to 500 mg/kg/day, resulting in respective relative systemic exposures (based on $AUC_{0\text{-}24h}$, maximum clinical dose of 75 mg twice daily) to oseltamivir phosphate and its active metabolite of 352 times and 52 times, respectively.

A two-year carcinogenicity study with oseltamivir phosphate in mice was negative at oral doses up to 400 mg/kg/day, resulting in respective relative systematic exposures (based on $AUC_{0\text{-}24h}$, maximum clinical dose of 75 mg twice daily) to oseltamivir phosphate and its active metabolite of 130 times and 15 times, respectively.

A 26-week dermal carcinogenicity study of oseltamivir carboxylate in FVB/Tg.AC transgenic mice was negative when tested at doses up to 780 mg/kg/day.

Mutagenicity

Oseltamivir phosphate was found to be non-genotoxic in the Ames test and the human lymphocyte chromosome assay, with or without metabolic activation, and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. The active metabolite of oseltamivir phosphate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay and negative in the SHE cell transformation test.

Driving and Operating Machinery

There have been no reported effects of TAMIFLU on driving performance or the ability to operate machinery. Adverse effects on such activities are not predicted from the pharmacology of TAMIFLU.

Drug Interactions

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

Oseltamivir phosphate is rapidly converted to the active metabolite by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in the literature. These esterases have been shown not to be saturable at concentrations of oseltamivir 100 times those which occur during treatment. Therefore, drug interactions caused by competition for these enzymes are highly unlikely.

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. As a result, drug interactions involving P450 isozymes are unlikely.

Oseltamivir is a weak substrate *in vitro* for the P-glycoprotein transport system; however, no adverse event for oseltamivir or the concomitant administrated drug, which could be due to an interaction at the P-glycoprotein level, has been detected.

Cimetidine 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.

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

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

Drug interaction studies have not been undertaken with oseltamivir and a number of drugs and drug classes, including erythromycin and macrolide antibiotics, theophylline derivatives and antihistamines.

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

Effects on Laboratory Tests

TAMIFLU has not been found to cause any clinically relevant changes in a range of biochemistry and haematology tests.

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.

ADVERSE EVENTS

Experience from Clinical Trials

Adult Treatment Studies

In adult phase III treatment studies, the adverse event profile was found to be similar across all four treatment studies (Studies WV15670, WV15671, WV15730 and WV15707) with comparable frequency and type(s) of adverse event(s) being recorded. Being essentially of similar design, these studies were subsequently pooled to better estimate the frequency of adverse events reported during 5 days of treatment with TAMIFLU (75 mg twice daily). A summary of adverse events in adults (including elderly patients) with an incidence of > 1% (irrespective of causality) and occurring more frequently in subjects taking TAMIFLU is presented in Table 5.

Table 5: Summary of Adverse Events in the Treatment of Naturally Acquired Influenza With Dose of 75 mg TAMIFLU Twice Daily (Excluding Nausea Associated With Vomiting) (Studies WV15670, WV15671, WV15730 and WV15707)

	Placebo ***n* = 475**		**75 mg TAMIFLU twice daily** ***n* = 496**	
Vomiting	15	(3.2%)	59	(11.9%)
Nausea (without vomiting)*	25	(5.3%)	52	(10.5%)
Insomnia	3	(0.6%)	7	(1.4%)
Headache	11	(2.3%)	13	(2.6%)
Abdominal Pain	11	(2.3%)	12	(2.4%)

* Table excludes reports of nausea associated with vomiting i.e. nausea reported within 1 day of report of vomiting

Nausea and vomiting were transient events and generally occurred with the first dose.

Other clinical adverse events of any intensity, which occurred with an incidence of > 1% in patients receiving 75 mg TAMIFLU twice daily in adult phase III treatment clinical studies, were diarrhoea and dizziness. These events were considered at least remotely related to treatment with TAMIFLU. The excess reporting of headache and abdominal pain in the 75 mg twice daily TAMIFLU group compared with placebo was numerically marginal.

Adult Prevention Studies

A total of 3434 subjects (adolescents, healthy adults and elderly) participated in phase III prevention studies with 1480 receiving the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing. There were no clinically relevant differences in the safety profile of the 942 elderly subjects, who received TAMIFLU or placebo, compared with the younger population.

The most frequently reported adverse events in all prophylaxis studies of naturally acquired influenza are summarised in Table 6. The adverse events are listed in descending order of frequency and are events occurring more frequently in the TAMIFLU group compared with the placebo group.

Table 6: Summary of Most Frequent Adverse Events in All Prophylaxis Studies in Naturally Acquired Influenza (Studies WV15799, WV15673, WV15697, WV15708 and WV15825)

	Placebo *n* = 1434		**75 mg TAMIFLU once daily *n* = 1480**	
Nausea	62	(4.3%)	118	(8.0%)
Headache	251	(17.5%)	298	(20.1%)
Vomiting	15	(1.0%)	31	(2.1%)
Diarrhoea	38	(2.6%)	48	(3.2%)
Pain	43	(3.0%)	53	(3.6%)
Fatigue	107	(7.5%)	117	(7.9%)
Rhinorrhoea	16	(1.1%)	23	(1.6%)
Abdominal pain	23	(1.6%)	30	(2.0%)
Insomnia	14	(1.0%)	18	(1.2%)
Dizziness (excluding vertigo)	21	(1.5%)	24	(1.6%)
Upper respiratory tract infection	115	(8.0%)	120	(8.1%)
Dyspepsia	23	(1.6%)	25	(1.7%)

The adverse events reported in prophylaxis studies were consistent with the established safety profile for TAMIFLU in the treatment of influenza. Adverse events experienced more frequently by subjects taking TAMIFLU than placebo included nausea (8.0% vs 4.3%), vomiting (2.1% vs 1.0%), diarrhoea (3.2% vs 2.6%) and abdominal pain (2.0% vs 1.6%). Headache was the most frequently reported adverse event with an incidence of 17.5% in the placebo group and 20.1% in the group receiving TAMIFLU.

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

Paediatric Treatment Studies

A total of 1032 paediatric patients aged 1 – 12 years old (including 698 otherwise healthy children aged 1 – 12 years old and 334 asthmatic paediatric patients aged 6 – 12 years old) participated in phase III studies investigating the use of TAMIFLU in the treatment of influenza. A total of 515 paediatric patients received treatment with TAMIFLU suspension.

Adverse events occurring in > 1% of paediatric patients receiving TAMIFLU treatment are listed in Table 7. The most frequently reported adverse event was vomiting. Other events reported more frequently by paediatric patients treated with TAMIFLU 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 majority of cases.

Table 7: Most Frequent Adverse Events Occurring in Children Aged 1 – 12 Years in Studies in Naturally Acquired Influenza Adverse Events Occurring on Treatment in > 1% of Paediatric Patients Enrolled in Phase III Trials of TAMIFLU Treatment of Naturally Acquired Influenza

	Treatment[a]				Treatment[b]		Prophylaxis[b]	
Adverse Event	**Placebo** *n* = 517		**Oseltamivir 2 mg/kg twice daily** *n* = 515		**Oseltamivir Unit dose[c]** *n* = 158		**Oseltamivir Unit dose[c]** *n* = 99	
Vomiting	48	(9.3%)	77	(15.0%)	31	(19.6%)	10	(10.1%)
Diarrhoea	55	(10.6%)	49	(9.5%)	5	(3.2%)	1	(1.0%)
Otitis media	58	(11.2%)	45	(8.7%)	2	(1.3%)	2	(2.0%)
Abdominal pain	20	(3.9%)	24	(4.7%)	3	(1.9%)	3	(3.0%)
Asthma (including aggravated)	19	(3.7%)	18	(3.5%)	-		1	(1.0%)
Nausea	22	(4.3%)	17	(3.3%)	10	(6.3%)	4	(4.0%)
Epistaxis	13	(2.5%)	16	(3.1%)	2	(1.3%)	1	(1.0%)
Pneumonia	17	(3.3%)	10	(1.9%)	-		-	
Ear disorder	6	(1.2%)	9	(1.7%)	-		-	
Sinusitis	13	(2.5%)	9	(1.7%)	-		-	
Bronchitis	11	(2.1%)	8	(1.6%)	3	(1.9%)	-	
Conjunctivitis	2	(0.4%)	5	(1.0%)	-		-	
Dermatitis	10	(1.9%)	5	(1.0%)	1	(0.6%)	-	
Lymphadenopathy	8	(1.5%)	5	(1.0%)	1	(0.6%)	-	
Tympanic membrane disorder	6	(1.2%)	5	(1.0%)	-		-	

[a] Pooled data from phase III trials of TAMIFLU treatment of naturally acquired influenza.
[b] Uncontrolled study comparing treatment (twice daily dosing for 5 days) with prophylaxis (once daily dosing for 10 days).
[c] Unit dose = age-based dosing

The adverse events reported in Table 7 are all events reported in the treatment studies with frequency ≥ 1% in the oseltamivir 75 mg twice daily group.

Paediatric Prophylaxis Studies

Paediatric patients aged 1 – 12 years participated in a post-exposure prophylaxis study in households, both as index cases (*n* = 134) and as contacts (*n* = 222). Gastrointestinal events, particularly vomiting, were the most frequently reported. TAMIFLU was well tolerated in this study. In a separate 6-week paediatric prophylaxis study (*n* = 49) the adverse events noted were consistent with those previously observed (see Table 7).

Post-Marketing Experience

Skin and subcutaneous tissue disorders: rare cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema and urticaria, and very rare cases of erythema multiforme and Stevens-Johnson-Syndrome have been reported. Rare reports of

toxic epidermal necrolysis. Allergy, anaphylactic/anaphylactoid reactions and face oedema have also been reported rarely.

Hepatobiliary disorders: very rare reports of 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.

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

Gastrointestinal disorders: in rare cases 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.

DOSAGE AND ADMINISTRATION

TAMIFLU may be taken with or without food (see PHARMACOLOGY). However, taking with food may enhance tolerability in some patients.

Treatment of Influenza

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

Adults and Adolescents

The recommended oral dose of TAMIFLU capsules in adults and adolescents ≥ 13 years of age is 75 mg twice daily, for 5 days. 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 instructions below).

Infants and Children ≥ 1 – < 13 years of age

The recommended dose of TAMIFLU for paediatric patients ≥ 1 year old is:

Body weight in kg	Recommended dose for 5 days
≤15 kg	30 mg twice daily
> 15 - 23 kg	45 mg twice daily
> 23 - 40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

Paediatric patients ≥ 1 year old who are able to swallow capsules may receive treatment with 30 mg, 45 mg or 75 mg capsules twice daily. A 75 mg dose may be achieved with a 75 mg capsule twice daily or one 30 mg capsule plus one 45 mg capsule twice daily.

Paediatric patients ≥ 1 year old who are unable to swallow capsules may receive the appropriate dose of TAMIFLU oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

For the oral suspension an oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. It is recommended that TAMIFLU powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.

Prophylaxis of Influenza

Adults and Adolescents

The recommended oral dose of TAMIFLU for prevention of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Therapy should begin within two days of exposure. The recommended dose for prevention 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 instructions below).

Infants and Children ≥ 1 – < 13 years of age

.The recommended prophylactic oral dose of TAMIFLU for infants and children ≥ 1 year old is:

Body weight in kg	Recommended dose for 10 days
≤ 15 kg	30 mg once daily
> 15 - 23 kg	45 mg once daily
> 23 - 40 kg	60 mg once daily
> 40 kg	75 mg once daily

Paediatric patients ≥ 1 year old who are able to swallow capsules may receive treatment with 30 mg, 45 mg or 75 mg capsules. A 75 mg dose may be achieved with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once daily.

Paediatric patients ≥ 1 year old who are unable to swallow capsules may receive the appropriate dose of TAMIFLU oral suspension or home-prepared or pharmacy-compounded TAMIFLU capsules (see instructions below).

For the oral suspension an oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is

recommended that patients use this dispenser. It is recommended that TAMIFLU powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.

Special Patient Populations

Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prevention of influenza (see PHARMACOLOGY). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

No studies have been carried out in paediatric patients with hepatic impairment.

Renal Impairment

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 – 30 mL/min, it is recommended that the dose is reduced to 75 mg of TAMIFLU once daily, for 5 days. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see PHARMACOKINETICS and PRECAUTIONS).

There is insufficient clinical data available in paediatric patients with renal impairment to make any dosing recommendation.

Prophylaxis of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with creatinine clearance between 10 – 30 mL/min receiving TAMIFLU it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg of suspension once daily. TAMIFLU should not be recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see PHARMACOKINETICS and PRECAUTIONS).

There is insufficient clinical data available in paediatric patients with renal impairment to make any dosing recommendation.

Immunocompromised Patients

Seasonal prophylaxis in immunocompromised patients ≥ 1 year of age is recommended for 12 weeks. No dose adjustment is necessary.

Infants < 1 year of age

The safety and efficacy of TAMIFLU have not been established in infants < 1 year of age. TAMIFLU should not be used in children under 1 year of age (see PRECAUTIONS - Toxicology)

Elderly

No dose adjustment is required for elderly patients (aged ≥ 65 years) in the treatment or prevention of influenza unless there is co-existent renal impairment (see PHARMACOLOGY and PRECAUTIONS).

Fructose Intolerance

A bottle of 30 g TAMIFLU powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg TAMIFLU oral suspension administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

Patients Unable to Swallow Capsules

When commercially manufactured TAMIFLU powder for oral suspension is not readily available, adults, adolescents, children and infants who are unable to swallow capsules may receive appropriate doses of TAMIFLU prepared at home by parents or caregivers or prepared by a pharmacist.

Home-prepared TAMIFLU for adults, adolescents, children and infants ≥ 1 year of age
This procedure describes the preparation of a **15 mg/mL** solution.

Adults, adolescents, children and infants who are unable to swallow capsules may receive their required 30 mg, 45 mg, 60 mg or 75 mg dose of TAMIFLU by following the instructions below.

1. Hold the TAMIFLU capsule(s), corresponding to the required dose, over a small bowl. Carefully pull the capsule(s) 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.

If the patient requires a dose of TAMIFLU, which is different to that available in capsule form, they may receive their appropriate 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. 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 (see tables above).

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

Recommended dose	Amount of TAMIFLU 15 mg/mL mixture for one dose
30 mg	2 mL
45 mg	3 mL
60 mg	4 mL

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 two years 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 TAMIFLU for adults, adolescents, children and infants ≥ 1 year of age

This procedure describes the preparation of a **15 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 (15 mg/mL) from TAMIFLU 30 mg, 45 mg or 75 mg capsules using water containing 0.1% 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 15 mg/mL suspension required is determined by the weight of the patient according to the recommendation in the table below:

Body Weight (kg)	Total Volume to Compound per Patient Weight (mL)
≤ 15 kg	30 mL
> 15 - 23 kg	40 mL
> 23 - 40 kg	50 mL

> 40 kg	60 mL

Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above: 30 mL, 40 mL, 50 mL or 60 mL) of compounded TAMIFLU 15 mg/mL suspension as shown in the table below:

Total Volume of Compounded Suspension to be Prepared	**Required Number of TAMIFLU Capsules (mg of oseltamivir)**			**Required Volume of Vehicle**
	75 mg	**45 mg**	**30 mg**	
30 mL	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	29 mL
40 mL	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	38.5 mL
50 mL	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	48 mL
60 mL	12 capsules (900 mg)	20 capsules (900 mg)	30 capsules (900 mg)	57 mL

* No integral number of capsules can be used to achieve the target concentration; therefore, please use either the 30 mg or 75 mg capsules.

Third, follow the procedure below for compounding the suspension (15 mg/mL) from TAMIFLU capsules:

1. Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU capsules into a clean mortar.
2. Triturate the granules to a fine powder.
3. Add one-third (1/3) of the specified amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) and triturate the powder until a uniform suspension is achieved.
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. 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.
6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
7. Close the bottle using a child-resistant cap.
8. Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension.
   (Note: Undissolved residue may be visible but is comprised of inert ingredients of TAMIFLU capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.)
9. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
10. Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this

information be provided by affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.

11. Place an appropriate expiration date label according to storage condition (see PRESENTATION AND STORAGE CONDITIONS).

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. Refer to the table below for the proper dosing instructions for pharmacy-compounded 15 mg/mL suspension from TAMIFLU capsules for infants and children ≥ 1 year old.

Body Weight (kg)	**Dose (mg)**	**Volume per Dose 15 mg/ml**	**Treatment Dose (for 5 days)**	**Prophylaxis Dose (for 10 days)**
≤ 15 kg	30 mg	2 mL	2 mL twice daily	2 mL once daily
> 15 - 23 kg	45 mg	3 mL	3 mL twice daily	3 mL once daily
> 23 - 40 kg	60 mg	4 mL	4 mL twice daily	4 mL once daily
> 40 kg	75 mg	5 mL	5 mL twice daily	5 mL once daily

Note: This compounding procedure results in a 15 mg/mL suspension, which is different from the commercially available TAMIFLU powder for oral suspension.

Dispense 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 (2 mL, 3 mL, 4 mL or 5 mL) on the oral syringe for each patient.

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

Preparation of Oral Suspension

It is recommended that TAMIFLU **12 mg/mL** 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 52 mL of purified water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add the total amount of purified water to the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push bottle adapter into neck of the bottle.
5. Close bottle with cap tightly. This will make sure that the bottle adapter fits in the bottle in the right position.
6. Write the date of expiry of the reconstituted oral suspension on the bottle label. (The shelf life of the reconstituted oral suspension is 10 days if stored at room temperature [below 25 °C] or 17 days if stored in a refrigerator [between 2 - 8 °C]).

Note: Shake TAMIFLU oral suspension well before each use.

OVERDOSAGE

Treatment of overdose should consist of general supportive measures.

At present there has been no experience with overdose; however, the anticipated manifestations of acute overdose would be nausea, with or without accompanying emesis. Single doses of up to 1000 mg of TAMIFLU and twice daily doses of up to 500 mg of TAMIFLU for 7 days have been well tolerated. A complete pack with ten 30 mg, 45 mg or 75 mg capsules of TAMIFLU will contain a total of 300 mg, 450 mg or 750 mg of oseltamivir, respectively.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

TAMIFLU 30 mg, 45 mg and 75 mg capsules are available in blister packages of 10 capsules.

TAMIFLU 30 mg capsules are supplied as hard gelatin capsules with a light yellow/opaque cap and a light yellow/opaque body. "ROCHE" is printed in blue ink on the yellow body and "30 mg" is printed in blue ink on the light yellow cap.

TAMIFLU 45 mg capsules are supplied as hard gelatin capsules with a grey/opaque cap and a grey/opaque body. "ROCHE" is printed in blue ink on the grey body and "45 mg" is printed in blue ink on the grey cap.

TAMIFLU 75 mg capsules are supplied as hard gelatin capsules with a light yellow/opaque cap and a grey/opaque body. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap.

TAMIFLU 12 mg/mL Powder for Oral Suspension is available in a 100 mL bottle with 30 g of white to light yellow powder for reconstitution. TAMIFLU suspension is supplied with a plastic adapter, a plastic oral dispenser and a measuring plastic cup. After reconstitution with 52 mL of water, the usable volume of oral suspension allows the retrieval of 10 doses of 75 mg oseltamivir.

Store TAMIFLU capsules below 25 °C.

After reconstitution, TAMIFLU Oral Suspension can be stored at room temperature (below 25 °C) for up to 10 days or in a refrigerator (2 - 8 °C) for up to 17 days. TAMIFLU Oral Suspension should not be frozen.

After pharmacy compounding of TAMIFLU capsules the 15 mg/mL suspension can be stored at room temperature (below 25 °C) for up to 3 weeks (21 days) or in a refrigerator (2 - 8 °C) for up 6 weeks. Pharmacy-compounded TAMIFLU suspension should not be frozen.

Home-prepared TAMIFLU mixture must be swallowed immediately after preparation.

Disposal of Medicines

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.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

TGA Approval Date: 25th March 2011

Therapeutic Goods Administration

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Reference/Publication #