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Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the renewal of the marketing authorisation for Tamiflu

International non-proprietary name: (oseltamivir)

Procedure No.: EMEA/H/C/000402/R/0089

Marketing authorisation holder (MAH): Roche Registration Ltd.

Note

Renewal assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

APD Ambulatory peritoneal dialysis

AUC Area under the curve

CAPD Continuous ambulatory peritoneal dialysis

CASG Collaborative Antiviral Study Group

CrCL Creatinine clearance

HD Haemodialysis

IRIS Influenza resistance information study

IV Intravenous

MAH Marketing authorization holder

NIH National Institutes of Health

OC Oseltamivir carboxylate

PK Pharmacokinetic

PD Pharmacodynamic

PSRs Pandemic Safety Reports

1. Background information on the renewal

1.1. Marketing authorisation

The European Commission granted the Marketing Authorisation for Tamiflu based on a favourable opinion adopted by the CHMP on 20 June 2002.

On 29 June 2007 the European Commission issued a Decision on the first Renewal of the Marketing Authorisation. The need for an additional renewal was based on the following pharmacovigilance grounds:

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Tamiflu remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

- Neuro-psychiatric adverse events are being thoroughly investigated,
- The resistance to oseltamivir needs to be monitored,
- The pandemic preparedness plan is ongoing.

Based upon the above defined safety issues of Tamiflu, the CHMP decided that the MAH should continue to submit yearly PSURs.

Finally, considering the safety profile of Tamiflu, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.

1.2. Renewal application

Pursuant to Article 14 (1-3) of Regulation (EC) No. 726/2004, the Marketing Authorisation Holder Roche Registration Ltd., submitted to the Agency on 17 October 2011 an application for renewal of the Marketing Authorisation for Tamiflu. The expiry date of the Marketing Authorisation is 24 June 2012.

2. Scientific discussion

2.1. Introduction

Tamiflu (Oseltamivir phosphate) is an ethyl ester prodrug that is rapidly absorbed from the gastrointestinal tract after oral administration and metabolised to form oseltamivir carboxylate (OC), a potent, stable and selective inhibitor of influenza A and B neuraminidase enzymes. Tamiflu is currently approved in the EU for the following indications:

Treatment of influenza

In patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see section 5.1).

Tamiflu is indicated for the treatment of infants below 12 months of age during a pandemic influenza outbreak (see section 5.2).

The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.

Prevention of influenza

- Post-exposure prevention in individuals one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g., in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants below 12 months of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

Oseltamivir phosphate is a highly water soluble white to off-white powder that is not subject to photolytic degradation. It is provided as hard gelatine capsules in dose strengths of 75, 45, and 30 mg, and is also available as a powder for oral suspension (6 mg/ml and 12 mg/ml). Oseltamivir intravenous is also available for compassionate use as a vial 100 mg/ml for intravenous (IV) infusion.

Tamiflu was first granted marketing approval in Switzerland and the United States in 1999. It received a marketing authorisation in the European Union on 20 June 2002 which was subsequently renewed on 29 June 2007. It is currently approved in approximately 100 countries worldwide for use in the treatment and prophylaxis of influenza in healthy adults and children aged 1 year and older.

The estimated cumulative exposure to oseltamivir since 1 April 2006 via commercially obtained drug and through clinical trials until 30 June 2011 is 42.062.464 patients. The total number of patients exposed to oseltamivir from October 1999 to the end of the reporting period, 30 June 2011, is estimated to be approximately 90.2 million.

2.2. Quality

The Marketing Authorisation Holder has confirmed that the quality, with respect to the method of preparation and control, has been regularly updated by variations to take account of technical and scientific progress in accordance with article 16(1) of Regulation (EC) No 726/2004 and that the product conforms to current CHMP quality guidelines.

Over the last five years the MAH applied for three extensions of the marketing authorisation to register two new capsule strengths 30 mg and 45 mg and a new strength for the oral suspension 6 mg/ml. In addition the MAH has submitted three variations related to the manufacture and the retest period of the active substance, nine variations related to the manufacture and the shelf-life of the finished product, two in relation to the excipients and one administrative change.

At the time of the opinion there was one post authorisation measure under evaluation in relation to confirming the precise content of oseltamivir in mg/ml in low administration volumes for the 6 mg/ml powder for oral suspension.
In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends that the MAH provides ongoing real-time stability data for all strengths of Tamiflu as soon as they are available, according to the table provided summarising the stability program. In this context, the MAH is recommended to keep the revised (relaxed) product shelf-life specification under review.

All the relevant sites of manufacture and testing are undergoing regular GMP inspections by an EEA competent authority or MRA partner authority. Appropriate declarations have been submitted concerning the GMP compliance status of the active substance manufacturer(s).

It should be noted that on 15 December 2011, the EC has initiated a procedure under Article 20 of Regulation (EC) No 726/2004 regarding the manufacturing of active substances and active substances' intermediates used in the manufacture of several medicinal products marketed in the EEA at Roche Caroline Inc (RCI) US which includes Tamiflu. In this regard, the assessment of this issue will be handled within the context of the ongoing article 20 procedure.

The quality of this product continues to be considered acceptable at this point of time.

2.3. Non-clinical

The overview provided by the MAH addresses non-clinical data that have become available since the submission of the last renewal of the Marketing Authorisation (December 2006) and a literature search on relevant published literature with the cut-off date of 15 August 2011.

An overview of the non-clinical studies performed by the MAH since 2006 is provided in Table 1. The information on GLP compliance status on the studies is also reflected in this table. The list of literature references provided in the non-clinical overview included over 100 articles and internal reports.

Table 1 Overview of internal studies since 2006

Study Type / Title	Species	Admin. Route	Treatm. Duration	Dose (mg/kg/day)	GLP Y/N	Report Number (year)
Pharmacology						
Assessment of inhibitory activity of oseltamivir and OC on recombinant human neuraminidases Neu1-4, and influenza virus neuraminidase	In vitro	N/A	N/A	N/A	N	1028436 (2008)
Assessment of OP and OC for inhibitory activity on brain-tissue extracted sialidase activity	In vitro	N/A	N/A	N/A	N	1027768 (2007)
Assessment of OP and OC for inhibitory activity on neuraminidases from non-human primate brain tissue	In vitro	N/A	N/A	N/A	N	1027926 (2007)
In-vitro pharmacology profile (not including neuraminidases) of oseltamivir phosphate and OC	In vitro	N/A	N/A	N/A	N	1026878 (2007)
Evaluation of pharmacological activities of oseltamivir on Cl- currents through recombinant α1β2γ2 $GABA_A$ receptor chloride channels	In vitro	N/A	N/A	N/A	N	1032974 (2009)
Emergence of oseltamivir resistance by natural selection: H275Y as a compensatory mutation	N/A	N/A	N/A	N/A	N	1032408 (2009)

Study Type / Title	Species	Admin. Route	Treatm. Duration	Dose (mg/kg/day)	GLP Y/N	Report Number (year)
Evaluation of pharmacological activities of oseltamivir carboxylate on paired-pulse protocols in the CA1 region of adult rat hippocampus	In vitro (slice culture)	N/A	N/A	N/A	N	1029566 (2008)
Drug Metabolism and Pharmacokinetics						
Studies on the substrate and inhibition properties of RO0640796 and RO0640802 by PEPT1 and 2	In vitro	N/A	N/A	N/A	N	1037739 (2010)
Influence of milk and GlySar co-administration on oral absorption in adult fed rats	Rat	po (gavage)	Single dose	30 mg/kg	N	1035034 (2010)
Influence of milk and GlySar co-administration on oral absorption in adult fasted rats	Rat	po (gavage)	Single dose	30 mg/kg	N	1035372 (2010)
Influence of breast feeding, milk and GlySar on oral absorption in juvenile rats	Rat (juv.)	po (gavage)	Single dose	30 mg/kg	N	1035375 (2010)
PK assessment after oral administration to wild type and Pept-1 KO mice	Mouse	po (gavage)	Single dose	5 mg/kg	N	1037322 (2010)
Disposition of the oseltamivir and OC in mice following single oral administration	Mouse	po (gavage)	Single dose	10 mg/kg	Y	1004494 (Revised 2008)
Studies on the substrate and inhibition properties of RO0640796 and RO0640802 by PEPT1 and 2	In vitro	N/A	N/A	N/A	N	1037739 (2010)
Influence of milk and GlySar co-administration on oral absorption in adult fed rats	Rat	po (gavage)	Single dose	30 mg/kg	N	1035034 (2010)
Influence of milk and GlySar co-administration on oral absorption in adult fasted rats	Rat	po (gavage)	Single dose	30 mg/kg	N	1035372 (2010)
Influence of breast feeding, milk and GlySar on oral absorption in juvenile rats	Rat (juv.)	po (gavage)	Single dose	30 mg/kg	N	1035375 (2010)
PK assessment after oral administration to wild type and Pept-1 KO mice	Mouse	po (gavage)	Single dose	5 mg/kg	N	1037322 (2010)
Disposition of the oseltamivir and OC in mice following single oral administration	Mouse	po (gavage)	Single dose	10 mg/kg	Y	1004494 (Revised 2008)
Iv single dose PK in rats following 10 or 100 mg/kg OP	Rat	iv	Single dose	10, 100 mg/kg	N	1026679 (2007)
Iv single dose PK in rats following 10 or 100 mg/kg OC	Rat	iv	Single dose	10, 100 mg/kg	N	1026678 (2007)
Iv single dose PK in rats following 30 mg/kg OP and distribution into the non-perfused and perfused brain	Rat	iv	single dose	30 mg/kg	N	1027310 (2009)
Iv single dose PK in rats following 30 mg/kg OC and distribution into the non-perfused and perfused brain	Rat	iv	Single dose	30 mg/kg	N	1027311 (2009)
Brain concentration of RO0640796-002 (OP) and RO0640802-002 (OC) following administration by various routes in rats	Rat	po (gavage), iv and intra-cerebroventricular (cv)	Single dose	0.2 µg/animal (OP) 0.08 µg/animal (OC) (icv) 5 mg/kg (OP, iv) 30 mg/kg (OC, iv) 200 mg/kg (OP, po)	Y	1027859 (2009)
Determination of Brain Concentration of RO0640796-002 (OP) and RO0640802-002 (OC) Following icv administration in Rats.	Rat	icv	Single dose	0.2 ug/animal 2 ug/animal (both test items)	Y	1029803 (2009)
Intraperitoneal single dose PK in 7-day old juvenile rats following 10 mg/kg OC and distribution into perfused brain	Rat (juv.)	ip	Single dose	10 mg/kg	N	1031581 (2009)
Pharmacokinetics of the prodrug, oseltamivir, and active metabolite - toxicity after a single oral administration to juvenile rats	Rat (juv.)	po (gavage)	Single dose	500, 700 and 1000 mg/kg	Y	*1008172 (amended 2008)*

Study Type / Title	Species	Admin. Route	Treatm. Duration	Dose (mg/kg/day)	GLP Y/N	Report Number (year)
An oral toxicity study of Tamiflu in juvenile rats	Rat (juv.)	po (gavage)	Single dose	300, 500, 600, 700, 850 and 1000 mg/kg	Y	*1027696 (amended 2009)*
Subcutaneous single oral dose PK in 7-day old juvenile rats	Rat (juv.)	sc	Single dose	10 mg/kg	N	1032043 (2009)
Blood and brain concentrations of RO0640802-002 following sc administration in juvenile rats	Rat (juv.)	sc	Single dose	25, 50 mg/kg	Y	1029873 (2009)
Pk of oseltamivir and OC in neonatal marmosets	Marmoset (juv, adult)	iv and po	Single dose	2, 10 mg/kg (po) 5 mg/kg (iv)	Y	1038614 (2011)
Physiologically based PK model development for marmoset and humans	In silico	N/A	N/A	N/A	N	1018216 (2011)
Transport of RO0640796 and RO0640802 by polarized cell lines	In vitro	N/A	N/A	N/A	N	1026298 (2007)
In vitro studies on the transport of RO064796 and RO0640802 by membrane vesicles expressing human MRP1, 2,3 or BCRP	In vitro	N/A	N/A	N/A	N	1029724 (2008)
Hydrolysis of RO0640796 to RO0640802 by brain S9 subcellular fraction from 7- and 42-day old rats	In vitro	N/A	N/A	N/A	N	1027267 (2007)
Hydrolysis of RO0640796 (OP) to RO0640802 (OC) by human brain S9 subcellular fractions	In vitro	N/A	N/A	N/A	N	1027737 (2007)
Hydrolysis of RO0640796 to RO0640802 by recombinantly expressed HCE1 and HCE2	In vitro	N/A	N/A	N/A	N	1029175 (2008)
Toxicology						
Single oral dose toxicokinetic study in male rat	Rat	po (gavage)	Single dose	763, 1000 mg/kg	Y	1029359 (2008)
An acute intravenous study in the male CD-1 mouse	Mouse	iv	Single dose	65, 100, 160, 250 mg/kg	Y	*1007080 (revised 2009)*
Pharmacokinetics of the prodrug, oseltamivir, and active metabolite - toxicity after a single oral administration to juvenile rats	Rat (juv.)	po (gavage)	Single dose	500, 700 and 1000 mg/kg	Y	*1008172 (amended 2008)*
An oral toxicity study of Tamiflu in juvenile rats	Rat (juv.)	po (gavage)	Single dose	300, 500, 600, 700, 850 and 1000 mg/kg	Y	*1027696 (amended 2009)*
The effects of RO0640796-002 (OP) and RO0640802-002 (OC) on hERG current in stably transfected HEK293 cells	In vitro	N/A	N/A	N/A	Y	*1028305 (amended 2007)*
Actions of RO640796-002 (OP) and its active metabolite (OC) on action potentials in isolated rabbit cardiac Purkinje fibers	In vitro	N/A	N/A	N/A	N	*1003174 (amended 2007)*
Effects of RO0640796-002 (OP) and RO0640802-002 (OC) on action potential duration in isolated guinea pig papillary muscle	In vitro	N/A	N/A	N/A	Y	1028306 (2007)
Cardiovascular and respiratory evaluation in the anaesthetized dog following intraduodenal administration.	Dog	intraduo-denal	Single dose	100 mg/kg	Y	*W-142692 (revised 2008)*
Modified Irwin test and effect on body temperature following single oral administration in the rat	Rat	po (gavage)	Single dose	500, 763 and 1000 mg/kg	Y	1029346 (2008)
Effect on body temperature following single oral administration in the rat	Rat	po (gavage)	Single dose	1000 mg/kg	N	1029138 (2008)
Local tolerance study with OP via perivenous (pv) and intra-arterial (ia) injections in rabbits	Rabbit	pv ia	Single dose	0.8, 1.6, 3.2 mg/site (pv) 2, 4, 8 mg/ site (ia)	Y	1025870 (2007)
Hemolysis and plasma precipitation and turbidity tests with canine heparinated blood and plasma	In vitro	N/A	N/A	N/A	N	1023809 (2007)

Study Type / Title	Species	Admin. Route	Treatm. Duration	Dose (mg/kg/day)	GLP Y/N	Report Number (year)
Bacterial reverse mutation test (Ames test) with OP SK (RO0640796), spiked with the degradation products RO5553071 and RO5909098	In vitro	N/A	N/A	N/A	Y	1041761 (2011)
2 Week Oral (Gavage) Administration Impurity Qualification Study in the Rat	Rat	po (gavage)	2-weeks	125 mg/kg/d (OP) 121.25 mg/kg /d (OP spiked with 1% RO5553071 and 2% RO5909098)	Y	1040903 (2011)

2.3.1. Pharmacology

Internal studies conducted by the MAH and literature related to the non-clinical pharmacology of oseltamivir included results of studies to understand mechanism of action of oseltamivir, such as binding of oseltamivir to neuraminidases, and on the mechanism of resistance to oseltamivir.

Mode of action and studies to characterize resistance mutants

Data from *in vitro* studies using structural analysis (ScrewFit algorithm, molecular dynamics simulations and chrystallography), enzyme inhibition assays and *in vivo* studies were included. New 6-8 mutations both alone and together with H275Y have been found in oseltamivir resistant influenza A/H1N1. Complementation of enhanced neuraminidase activity due to a D344N mutation by the H275Y mutation is suggested as an explanation for the predominance of oseltamivir-resistant influenza A/H1N1 viruses. The MAH provided data from several *in vivo* studies that have characterised mutations affecting the susceptibility and fitness of influenza virus A/H1N1, H3N2 and H5N1.

***In vitro* selectivity**

New non-clinical data were provided by the MAH in respect to oseltamivir selectivity. High degree of selectivity of oseltamivir as both phosphate and carboxylate for influenza neuraminidase versus human (or rodent or primate) neuraminidases was shown (Studies 1028436, 1027768, 1027926). Moreover, high degree of selectivity of oseltamivir for influenza neuraminidase over the studied 155 human molecular targets of high relevance for the mood, cognition and behaviour molecules including ion channels, receptors and enzymes was shown (Study 1026878, Lindemann et al. 2010). Furthermore, neither oseltamivir nor OC showed to affect the $GABA_A$ receptors or activate the GABAergic system (Studies 1026878, 1032974).

Studies on combination therapy

Work has been continuing on combinations of oseltamivir with older antivirals with differing mechanisms of action. Synergism between combination therapy of oseltamivir and other agents such as adamantanes, ribavirin and other neuraminidase inhibitors have been shown within *in vitro* and *in vivo* studies which are summarised in Table 2.

Table 2 In vitro and animal studies of combination therapy including oseltamivir

Reference	Type of study	Virus types and drugs studied	Results
Combinations with other NAIs			
Smee et al. 2010a [10123]	In vitro and mice	H1N1, H3N2, H5N1 Oseltamivir, favipiravir	Survival in mice was significantly improved in H1N1 and H3N2 infection by combination therapy; slight improvement in H5N1 infection.
Smee et al. 2010b [10124]	In vitro and mice	H1N1 Oseltamivir, peramivir	Numbers of survivors increased when twice daily oseltamivir was combined with peramivir. Additivity with a narrow region of synergy was shown; no significant synergistic or antagonistic interactions in a viral neuraminidase assay
Combinations with amantadine and/or ribavirin (including triple combinations)			
Nguyen et al. 2010 [10121]	In vitro (MDCK cells)	H1N1 Oseltamivir, amantadine, ribavirin	Triple combination was highly synergistic against drug-resistant seasonal and pandemic H1N1 strains; superior to any double combination tested (including 2 NAIs)
Smee et al. 2009 [10120]	In vitro and mice	H5N1 Oseltamivir, amantadine, ribavirin	Amantadine + oseltamivir and amantadine + ribavirin (but not oseltamivir + ribavirin) synergistic in wild-type virus in MDCK culture. Oseltamivir + ribavirin was primarily additive against amantadine-resistant virus
Nguyen et al. 2009 [10122]	In vitro	H1N1, H3N2, H5N1 Oseltamivir, amantadine, ribavirin	Triple combinations were highly synergistic against these seasonal and avian strains Synergy of triple combinations was 2 to 13 times greater than any double combination
Ilyushina et al. 2008 [10118]	Mice	H5N1 Oseltamivir, ribavirin	Oseltamivir + ribavirin were principally additive, with marginal synergy or antagonism at some doses. Optimal concentrations prevented H5N1 spread beyond the respiratory tract and abrogated the cytokine response
Ilyushina et al. 2007 [10165]	Mice	H5N1 Oseltamivir, amantadine	Combination therapy provided up to 90% greater protection against lethal infection than monotherapy in amantadine-sensitive infection. Combination efficacy against amantadine-resistant virus was similar to oseltamivir alone No mutations in HA, NA or M2 were seen with combination therapy
Masihi et al. 2007 [10119]	Mice	H1N1, H3N2 Oseltamivir, amantadine	Doses providing 50–60% survival alone were capable of conferring complete protection when given in combination. Addition of amantadine to oseltamivir allowed 15 times less oseltamivir to be used for complete protection against lethal aerosol infection
Others			
Garozzo et al. 2007 [10125]	Mice	H1N1 Oseltamivir, N-acetylcysteine	20% survival with N-acetylcysteine; 60% with oseltamivir; 100% with combination therapy

HA, haemagglutinin; MDCK, Madin Darby canine kidney; NA, neuraminidase; NAI, NA inhibitor

2.3.2. Pharmacokinetics

During the last 5-year period, number of non-clinical pharmacokinetic investigations have been conducted by the MAH or published in the public domain. New information includes data from oral absorption, distribution into the brain and placenta, active transport, metabolism and drug-drug interactions, including questions regarding the ontogeny of the various processes. Pharmacokinetics of oseltamivir and OC in pivotal preclinical safety studies in juvenile and adult rodents and marmosets are presented in Table 3.

Absorption

Ogihara *et al.* published *in vivo* data from rats that indicated oseltamivir to function as a substrate of intestinal peptide transporter 1 (PEPT1). The MAH performed an *in vitro* study and *in vivo* rodent studies investigating the role of intestinal uptake transport proteins and effect of food on the bioavailability of oseltamivir and its active metabolite. These studies suggest that active transport processes mediated by PEPT1 are not playing a clinically relevant role in the absorption of oseltamivir. Food was seen to have tendency to reduce the plasma concentrations of oseltamivir and OC both in juvenile and adult rats but these effects were not statistically significant.

CNS exposure

Due to clinical reports describing adverse CNS effects after administration of Tamiflu, the MAH has performed several non-clinical studies to investigate the extent and mechanism of CNS exposure of

oseltamivir and OC. New pharmacokinetic data and re-analysed data on the distribution of oseltamivir and its active metabolite into the CNS of adult and juvenile small rodents is summarised below.

In vivo rat and mouse studies show low concentrations of both compounds in the brain compared to plasma following administration of oseltamivir or OC by oral, IV, IP and SC delivery routes. Further details of the C_{max} and $AUC_{0\text{-}inf}$ in brain tissue and in plasma of oseltamivir and OC in pivotal preclinical safety studies are described in Table 3. Positron emission tomography (PET) have been utilised to determine the oseltamivir exposure in living animals. Low brain penetration was seen in adult rhesus monkeys, slightly lower than that in infant and adolescent animals in a PET study after IV administration of 11C-oseltamivir (Takashima et al. 2011). The CNS penetration of oseltamivir and its active metabolite into the brain was investigated after lipopolysaccharide (LPS) -induced inflammation in mice (Oshima et al. 2009). Concentration of oseltamivir in both brain and plasma was 2-fold higher in mice treated with LPS than in the control mice and the concentration of the OC in the brain was increased 2.7-fold in mice treated with LPS.

Disposition in juvenile animals

Special attention was given to the disposition of oseltamivir and OC in juvenile animals due to the increased clinical use of Tamiflu in the young population and the finding of toxic effects accompanied with very high brain concentrations. In summary, low brain/plasma ratios of both oseltamivir and OC were found up to very high doses following oral administration of oseltamivir or SC administration of OC in juvenile and adult rats (Table 3). The observed higher absolute exposures in juvenile compared to adult rats are thought to be due to immature physiological processes such as lower carboxylesterase activity or a lower renal clearance. Earlier study in juvenile (7-day old) rats showed that single oral doses of oseltamivir phosphate of 700 or 1000 mg/kg caused toxicity including mortality, while a dose of 500 mg/kg was well tolerated (Study 1008172). Calculation error was identified in this study in 2007 that had resulted in an overestimation of the concentrations of both oseltamivir and OC in the brain and the plasma. Recalculated results in the amended report showed that the brain/plasma ratios of oseltamivir and OC in juvenile rats were low. In newborn and adult marmosets, after IV and oral administration of oseltamivir, the plasma concentrations of oseltamivir and OC in plasma were at least 4-fold higher in juvenile as compared to adult marmosets (Study 1038614). The clearance of oseltamivir after IV administration was lower in juvenile compared to adult marmosets. Physiologically based models simulating pharmacokinetics of oseltamivir and OC have been developed to help translate these findings in humans (Study 1018216, Parrott et al. 2011). Key processes modelled include metabolic conversion of the pro-drug by carboxylesterases, slow permeability-limited release of carboxylate from hepatocytes and renal clearance of both pro-drug and metabolite.

Transporters

New non-clinical studies have been published on active transport processes partly due to concerns that an impairment or inhibition of the active export system can increase levels of oseltamivir in the CNS. These have shown that oseltamivir is a substrate of MDR1 P-glycoprotein and OC a substrate of Mrp4 and Oat3. The latter result suggests that OC may be able to cross the BBB from the blood, but its brain distribution is limited by its active efflux by Mrp4 and Oat3.

Transplacental transfer

The metabolism and transplacental transfer of oseltamivir was tested in an *ex vivo* human placental model. It was shown that oseltamivir was extensively hydrolyzed to OC, but that the transplacental transfer of the metabolite was incomplete and accumulation was minimal (Worley et al. 2008). Similar results are reported in a recent review article by Tomi et al. 2011 which concluded that the safety of

oseltamivir for pregnant women is supported by the low transplacental permeability to the foetus. This observation is consistent with the hypothesis that fetal transfer of oseltamivir is restricted by transport system(s) operating in the foetus-to-mother direction at the placental barrier.

Metabolism and drug-drug interactions

Multiple *in vitro* studies investigated the metabolic cleavage of the pro-drug to the active drug. The hydrolytic cleavage of oseltamivir into OC was found to be dominated by one isoenzyme (carboxylesterase 1, CES1) in human and in the preclinical species evaluated, rat and marmoset (Studies 1027267, 1027737, 1029175). Cleavage of oseltamivir in brain is unlikely due to low activity of this isoenzyme in rat and human brain (Study 1027267).

Table 3 Pharmacokinetics of Oseltamivir and OC in Pivotal Preclinical Safety Studies

Species [Roche ref no]	Route; duration	Age day	Dose (mg/kg)	Plasma Cmax (ng/mL)		Plasma AUC0-inf (ng·h/mL)		Cmax (ng/g) in brain tissue		AUC0-inf (ng·h/g) in brain tissue	
				OP	OC	OP	OC	OP	OC	OP	OC
Mice [1004494]	Oral, single dose (OP)	adult	10	66.1	1410	-*	3730	34.8	31.4	156	104
Rat [1026679]	IV, single dose (OP)	adult	10 100	2890 36200	2150 25900	1430 18900	3400 45300	163 1780	71.2 1010	128** 3640	NC 1350
Rat [1026678]	IV, single dose (OC)	adult	10 100	_	13900 278000	_	7080 122000	_	400 7890	_	186 3800
Rat [1027310]	IV, single dose (OP)	adult	30 (NP) 30 (P)	12000 12500	6880 6300	5330 5330	13600 12800	712 491	164 75.5	1310 1160	145 NC
Rat [1027311]	IV, single dose (OC)	adult	30 (NP) 30 (P)	_	73200 86300	_	28600 33800	_	1710 605	_	687 305
Rat [1027859]	Oral, iv, single dose (OP and OC)	adult	5 (OP iv) 30 (OC iv) 200 (OP oral)	1880 _ 7620	1380 60300 14600	702 _ 32200	1410 24400 77400	115a 92.4b _c – 489a 926b 194c	_a _b _c 1370a 684b 900c 177a 128b 232c	57.7a 114b _c _ 3060a 8220b** 1460c	_a _b _c 369a 262b 450c NCa 1290b** 3680c**
Rat [1029359]	Oral, single dose (OP)	Adult	763 1000	16200 16300	41700 49700	109000d 107000d	260000 d 286000 d	2060 2310	544 641	12200d 13600d	2810d 3450d
Mice [1007080]	IV, single dose (OP)	Adult	100	31600	17400	17000	42800	2010	673	4240	1790
Rat [1031581]	IP; single dose (OC)	7	10	_	16600	_	22900	_	313	_	2110
Rat [1008172]	Oral; single dose (OP)	7 14 24 42	1000 1000 1000 1000	58700 66900 15200 8630	26200 142000 31000 45200	720000 651000** 156000 79700	371000 905000 431000 509000	4120 0 9490 1900 713	1850 1180 449 617	506000 225000** 23200 10400	29100 105000** 6160 8070

Rat [1027696]	Oral; single dose (OP)	7 7 7 7 7 7 7 42	 300 500 600 700 850 1000 1000	42400 58000 70200 83100 91000 *** 11500	9380 16100 22100 17800 17300 *** 38400	410000e 671000e 670000e 946000e 775000e *** 82700e	139000e 242000e 299000e 291000e 228000e *** 467000e	10700 16300 14100 18700 17600 *** 1280	530 883 874 819 820 *** 518	126000e 231000e 221000e 285000e 206000e *** 18200e	7670e 12300e 14100e 13700e 12400e *** 6650e
Rat [1032043]	SC; single dose (OC)	7	10	_	14200	_	23400	_	254	_	1690
Rat [1029873]	SC; single dose (OC)	7 7	25 50	– –	44800e 88900e	– –	68100e 152000e	– –	1240e 2500e	– –	6060e 14700e
Marmoset [1038614]	Oral and iv; single dose (OP)	4 4 4 adult adult adult	2 (oral) 10 (oral) 5 (iv) 2 (oral) 10 (oral) 5 (iv)	1090 5860 7830 88.8 647 4590	1170 17900 5150 303 1960 1000	1860 15400 7340 327 2090 3970	12400 126000 30600 1640 9390 4110	_ _ _ _ _ _	_ _ _ _ _ _	_ _ _ _ _ _	_ _ _ _ _ _

a, Cerebellum; b, Hippocampus; c, Olfactory bulb; d, Data for AUC0-8h; e, Data for AUC0-24h; *, not reported, **, approximate value / rough estimate, ***, values excluded; OC, oseltamivir carboxylate; OP, oseltamivir phosphate; NC, not calculated; NP, non perfused; P, perfused.

CES1 expression and hydrolysis of oseltamivir in liver samples were 4 and 10 times higher in adults than in children or in foetuses, respectively (Dongfang et al. 2008). Two CES1 mutations have been recently identified (Zhu et al. 2009). Inflammatory cytokines such as IL-6 have shown to reduce expression of CES1 in hepatocyte in *in vitro* studies (Yang et al. 2007). Related to this finding, patients with liver conditions such as cirrhosis have shown to have increased secretion of IL-6 and decreased hydrolytic capacity of CES. Recent publication suggests that prescribed drugs with significant carboxylesterase-mediated metabolism, such as oseltamivir, may interact with ethanol and thereby decrease the efficacy of oseltamivir against influenza viruses (Parker et al. 2010).

2.3.3. Toxicology and safety pharmacology

Since the last license renewal, a number of new toxicology and safety pharmacology investigations have been performed. These include studies performed after single oral, IV, SC and intracerebro-ventricular doses of oseltamivir and OC to adult and juvenile rats, safety pharmacology studies on cardiovascular parameters, CNS effects and body temperature as well as qualification of two impurities in genotoxicity and repeat-dose rodent toxicity studies (Table 1). A number of reports have been revised due to calculation errors detected in the reported plasma and brain concentrations. The

recalculation of data and the revision of the reports did not negatively impact the benefit/risk assessment. Reports affected included Studies 1007080, 1008172, 1028305 and 1003174.

Single-dose toxicity

Single-dose oral delivery studies have caused toxicity including mortality in juvenile rats with the doses higher than 500 mg/kg (Study 1008172). A dose of 500 mg/kg was well tolerated and no effects on functional observation battery were seen (Study 1027696), confirming previous findings. A subsequent SC study was performed to obtain more insight into the underlying reasons for the unscheduled deaths observed after oral doses higher than 500 mg/kg in juvenile rats (Study 1029873). Resulted higher maximum plasma and brain levels of OC seen after SC delivery of OC as compared to oral delivery of oseltamivir indicate that toxicity was related to the pro-drug levels and not to OC (Study 1029873, Freichel et al. 2011). Toxicity of the pro drug is likely to be associated with the slower conversion of oseltamivir phosphate to the carboxylate.

Safety pharmacology

- Cardiovascular

The available data from preclinical and clinical studies of oseltamivir was reviewed in a cardiovascular expert report by Dutkowksi et al. 2007. No evidence of cardiac effects was stated. Cardiac K channel (HERG channel) assays have shown no inhibition of potassium current (Studies 1003173, 1028305), no evidence of de- or repolarization abnormalities or effects on action potential duration have been identified from in vitro studies (Studies 1003174, W-0143050, 1028306) and no evidence of ECG/QTc abnormalities have been seen in *in vivo* studies (Studies 1003167, W-0142692, W-0143176, W-0142974).

- Central Nervous System (CNS)

An extensive package of pre-clinical safety pharmacology studies were conducted in adult and juvenile rats, due to reported human CNS adverse events. In summary, the non-clinical studies showed low CNS penetration of oseltamivir and OC. Data generated up until 2008 were published in a comprehensive report by Toovey et al. Data generated since this report was described by MAH and summarized below and additionally documented in a drug safety report on neuropsychiatric adverse events (DSR 1040400). The new data from 2008 onwards includes the publication by Hoffmann et al. in 2009 on the investigation on the penetration of oseltamivir prodrug and the active metabolite previously reported to the CHMP concludes that the potential for oseltamivir and OC to reach the central nervous system in high quantities is low and the involvement of oseltamivir and OC in neuropsychiatric events in influenza patients is unlikely. In adult rats doses up to 1314 mg/kg of oseltamivir showed no effect on CNS function (Study 1029346). In 7-day old rats general toxicity and behavioral effects occurred at doses of 657 mg/kg oseltamivir prodrug and above (Study 1027696, Freichel et al. 2009). Intra-cerebroventricular administration of up to 2 µg/ rat of oseltamivir or OC did not result in gross behavioral changes or clinical signs of overt toxicity (Study 1029803). In contrast, IV or oral administrations resulted in sufficient exposures of oseltamivir and OC in the brain but no test-item related gross behavioral changes or clinical signs (Study 1027859, Freichel et al. 2011). According to results oseltamivir, but not OC, appeared to underlie the toxicity in 7-day old juvenile rats (Study 1029873).

Comparing the maximum plasma exposure achieved in the study in juvenile rats (Study 1027696) at the No-Observed-Effect-Level to the currently available youngest age human data (<3months age, 3 mg/kg, Study WP20749) MAH have provided robust safety margins of 750 and 2500 for oseltamivir prodrug and 28 and 48 for OC based on Cmax and AUC exposure, respectively. A recent publication by

Lindemann et al. (2010) of the in vitro selectivity profile of oseltamivir prodrug and active metabolite was also previously communicated to the CHMP in 2007. In summary, both compounds lacked clinically relevant pharmacological activities on human, rodent and primate neuraminidases and on a panel of 155 other molecular targets, including those responsible for the regulation of mood, cognition and behaviour. Neuropsychiatric adverse events observed in influenza patients are therefore likely to be a phenomenon caused by the infection rather than by oseltamivir.

- Body temperature

Recent publications have suggested a hypothermic effect of oseltamivir in rodents (Ono et al. 2008), while, to date, observations in other preclinical and clinical studies of this drug have not shown such effects. The hypothermic effect noted in this study was attributed to OC. The studies conducted by MAH showed a slight transient dose independent decrease in body temperature 0.5 and 1 h post dosing in rats that received oseltamivir up to 1000 mg/kg orally (Study 1029346, 1029138). No abnormal clinical observations were noted. Short-lived small but statistically significant decrease in temperature was considered as a non-physiologically relevant effect on body temperature in rats at single supratherapeutic oral doses up to 1000 mg/kg (Freichel et al. 2011).

Other toxicity studies

Qualification of the formulation to be used for intravenous injections: A local tolerance study in rabbits with OP, intra-arterial and perivenous injections were well tolerated up to concentrations of 16 mg/mL or 8 mg/mL, respectively (Study 1025870). Perivenous administration of 16 mg/mL of OP was associated with erythema, discoloration, and an increased incidence and severity of haemorrhage at the injection site. The influence of the formulation on blood and plasma components was analysed in vitro with haemolysis and compatibility (turbidity and precipitation) tests (Study 1023809). Based on the results MAH concluded that the IV formulation RO0640796-F07, which is comparable to the clinical formulation, does not have any significant effect on red blood cell integrity and was tested negative for precipitation. Qualification of Impurities: The pre-clinical qualification for the degradation products RO5553071 and RO5909098 has been performed and the results have been summarized for recommendation of new specification limits in the drug product (Koerner A, 2011). Both degradation products when investigated in an AMES assay have been classified as non-mutagenic. No adverse effects were observed in a 2-week repeat-dose toxicity study in rats which included investigations on toxicokinetics, clinical signs, body weight, food consumption, haematology, clinical chemistry, organ weights, macroscopic findings, histopathology and a bone marrow micronucleus assay.

2.3.4. Non-clinical discussion

The pharmacokinetics studies cited by the MAH on the distribution of oseltamivir and its active metabolite into the CNS of adult and juvenile animals have shown low concentrations of prodrug and its active metabolite in the brain and in CNS as compared to plasma followed by IV and oral administration. The MAH cited *in vivo* mice study which shows that in the inflammation-induced condition the penetration of OP and OC into the brain was significantly increased (Oshima et al. 2009). The increased concentration and higher concentrations in the context of immature enzyme activities in juvenile animals are adequately covered by high safety margins of oseltamivir.

Reported hydrolytic activity on oseltamivir metabolism is dependent on species, tissue (lower in rat brain than in rat liver), age (less in juvenile rats than adult rats), individual (large variability especially in foetal and child groups) and other conditions such as inflammation. Moreover, the MAH cited the

study in which two newly identified CES1 mutations were postulated to impair activation of prodrug oseltamivir and thus lead to increase of adverse effects or toxicity associated with the elevated pro-drug concentrations (Zhu et al. 2009). The clinical relevance of these findings remains unclear.

None of the studies concerning absorption, distribution, metabolism, and drug-drug interactions compromised the high safety margins relating to oseltamivir and its active metabolite, and did not identify any mechanism that may lead into relevant reduction in the exposure to the active compound or do not contain data that would have an impact on the favourable benefit/risk ratio of oseltamivir.

The mechanism by which oseltamivir might induce side effects in the CNS was not discovered in these studies. The results point to a low exposure of oseltamivir in the brain, which is in consistency with the previous studies. Substantial changes made to the product information related to the non-clinical study results include the update of section 5.3 of the SmPC to amend the data related to brain penetration in juvenile rats (Variation II/62, Commission Decision issued on 26 January 2009), and the update of section 4.6 and 5.3 of the SmPC to include information concerning pregnancy and lactation (Variation II/0067, Commission decision issued on 09 September 2009).

In conclusion, new (or re-analysed previous) non-clinical pharmacological, pharmacokinetic, toxicity or safety pharmacology data do not change the overall benefit/risk assessment for Tamiflu in the currently approved clinical indications.

2.4. Clinical

The clinical overview provided by the MAH includes an updated benefit/risk evaluation which addresses data that have become available since the first renewal application for the Tamiflu marketing authorisation (December 2006). The updated benefit/risk evaluation is based on clinical trial experience, clinical experience compiled in Periodic Safety Update Reports (PSURs), and relevant published literature.

Since the last renewal, there have been several variations resulting in changes to the SmPC and Package Leaflet. This has been partly due to the emergence of the 2009–2010 A(H1N1)v pandemic. The target groups for oseltamivir treatment and prophylaxis was widened to include children below 12 months of age during a pandemic influenza and new extemporaneous formulations were introduced. Due to the massive use and stimulated reporting during the pandemic, reports of adverse events were increased accordingly. In spite of the difficulties in determining causality, the safety information of Tamiflu has expanded considerably.

2.4.1. Clinical Pharmacology

Since the last renewal, the MAH has conducted clinical pharmacology studies on the following aspects: Interactions of oseltamivir with rimantadin and amantadine, warfarin, and drug interactions involving competition for hepatic carboxyl esterases; Renal secretion of oseltamivir; Distribution of oseltamivir; Pharmacokinetics in special populations; Pharmacokinetics in adults with reduced renal clearance; Pharmacokinetics in adults receiving dialysis; Pharmacokinetics following intravenous administration; Effects of oseltamivir on sleep.

An overview of the results of the pharmacology studies is provided below.

Interactions of oseltamivir with other drugs

Amantadine and Rimantadine

Interaction with amantadine and with rimantadine was studied in healthy subjects. Co-administration with oseltamivir had no clinically significant effect on the pharmacokinetics (PK) of either drug, and vice versa.

Warfarin

Administration of oseltamivir in volunteers stabilized on warfarin therapy had no marked effect on the PK parameters of warfarin enantiomers, and vice versa. Oseltamivir did not enhance the effects of warfarin.

Drug interactions involving competition for hepatic carboxyl esterases

Drug interactions due to competition for carboxyl esterases were investigated between oseltamivir and acetylic salicylic acid. The major PK parameters of oseltamivir, oseltamivir carboxylate (OC), salicylic acid, and salicyluric acid were bioequivalent in the absence and presence of concomitant administration.

OC is not metabolized and is excreted in urine without further change. Levels of OC were comparable in patients with moderate hepatic impairment compared with healthy volunteers. Therefore, no dose adjustments are necessary in this patient group.

Clopidogrel

In 2006, Shi et al concluded that clopidogrel inhibits the hydrolysis of oseltamivir thus rendering oseltamivir therapeutically inactive. The MAH reviewed the publication and stated that the clinical conclusions were made based on in vitro data without discussing the limitations of the study or clinical relevance of the results. The MAH analyzed the data using FDA-recommended methods, and judged the risk of interaction between clopidogrel and oseltamivir at clinically achievable concentrations to be remote.

Probenecid

In the original marketing authorisation application, the MAH reported that co-administration of oseltamivir with probenecid increased the plasma OC concentrations 2.5-fold. Due to the emergence of H5N1 avian influenza in 2005, the MAH was requested to provide a benefit-risk assessment on the potential of concomitant use of these agents to reduce dosage and thus extend supplies of oseltamivir. The MAH explored this strategy by using a population PK model to simulate the PK of potential dosing options. In this population PK analysis, it was shown that probenecid decreases the clearance of OC (~42% of that observed with oseltamivir alone). However, it also decreases its central volume of distribution (~63% of that observed with oseltamivir alone). According to the MAH, given the complexity of the interaction, the efficacy and resistance profile of such a combined regimen may be compromised.

Distribution of oseltamivir

The MAH has investigated the pharmacokinetics of oseltamivir and OC in the plasma and cerebrospinal fluid (CSF). The concentrations were low in CSF compared with plasma for both oseltamivir and OC. Overall exposure to oseltamivir and OC (mean AUC CSF/plasma ratio) was 2.4 % for oseltamivir and 2.9 % for OC.

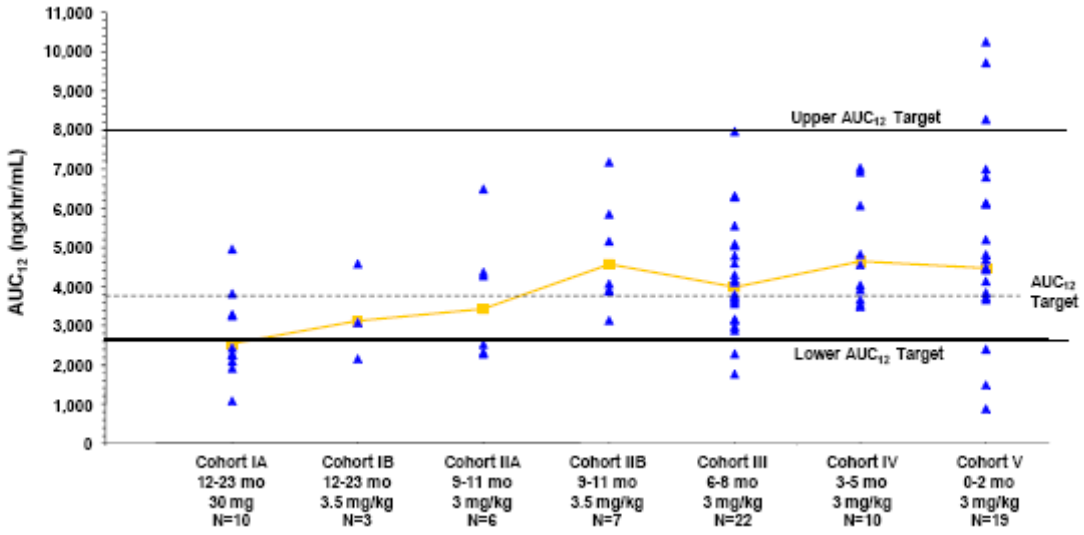
Pharmacokinetics in special populations

Since the last renewal, the MAH has performed PK investigations in infants aged 0 to 2 years, adults with reduced renal clearance, and adults receiving dialysis.

Infants aged 0 to 2 years

The study CASG114 was a prospective, age-stratified PK, pharmacodynamic and safety evaluation of oseltamivir therapy conducted by the NIH in infants less than 2 years of age with confirmed influenza infection. A dose of 3.0 mg/kg produced drug exposure within the target range in infants 0–8 months of age with greater variation in AUC in subjects below 2 months of age. In the age group 9–11 months 3.0 mg/kg was not adequate to reproducibly produce exposure above the minimum value. Therefore, the protocol was amended and more patients were recruited and given 3.5mg/kg twice daily, which more closely met the target. In patients aged 12–23 months, 30mg twice daily did not provide adequate exposure, therefore, the dosage was changed to weight-based dose of 3.5mg/kg. The three subjects receiving this dosage achieved adequate exposures.

Figure 1 Oseltamivir carboxylate AUC12 by age cohort with target and range



Another open-label, prospective PK/PD and safety study of oral oseltamivir in infants up to 12 months with confirmed influenza infection is ongoing (WP22849). The patients received extemporaneously prepared oseltamivir suspension (10mg/ml) at doses of 3mg/kg (subjects aged 91 to <365 days), 2.5mg/kg (subjects aged 31 to 90 days) and 2 mg/kg (subjects aged 0 to 30 days).

Pharmacokinetics in adults with reduced renal clearance

The re-evaluation of dosing in patients with renal impairment was driven by the availability of 30mg and 45 mg capsules. A population PK model describing the impact of CrCL on oseltamivir and oseltamivir carboxylate PK was developed and qualified for simulation using eighty subjects with varying degrees of renal function identified from three clinical studies. The recommended dosage based on the simulations are as follows:

- severe renal impairment (CrCL 10–30 mL/min): 30mg once daily (treatment) and 30mg every other day (prophylaxis)

- moderate renal impairment (CrCL 30–60 mL/min): 30mg twice daily (treatment) and 30mg once daily (prophylaxis)

- mild renal impairment (CrCL> 60 mL/min): no dose modification.

Further data to validate the PK model has been submitted by the MAH and the assessment is ongoing. Additional PK data from renal impaired patients have been identified for this purpose from either existing studies or collected during the conduct of a planned clinical pharmacology study in patients on ambulatory peritoneal dialysis.

Pharmacokinetics in adults receiving dialysis

In order to define the PK of oseltamivir in renally impaired patients, two studies, a single dose study and a repeat dose study, have been performed in patients undergoing either haemodialysis (HD), or continuous ambulatory peritoneal dialysis (CAPD). Plasma concentrations declined more rapidly in HD patients than in CAPD patients, with about 70% of OC eliminated during the 5 hours of haemodialysis and about 30% cleared by CAPD. Further evaluation by PK modelling and simulation was used to include recommendations for dosing regimens for treatment and prophylaxis as reflected in the current SmPC.

Pharmacokinetics following intravenous administration

Intravenous (IV) formulations of oseltamivir phosphate and OC have been investigated in three clinical studies in healthy volunteers. Oseltamivir administered by 2 hour IV infusion at a dose of 100 mg or 200 mg, provides similar single dose and multiple dose OC profiles to those obtained following oral administration of the 75 mg and 150 mg oral dose, respectively.

There are three ongoing studies investigating the PK/PD and safety of IV oseltamivir in influenza patients, one in adolescent/adult patients and two in younger paediatric patients. The paediatric studies are according to the Renewal application anticipated to continue to recruit over multiple influenza seasons due to challenging recruitment.

Effects of oseltamivir on sleep

In response to reports of sleepwalking-like events reported in patients with influenza receiving oseltamivir, particularly in Japan, a randomized cross-over study in 31 healthy Japanese male volunteers was conducted to investigate the potential effects of oseltamivir on sleep. Repeated administration of oseltamivir 75 mg was well tolerated and did not produce any clinically significant effects on sleep parameters determined by nocturnal polysomnography testing.

Discussion on clinical pharmacology

The MAH provided an overview of the pharmacokinetics data available in infants below 2 years of age. In the study CASG114, the dose of 3.0 mg/kg twice daily provided lower OC exposures than targeted for subjects 9–11 months of age, and dosage was subsequently increased to 3.5 mg/kg.

In the current SmPC there is a choice of dose recommendations for this age group, some based on age and some on weight. The growth velocity varies significantly among infants and small children. Therefore, dosing according to weight may be more appropriate for this population. The current recommended dose for children aged > 3 months to 12 months is 3 mg/kg twice daily for 5 days for treatment of influenza and 3 mg/kg once daily for 10 days for prophylaxis. For infants 1–12 months of age, section 6.6 of the SmPC also includes a dosing chart for oral suspension prepared extemporaneously (10 mg/ml). The doses are expressed in volumes, but correspond to 3 mg/kg twice daily (treatment) or once daily (prophylaxis).

For children one year of age or older weighing 10–15 kg, the recommended dose for oral suspension prepared extemporaneously (15 mg/ml) is 2 ml (30mg) twice daily (treatment) or once daily (prophylaxis), corresponding to a 2–3 mg/kg/dose. In CASG114, this age group received either 30mg

(Cohort IA) or 3.5 mg/kg (Cohort IB). Therefore, the doses recommended in the SmPC for infants and small children seem to be below those demonstrated adequate in CASG114. Adequacy of dose is important not only for efficacy but also for preventing oseltamivir resistance. Development of resistance seems to be related to prolonged virus shedding facilitating selection of resistance. As resistance to oseltamivir is more frequent in children and immunocompromised patients, sufficient dosage is of utmost importance in these patients. Therefore, studies CASG114 and WP22849 need to be finalized and analyzed according to accepted plans to gain sufficient data for defining posology for infants and small children.

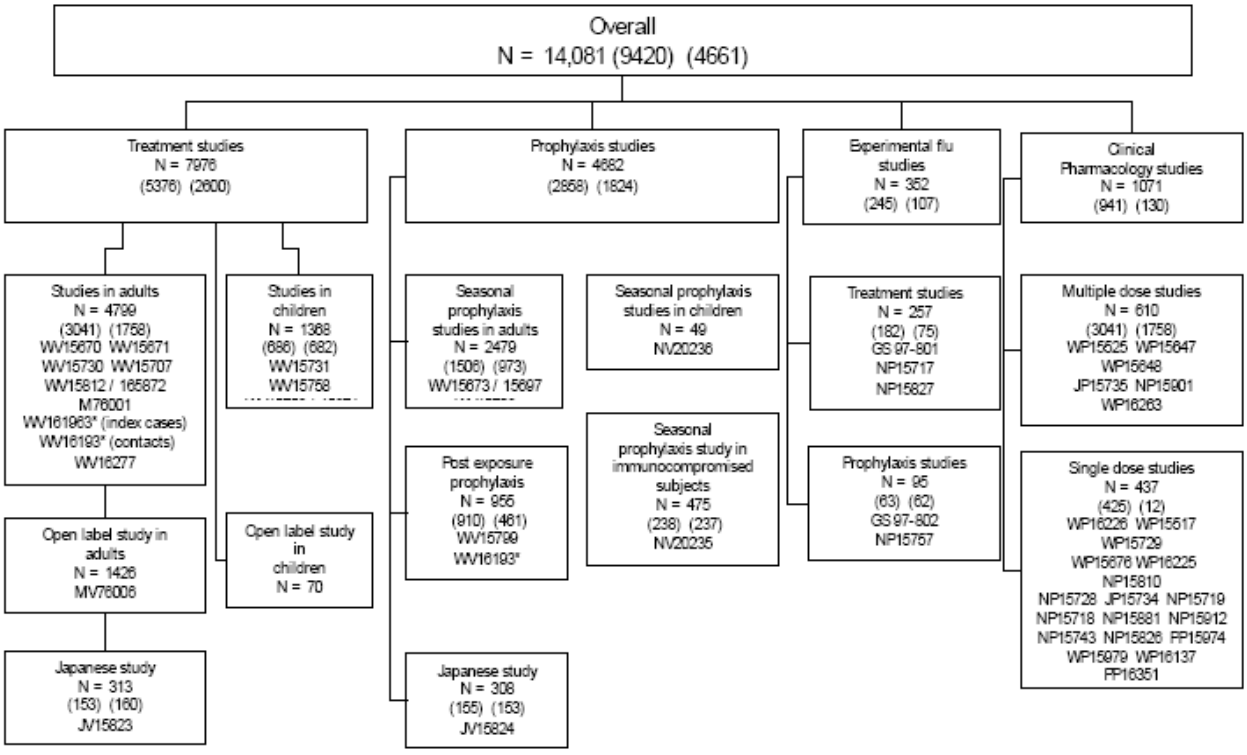
The recommended doses for adults with different degrees of renal impairment and for dialysis patients in the current SmPC are in line with the study results. The CHMP recommends that the MAH further validates the PK model by adding further patients (with CrCL 10-30 ml/min) to the dataset and includes detailed data and discussion in the final PK model report.

The reports of sleepwalking-like events have been rare. Therefore, a small study of 31 volunteers cannot rule out a potential connection between the symptoms and oseltamivir. The MAH will continue to follow closely reports of neuropsychiatric adverse events.

2.4.2. Clinical efficacy

An overview of the clinical studies performed by the MAH at the time of the renewal is presented in Figure 2. The clinical program for Tamiflu has included studies in the treatment and prevention of influenza, experimental flu studies and clinical pharmacology studies, comprising a total of 14,018 subjects.

Figure 2 Overview of clinical program at the time of renewal



Efficacy in Special Populations

Since the last renewal the MAH has investigated the efficacy and safety of oseltamivir in the immunocompromised population (studies NV20235, NV20234) and in children aged 1 to 12 years old (study NV20236). The PK/PD and safety of oseltamivir intravenous is also under investigation in three ongoing MAH sponsored studies.

Immunocompromised Patients

Study NV20235 was a prospective, randomized, double-blind, multi-centre trial of oseltamivir versus placebo for seasonal prophylaxis of influenza in 477 immunocompromised transplant patients ≥ 1 year of age. Subjects received either oseltamivir or placebo once daily for 12 weeks.

In the intent-to-treat (ITT) population, a total of 37 subjects in the placebo group (15.5%) and 31 subjects in the oseltamivir group (13.1%) had laboratory-confirmed influenza (by RT-PCR, viral culture or serology). With the exception of two subjects (one per group) who had RT-PCR confirmed influenza 'off treatment', all other laboratory-confirmed cases were considered 'on treatment'.

Overall, a higher percentage of placebo recipients were RT-PCR positive (8.4%) or viral culture positive (3.8%) compared with oseltamivir recipients (1.7% and < 1.0%, respectively). In contrast, the proportion of subjects who were positive by serology was lower in the placebo group (8.4%) than in the oseltamivir group (12.2%). A large portion of patients met the definition of having laboratory confirmed influenza based upon a serological response only. However, immunosuppression may have confounded laboratory confirmation of influenza based upon positive serology. For example, delayed immune response to vaccination may give rise to false positives. Thus, there appeared to be a low predictive value of influenza serology in immunosuppressed patients compared with RT-PCR and culture.

Study NV20234 is a prospective, randomized, double-blind multi-centre trial comparing 10 days b.i.d. conventional and high-dose oseltamivir for the treatment of influenza in immunocompromised patients ≥ 1 year of age. Following the 2009 pandemic, the study was amended to additionally address the risk for development of resistance. Between 2007 and 2011, 23 patients have been recruited, and the study is ongoing.

Children aged 1 to 12 Years

Study NV20236 was an open-label seasonal prevention study, with a 6 week therapy period, conducted in otherwise healthy children aged 1 to 12 years. Forty-five subjects were exposed to oseltamivir. During the study there were no cases of laboratory-confirmed clinical influenza. In total, 6 subjects had laboratory confirmed influenza, 4 of which were asymptomatic and 2 experienced limited influenza symptoms that did not meet the criteria for clinical influenza.

Intravenous Formulation

Oseltamivir IV formulation is available in compassionate use programs in the USA (3 patients) and in the EU (116 critically ill patients with a life-threatening condition due to suspected or confirmed pandemic or seasonal flu). In addition, the PK/PD and safety of IV oseltamivir is under investigation in three ongoing MAH sponsored studies:

- Study NP25138: open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of intravenous oseltamivir in the treatment of infants less than one year of age with influenza infection

- Study NP25139: open label, prospective, pharmacokinetic/pharmacodynamic and safety evaluation of intravenous oseltamivir in the treatment of children 1 to 12 years of age with influenza infection

- Study NV25118: Multicenter, study of the Safety of Oseltamivir Administered Intravenously for the Treatment of Influenza in patients Aged > 13 years

No efficacy data is yet available from these studies.

Literature information

In a recently published Cochrane review, some concerns were raised regarding the appropriate analysis in the clinical trials with Tamiflu (ITT vs. ITT infected population) as well as potential effect of Tamiflu on antibody production. The MAH provided a summary table of key outcomes of ITTI in adults (Table 4). The efficacy of oseltamivir was primarily assessed in the population of influenza-infected persons (the ITTI or Intent to Treat Influenza-infected population). Because oseltamivir has activity against both influenza A and B viruses, individuals infected with either virus type were included in the ITTI population. With respect to the median time to alleviation of all symptoms this data shows that clinically and statistically significant differences between oseltamivir and placebo have been found in the clinical studies (apart from the elderly and chronic cardiac/respiratory disease studies, in line with the current SmPC wording section 5.1).

When the ITT population is analysed separately for the median time to alleviation of all symptoms, a much smaller difference was observed, but still significantly in favour of the oseltamivir group, (apart from the elderly and chronic cardiac/respiratory disease studies).

Table 4 Summary of key outcomes of individual studies in the treatment of influenza in adults

Study (Protocol Number) Treatment group	ITT Infected Median Time to alleviation of all symptoms (h) [95% CI]	ITT Median Time to alleviation of all symptoms (h) [95% CI]	
US phase III study (WV15671)			
placebo (N = 129)	103.3 [92.6 - 118.7]	placebo (N = 209)	97.0 [86.3 – 113.6]
oseltamivir 75 mg b.i.d. (N = 124)	71.5 [60.0 - 83.2]	oseltamivir 75 mg b.i.d. (N = 210)	76.3 [66.3 – 89.2]
difference between medians	31.8 [16.5 – 50.7]	difference between medians	20.7 [ND]
p-value	p<0.0001	p-value	p=0.0040
Non-US phase III study (WV15670)			
placebo (N = 161)	116.5 [101.5 - 137.8]	placebo (N = 235)	116.1 [99.8 – 129.5]
oseltamivir 75 mg b.i.d. (N = 158)	87.4 (73.3 - 104.7)	oseltamivir 75 mg b.i.d. (N = 241)	97.6 [79.1 – 115.3]
difference between medians	29.1 [4.9 – 55.5]	difference between medians	18.5 [ND]
p-value	p =0.0168	p-value	p=0.0506
US phase IIIb study (M76001)			
placebo (N = 361)	120.5 [109.0 - 127.6]	placebo (N = 482)	114.7 [105.5 – 126.4]
oseltamivir 75 mg b.i.d. (N = 702)	96.3 [88.3 to 102.9]	oseltamivir 75 mg b.i.d. (N = 965)	97.7 [90.2 – 103.9]
difference between medians	24.2 [9.1 – 35.3]	difference between medians	17.0 [ND]
p-value	p<0.0001	p-value	p=0.0006
Patients with onset of symptoms ≤24 h pior to initiation of treatment:			
placebo (N = 170)	124.2 [106.0 – 138.1]		
oseltamivir 75 mg b.i.d. (N = 349)	94.4 [81.3 – 105.8]		
difference between medians	29.8 [8.0 – 46.4]		
p-value	p =0.0031		
Study in Subjects with Chronic Respiratory or Cardiac Conditions (WV15812 + WV15872)			
placebo (N = 133)	161.0 [117.3 – 215.5]	placebo (N =203)	163.0 [133.2 – 197.0]
oseltamivir 75 mg b.i.d. (N = 118)	151.5 [114.1 – 201.0]	oseltamivir 75 mg b.i.d. (N = 199)	143.0 [118.0 – 170.6]
difference between medians	9.5 [-54.8 – 81.9]	difference between medians	20.0 [ND]
p-value	p =0.7672	p-value	p=0.3314
Acute Febrile Illness (time to alleviation of fever, aches and pains and chills – i.e. omitting symptoms of underlying illness)			
placebo (N = 133)	57.9 [47.8 – 64.8]		
oseltamivir 75 mg b.i.d. (N = 118)	40.8 [30.8 – 47.3]		
difference between medians	17.4 [5.0 – 29.8]		
p-value	p =0.0005		

Study in Elderly Subjects (≥ 65 years) (WV15819 + WV15876 + WV15978)			
placebo (N = 254)	174.9 [137.0 – 207.0]	placebo (N = 376)	149.0 [126.5 – 178.5]
oseltamivir 75 mg b.i.d. (N = 223)	150 [123.0 – 171.5]	oseltamivir 75 mg b.i.d. (N = 360)	139.2 [116.3 – 164.0]
difference between medians	24.9 [-19.0 – 66.9]	difference between medians	9.8 [-24.0 – 47.1]
p-value	p =0.434	p-value	p=0.8011
Acute Febrile Illness (time to alleviation of fever, aches and pains and chills)			
placebo (N = 254)	50.5 [45.5 –54.3]		
oseltamivir 75 mg b.i.d. (N = 223)	36.0 [29.3 – 41.3]		
difference between medians	14.5 [6.2 – 22.7]		
p-value	p =0.0049		
Standard Analysis Population			
placebo (N = 232)	180.2 [149.1 – 213.2]		
oseltamivir 75 mg b.i.d. (N = 213)	144.5 [121.0 – 169.9]		
difference between medians	35.7 [-4.2 – 81.5]		
p-value	p =0.1244		

The MAH also provided data on HA antibody titres for the ITT-infected population pooled for the studies. The proportion of subjects with protective baseline levels of antibody (titre ≥ 1:40) to the infecting virus wild type was similar in each treatment group (37% in the placebo group and 43% in the 75 mg oseltamivir group) (Table 5). The increase from baseline levels in type-specific influenza virus antibody titres is summarized in Table 6. The geometric mean-fold increase is reduced in the 75mg oseltamivir group relative to the placebo group in this pool of studies, this difference being statistically significant at the 5% level. This provides corroborative evidence of the anti-viral effect of oseltamivir.

This decreased magnitude of antibody response does not, however, imply that oseltamivir recipients will be at greater susceptibility of infection in future seasons. The proportion of subjects with protective antibody titres (≥ 1:40 post-baseline) was identical (94%) in each group (Table 7) indicating that oseltamivir recipients are equally protected against future infection.

Table 5 Summary of type-specific viral antibody titers at baseline (ITTI population – pool of studies)

Protocols included: M76001, WV15670, WV15671, WV15707, WV15730, WV15812, WV15819, WV15872, : WV15876, WV15978

VIRAL ANTIBODY TITERS	Placebo N=1063	Ro 64-0796 75mg bid N=1350
Baseline		
Not detectable (<1:10)	298 (30%)	293 (24%)
Detectable but not protective (>=1:10 and <1:40)	320 (32%)	405 (33%)
Protective (>=1:40)	369 (37%)	527 (43%)
All	987 (100%)	1225 (100%)

Table 6 Summary of change from baseline in viral antibody titers (ITTI population – pool of studies)

Protocols included: M76001, WV15670, WV15671, WV15707, WV15730, WV15812, WV15819, WV15872, : WV15876, WV15978

CHANGE FROM BASELINE FOR VIRAL ANTIBODY TITERS (a)	Placebo N=1063	Ro 64-0796 75mg bid N=1350
<4-fold increase	122 (12%)	230 (19%)
4 to <8-fold increase	130 (13%)	186 (15%)
8 to <16-fold increase	162 (16%)	211 (17%)
16 to <32-fold increase	155 (16%)	215 (18%)
32 to <64-fold increase	180 (18%)	174 (14%)
64 to <128-fold increase	123 (13%)	107 (9%)
128 to <256-fold increase	69 (7%)	57 (5%)
256-fold or more increase	42 (4%)	43 (4%)
All	983 (100%)	1223 (100%)
Geometric mean fold change	16.0	11.3

	Median Difference (b)	p-value (c)	95% C.I. for difference (b)
Placebo minus 75mg bid	1.5	0.0474	1.0 to 2.0

(a) Maximum titer used for each subject.
Subjects included only if both baseline and post-baseline values were available.
(b) Using pairwise difference method (unstratified) on log-scale then back-transformed.
(c) Using an extended Wilcoxon Rank Sum test stratified for Region

Table 7 Summary of post-baseline viral antibody titers (ITTI population – pool of studies)

Protocols included: M76001, WV15670, WV15671, WV15707, WV15730, WV15812, WV15819, WV15872,
: WV15876, WV15978

VIRAL ANTIBODY TITERS	Placebo N=1063		Ro 64-0796 75mg bid N=1350	
Baseline				
Not detectable (<1:10)	298	(30%)	293	(24%)
Detectable but not protective (>=1:10 and <1:40)	320	(32%)	405	(33%)
Protective (>=1:40)	369	(37%)	527	(43%)
All	987	(100%)	1225	(100%)
Post-baseline (a)				
<1:10	7	(1%)	8	(1%)
1:10	20	(2%)	32	(3%)
1:20	20	(2%)	27	(2%)
1:30	5	(1%)	5	(0%)
1:40	50	(5%)	68	(6%)
1:60	8	(1%)	9	(1%)
1:80	92	(9%)	137	(11%)
1:120	11	(1%)	16	(1%)
1:160	145	(15%)	201	(16%)
1:240	13	(1%)	12	(1%)
1:320	199	(20%)	248	(20%)
1:480	9	(1%)	5	(0%)
1:640	178	(18%)	220	(18%)
1:960	3	(0%)	4	(0%)
1:1280	148	(15%)	156	(13%)
1:1920	1	(0%)	2	(0%)
1:2560	44	(4%)	54	(4%)
1:5120	22	(2%)	19	(2%)
1:10240	10	(1%)	8	(1%)
>=1:20480	3	(0%)		
All	988	(100%)	1231	(100%)

(a) Maximum titer used for each subject.

Discussion and Conclusion on clinical efficacy

Oseltamivir prophylaxis has been very effective in the normal population. On the basis of study NV20235, the achieved benefit in the prophylaxis of influenza with oseltamivir in immunocompromised subjects is disappointingly low at least with the current dosage. Study NV20234 may shed light on the best dosage of oseltamivir in the treatment of influenza in immunocompromised patients, as well as yield information on the development of resistance in this patient group. The finding that RT-PCR or viral culture are more reliable methods for diagnosis than serology in immunocompromised patients is clinically important.

Study NV20236 supports the fact that oseltamivir is efficacious in prevention of influenza in children during an epidemic. This naturally depends on the susceptibility of the circulating viral strain to oseltamivir, as already underscored in the SmPC.

In the submission, no data was provided for study ML16369 conducted in China by Roche Shanghai. The CHMP recommends that the MAH provides the study report for study ML16369 including relevant annexes as well as an expert summary/statement.

Regarding the ITT versus ITTI analysis, the findings in the ITT population are reassuring and in line with the results from the ITTI population. Similar results were obtained in the Cochrane analysis, where oseltamivir treatment shortened the median time to first symptom alleviation by around 21

hours compared to placebo. In general, the ITT analysis is not a good measure of the efficacy of an influenza antiviral agent since the ITT analysis reflects the nature of the epidemics studied and cannot be generalised for future epidemics. ITTI represents the best case scenario that can be pursued during an epidemic with high number of influenza vs. other influenza-like illnesses. In addition, it is reassuring that the proportion of subjects with protective antibody titres was identical and high (94%) in both oseltamivir and placebo groups, even though the increase in antibodies was lower in subjects having received oseltamivir compared with placebo. The analyses indicate that Tamiflu is not impairing the occurrence of immune response. It is expected that the antibody response is lower with oseltamivir treatment due to treatment effect. The MAH is recommended to provide pooled analyses on serological response separately for treatment studies in adults, treatment studies in children, and prevention studies and separate analyses for each study for the ITT and ITTI populations.

No data are available so far to verify a change to the dose of oseltamivir in immunocompromised patients. The ongoing study NV20234 may provide relevant information in this regard. Resistance is a very important aspect which is continuously monitored within the IRIS study (NV20237). At this stage, no changes to the SmPC are feasible based on the current knowledge.

2.4.3. Clinical safety

As part of the renewal application the MAH has submitted:

- one addendum PSUR report covering the period from 21 September 2010 to 15 August 2011

- one summary bridging report (SBR) covering the period from 01 April 2006 to 15 August 2011

- a clinical overview for product license renewal

In the period under review the following PSURs were submitted and assessed by the CHMP:

PSUR number	Estimated No. of Patients Exposed	PSUR Reporting Period
PSUR 6	2,054,600	01 April 2006 to 30 September 2006
PSUR 7	7,322,289	01 October 2006 to 20 September 2007
PSUR 8	6,363,656	21 September 2007 to 20 September 2008
PSUR 9	10,399,635	21 September 2008 to 20 September 2009
PSUR 10	14,689,982	21 September 2009 to 20 September 2010
PSUR addendum	6,957,000	21 September 2010 to 15 August 2011

Patient exposure

The estimated cumulative exposure to oseltamivir since 01 April 2006 via commercially obtained drug and through clinical trials until 30 June 2011 (cut off date of available patient exposure data) is 42,062,464 patients. For calculation purposes it was assumed that one bottle represents one patient, although in children dosage is based on weight, therefore less or more than one bottle/patient may have been used.

2.4.3.1. Cumulative experience from 01 April 2006 to 15 August 2011

Update of regulatory authority or marketing authorisation holder actions taken for safety reasons

During the review period of the SBR several type II variations to include safety information in the EU SmPC were approved (see section 1.2). Among the approved changes, several new adverse drug reactions were included in the product information: neuropsychiatric events, fatal fulminant hepatitis/hepatic failure, gastrointestinal bleeding, visual disturbance, cardiac arrhythmia, and thrombocytopenia. Information concerning viral resistance to oseltamivir was also reflected in section 5.1 of the SmPC.

Three Dear Healthcare Professional letters (DHPL) on the potential of developing abnormal behaviour after taking oseltamivir were sent to Japanese healthcare providers between 2006 and 2007. A DHPL regarding the occurrence of neuropsychiatric events was also issued in the USA in February 2008.

Adverse drug reactions

Overview of adverse drug reactions

During the period 1 April 2006 to 15 August 2011, a total of 8138 medically-confirmed cases (comprising 12 795 AEs) were received for oseltamivir of which 2 532 cases were serious (comprising 4188 Aes).

Table 8 presents all serious and non serious reports including spontaneous case reports containing non-serious listed events only.

Table 8 Summary tabulation of case reports during the review period of the SBR

PSUR number	PSUR Reporting Period	Estimated No. of Patients Exposed	No. of Case Reports (Serious Case Reports)	No. of Adverse Events (Serious Adverse Events)	No. of Case Reports with Fatal Outcome
6	01 April 2006 to 30 September 2006	2,054,600	242 (48)	336 (66)	6
7	01 October 2006 to 20 September 2007	7,322,289	2,210 (461)	3,090 (684)	38
8	21 September 2007 to 20 September 2008	6,363,656	718 (228)	1155 (376)	23*
9	21 September 2008 to 20 September 2009	10,399,635	1561 (475)	2616 (847)	64**
10	21 September 2009 to 20 September 2010	14,689,982	2472 (923)	4049 (1,524)	262
Addendum	21 September 2010 to 15 August 2011	6,957,000	935 (397)	1549 (691)	54
TOTAL		**47,787,162**	**8138 (2,532)**	**12,795 (4,188)**	**447**

Adverse reactions in special age group

The number of case reports in special age groups during the reporting period of this SBR is presented below:

- Neonate (birth to <1 month) or infant (≥1 month to <2 years) : 205 case reports
- Child (≥2 to <12 years) or Adolescent (≥12 to <16 years for the PSURs 6 and 7 and ≥12 to <18 years for the PSURs 8, 9 and 10 and addendum PSUR). : 2588 case reports
- Elderly (≥65 years): 544 case reports

Summary of adverse events by System Organ Class

A summary of the AE data by system organ class (excluding spontaneous case reports containing non-serious listed events only) received during the reporting period of this SBR is presented in Table 9.

Table 9 Summary of Adverse Events by SOCs for all Submitted PSURs (01 April 2006 to 15 August 2011)

System Organ Class	No. Patients with at least 1 AE/SOC	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
Infections and Infestations	449	427	10.4	536	6.4
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	6	6	0.1	6	0.1
Blood and Lymphatic System Disorders	100	93	2.3	116	1.4
Immune System Disorders	64	57	1.4	64	0.8
Endocrine Disorders	7	5	0.1	7	0.1
Metabolism and Nutrition Disorders	66	30	0.7	68	0.8
Psychiatric Disorders	1074	963	23.4	1558	18.7
Nervous System Disorders	851	495	12.0	1060	12.7
Eye Disorders	213	39	0.9	239	2.9
Ear and Labyrinth Disorders	49	12	0.3	56	0.7
Cardiac Disorders	166	120	2.9	184	
Vascular Disorders	73	48	1.2	74	0.9
Respiratory, Thoracic and Mediastinal Disorders	273	213	5.2	319	3.8
Gastrointestinal Disorders	639	374	9.1	914	11.0
Hepatobiliary Disorders	175	155	3.8	186	2.2
Skin and Subcutaneous Tissue Disorders	449	252	6.1	564	6.8
Musculoskeletal and Connective Tissue Disorders	159	55	1.3	190	2.3
Renal and Urinary Disorders	133	79	1.9	139	1.7
Pregnancy, Puerperium and Perinatal Conditions	4	3	0.1	4	0.0
Reproductive System and Breast Disorders	95	8	0.2	96	1.2
Congenital, Familial and Genetic Disorders	4	3	0.1	4	0.0
General Disorders and Administration Site Conditions	1162	463	11.2	1308	15.7
Investigations	223	167	4.1	283	3.4
Injury, Poisoning and Procedural Complications	317	46	1.1	335	4.0
Surgical and Medical Procedures	3	3	0.1	3	0.0
Social Circumstances	4	0	0	4	0.0
Total	**N/A**	**4116**	**100.0**	**8317**	**100.0**

Fatal cases

There were 447 case reports with a fatal outcome. Overall, according to the MAH, the fatal cases presented in the individual PSURs were either considered unrelated to the use of oseltamivir, had insufficient information, had information on the fatal events consistent with the known safety profile of oseltamivir or alternative explanations did not permit a causal relationship to be established between the fatal events and oseltamivir.

Adverse events of special interest

Based on the review of the events reported in the Addendum PSUR, covering the period 21 September 2010 to 15 August 2011, the MAH will continue to monitor for future cases of dehydration, hypoglycaemia, sudden death, cardiac arrest, cardio-respiratory arrest, encephalopathy, encephalitis, cerebral infarction, somnolence, paraesthesia, bone marrow failure, pancytopenia, aplastic anaemia, leukopenia, disseminated intravascular coagulation (DIC), thrombocytopenia, platelet count decreased, white blood cell count deceased, decreased appetite, shock, hypotension, respiratory failure, respiratory arrest, blood creatine phosphokinase increased, rhabdomyolysis, AEs in Renal Disorders SOC, hypothermia, International Normalised Ratio (INR) increased and neuropsychiatric AEs.
In addition, the MAH monitored the following events for oseltamivir during the review period of this SBR: anaemia, agranulocytosis, sudden death related to encephalitis/encephalopathy, eye pain, cardiac failure, myocardial infarction, hepatic failure, pregnancy, and potential interaction of oseltamivir with warfarin and clopidogrel.

Drug Interactions

During the reporting period of this SBR, 20 case reports of potential drug interaction, concerning oseltamivir, were received, and are summarised in Table 10.

Table 10 Summary of Interaction case reports

PSUR period	Interaction
01 April 2006 to 30 September 2006	2 (azithromycin; warfarin sodium)
01 October 2006 to 20 September 2007	1 (valproate sodium)
21 September 2007 to 20 September 2008	1 (fluindione/pentoxifylline)
21 September 2008 to 20 September 2009	9 (trimethoprim; naproxen, hydrocodone; aspirin dL-lysine; metformin, atenolol, atorvastatin, valsartan, desloratadine; warfarin sodium; nelfinavir, emtricitabine/tenofovir, azithromycin; methotrexate; antivitamin K, fluindione/pentoxifylline; moxifloxacin)*
21 September 2009 to 20 September 2010	5 (interferon beta-1A; naratriptan; an unspecified oral contraceptive; valproate sodium; propofol;)
21 September 2010 to 15 August 2011	2 escitalopram; clarithromycin, amiodarone)
Total	20

None of the reports of potential drug interaction with the other agents received during the review period covered by this SBR indicated any significant or consistent safety risks which could represent a hazard to the population receiving oseltamivir.

Overdose

During the reporting period of this SBR, 207 case reports of potential overdose, concerning oseltamivir, were received. According to the MAH, no relevant new information concerning overdose with oseltamivir was received during the SBR period. During the Addendum period, 23 cases concerned overdose comprising 42 ADRs. The majority of the events were No AE (17), overdose (14), accidental overdose (5), and incorrect dose administered (4). Eight cases concerned children. On 23 September 2009, Roche distributed a Dear Healthcare Provider Letter (DHPL) in the USA to remind of importance of following the dosing instructions for oseltamivir oral suspension. During the PSUR period covering from September 2009 to September 2010, the greatest number of overdose cases concerned patients of age group 1–12 years (43 case reports) followed by >18 years (31 case reports), 13-18 years (seven case reports), ≥6 – <12 months (six case reports) and 0 –<3 months (one case report). Also during the PSUR period covering from September 2008 to September 2009, 19 reports were reported in children and adolescents.

Abuse, Misuse, Dependence and Withdrawal

During the reporting period of this SBR, one case report of potential abuse, misuse, dependence or withdrawal, concerning oseltamivir, was received. According to the MAH, there is no relevant new information concerning abuse, misuse, dependence or withdrawal with oseltamivir.

Use in Pregnancy or Lactation

Maternal Exposure to oseltamivir

The cumulative (up to 15 August 2011; data lock point for the latest addendum PSUR included in this SBR) pregnancy experience with oseltamivir (maternal exposure) comprised a total of 2,478 medically confirmed pregnancy cases (4,954 events). The most frequently reported event (MedDRA PT) was 'normal newborn' (1375 events), 'followed by 'No adverse event' (717 events), 'pregnancy' (418 events) and 'caesarean section' (235 events). The notable AEs (MedDRA PT) were drug exposure during pregnancy (1568 AEs), followed 'premature labour' (39 AEs), 'abortion spontaneous' (28 AEs) and 'abortion induced' (26 AEs). The cumulative pregnancy experience with oseltamivir (maternal exposure) also comprised a total of 158 non-medically confirmed pregnancy cases (294 events). The most frequently reported event (MedDRA PT) was 'No adverse event' (84 events) followed by 'normal newborn' (52), 'pregnancy' (43 events) and 'caesarean section' (nine events). Notable AEs (MedDRA PT) were 'drug exposure during pregnancy' (77 events), 'abortion spontaneous' and 'intra-uterine death' (three AEs each).

Following a request from the CHMP, the MAH has established an observational study (Protocol NV25577) to monitor existing pregnancy registries. This study aimed to monitor all pregnant women receiving oseltamivir in the EU and follow up for foetal outcomes. According to the MAH, the reports concerning pregnancy or lactation, received during the review period of this SBR, presented no significant safety information regarding the use of oseltamivir in this patient group.

Paternal Exposure to oseltamivir

The cumulative paternal exposed pregnancy experience with oseltamivir comprised four medically confirmed cases with five events. Cumulatively there were two non-medically confirmed pregnancy case reports (paternal exposure) associated with oseltamivir having three events.

Efficacy Related Information

During the reporting period, 299 case reports of lack of drug effect concerning oseltamivir were received and are summarised in Table 11.

Table 11 Summary of Efficacy related case reports

PSUR period	Efficacy related reports
01 April 2006 to 30 September 2006	None
01 October 2006 to 20 September 2007	5
21 September 2007 to 20 September 2008	5
21 September 2008 to 20 September 2009	24*
21 September 2009 to 20 September 2010	106*
21 September 2010 to 15 August 2011	159
Total	299

*The cases identified for discussion in PSURs 9 and 10 are based on a broader search criteria using a SMQ for Lack of Effect/Efficacy and includes MedDRA PTs "pathogen resistance" and "drug resistance".

According to the MAH, none of the individual reports of lack of efficacy indicated any significant or consistent reason for therapeutic failures which could represent a hazard to the population receiving oseltamivir. During the reporting period of PSUR 10, the MAH prepared a Drug Safety Report (DSR) on Lack of Effect/Efficacy with oseltamivir. This DSR concluded that lack of effect and viral resistance are adequately described in the Tamiflu SmPC. The MAH also presented yearly Tamiflu Resistance Updates in three PSURs covered by this SBR. No new safety concern or ADR was identified within this report.

Drug Safety Reports

The Drug Safety Reports concerning oseltamivir prepared during the reporting period (01 April 2006 to 15 August 2011) have concerned the following issues: pregnancies with exposure to oseltamivir; fulminant hepatitis; DIC: neuropsychiatric events; bone marrow failure and different cytopenias; rhabdomyolysis; GI haemorrhages; cardiac toxicity including arrhythmia, cardiac failure, myocardial infarction and bradycardia; renal toxicity; decreased appetite; sudden death and sudden cardiac and/or respiratory arrest; fatal encephalitis and encephalopathy; concomitant use with clopidogrel, antibiotics, warfarin, and other antivirals; hypothermia; use in preterm and premature infants and lactating women; suicidal behaviour; dehydration; and medication error.

In accordance with the European Pharmacovigilance Strategy for Pandemic Influenza Antivirals, the MAH has prepared 19 Pandemic Safety Reports (PSRs) continuously since 01 May 2009 until the data-lock point of this SBR (15 August 2011). The PSR has focused on cases corresponding to Areas of Special Interest (ASI) during the prevailing influenza A H1N1 (2009) pandemic (patients aged <12 months of age, cases with a fatal outcome and cases concerning pregnancy or lactation, lack of efficacy, neuropsychiatric AEs and serious ADRs).

Through this continuous intensive monitoring, the MAH has not observed any consistent safety information likely to warrant amendment of the current oseltamivir CDS. Based on CHMP feedback received on 26 July 2011 after the MAH's proposal to stop pandemic safety reporting because the end of the 2009 H1N1 pandemic had been declared, the next PSR will cover the seasonal influenza period 21 September 2011 to 20 March 2012 (inclusive). If the current post-pandemic situation persists, this PSR is assumed to be the last one.

On 16 September 2010, the MAH introduced a web-based entry form for consumer and healthcare professional reporting of oseltamivir-related AEs. No reports have been received as of now. This tool is not available in the USA and Japan.

Safety data from MAH sponsored therapeutic studies

Clinical studies in children

Study NV20236 was a seasonal prophylaxis study in children aged 1 to 12 years. There were no unexpected safety concerns and no deaths reported. Over the treatment period of 42 days (up to and including 2 days after last day of oseltamivir administration) 17 of the 49 subjects, (35%) reported 22 AEs. The most common AEs were gastro-intestinal disorders, infection, and respiratory disorders. Six subjects reported a further 6 Aes after stopping treatment up until the Day 70 follow-up.

Study CASG 144 evaluated the pharmacokinetics and safety of oseltamivir therapy in infants less than 2 years of age with confirmed influenza infection. There were no unexpected safety concerns reported. 99 non-serious AEs were reported in 53 subjects with the majority considered not related to study treatment. Of the 53 events that occurred among 39 subjects on-treatment, the most common classes of AEs were skin and subcutaneous tissue disorders, gastrointestinal disorders, and infections and infestations. There were no reported seizures. Eight serious adverse events were reported in 8 subjects: pyrexia, hypersensitivity reaction, influenza (2 events), pneumonia, viral upper respiratory tract infection, decreased oxygen saturation, and respiratory distress. Only the hypersensitivity reaction was considered related to study treatment.

Study WP22849 is an ongoing, open label, multicenter study to evaluate the PK, PD and safety of oseltamivir in the treatment of influenza in infants < 1 year of age. For the 24 infants who have completed the study, there have been 5 SAEs in 4 infants (diarrhoea, orbital cellulitis and respiratory syncytial virus (RSV) bronchiolitis, RSV infection, and ventricular septal defect (VSD)). None of the events were considered related to the study drug and all events (except VSD) resolved without sequelae. There have been no early withdrawals due to an adverse event.

Study NV25182 is an ongoing observational safety study in children ≤24 months of age. As of April 2011, 1066 patients have been enrolled (327 in the treatment group, 719 in the control group and 20 in the prophylaxis group) and 79 SAEs have been reported (27, 50, and 2 in each group, respectively). In the interim data no new concerns have been identified.

Clinical studies in immunocompromised patients

Study NV20235 was a 12 week seasonal prophylaxis study for transplant recipients ≥ 1 year of age (475 transplant recipients, 238 of which received oseltamivir). The safety findings were largely consistent with the known safety profile of oseltamivir. No deaths were reported in the oseltamivir group.

AEs were reported for 58 % of the placebo group and 55 % of the oseltamivir group. Most common were gastrointestinal disorders (22% and 21%, respectively) and infections and infestations (19% and 18%, respectively). Nausea and fatigue were reported more frequently in the oseltamivir group (5% vs. 4% and 5% vs. 3%, respectively). SAEs were reported by 10% in the placebo group and 8 % in the oseltamivir group. Most common were infections and infestations (placebo 4 %, oseltamivir 3 %).

Graft-versus-host disease developed in 4 subjects in the oseltamivir group and 2 in the placebo group. Four subjects developed transplant rejection; all were in the placebo group. Withdrawals due to AEs were reported with a higher frequency in the placebo group (6%) than in the oseltamivir group (3%).

Study NV20234 is an ongoing study evaluating conventional and high dose oseltamivir in the treatment of immunocompromised patients with influenza. One serious adverse event (bronchopneumonia – unrelated to study treatment) and one adverse event leading to premature withdrawal (epistaxis – possibly related to treatment) have been reported in the 23 patients enrolled up to March 2011. The study will continue recruiting in the 2011/2012 influenza season.

Clinical study in patients with pandemic H1N1 influenza

NV22155 was a double blind randomized controlled study in patients with pandemic H1N1 influenza evaluating increased oral oseltamivir dose and increased duration of therapy. No deaths of SAEs was noted in the unblinded safety data. Two patients discontinued due to vomiting, possibly related to study medication.

Clinical studies in influenza patients receiving oseltamivir IV

Study NV25118 (adolescents ≥ 13 years of age)

Of the 63 subjects enrolled by March 2011, 52% reported at least one AE (mostly nausea, vomiting, headache and infusion site pain). Nine SAEs were reported in 7 patients (atrial fibrillation, sinus arrhythmia, sinus bradycardia, COPD, respiratory failure, pyrexia, sepsis, cerebrovascular accident, and acute renal failure). Three deaths, considered to be unrelated to study medications, were reported: a 80-year-old male patient receiving 40 mg bid IV oseltamivir died of ventricular fibrillation due to cardiomyopathy; a 48-year-old female receiving blinded IV oseltamivir (100 mg or 200 mg) died of a pseudomonal lung infection; a 69-year-old male receiving blinded IV oseltamivir (100 mg or 200 mg) died of a cerebrovascular accident.

Study NP25138 (infants < 1 year of age)

By April 2011, 6 patients have been enrolled, for which three fatal SAEs have been reported. All of the SAEs were considered to be unrelated to study medication:

- A 4-month old infant presenting with acute respiratory distress syndrome and cerebral edema, treated with IV oseltamivir and extracorporeal membrane oxygenation died due to cerebral ischemia. The investigator considered the event and the infant’s death to be unrelated to study treatment.

- A 3-month old infant with congenital cardiac fibroma, a pericardial window biopsy, respiratory insufficiency and failure to thrive receiving IV oseltamivir died due to respiratory distress requiring intubation. The investigator considered the event and the infant’s death to be unrelated to study treatment.

- A 9-month old infant with congenital generalized hypotonia and cardiomyopathy presenting with respiratory failure and receiving IV oseltamivir died due to multi system organ failure (oseltamivir was later withdrawn). The investigator considered the event and the infant’s death to be unrelated to study treatment.

Study NP25139 (children 1-12 years of age)

Five patients enrolled by April 2011. To date, one SAE (sepsis) has been reported and there have been no premature withdrawals due to adverse events.

Surveillance analyses of safety data in infants < 1 year of age

Retrospective and prospective analyses of safety data in Japanese infants aged < 1 year administered antiviral use (including oseltamivir) for the treatment of influenza were described previously in the last renewal application. These analyses did not identify the emergence of any new safety signals.

More recently, retrospective analyses of antiviral use for the treatment of influenza in infants < 1 year of age have taken place:

- in the US (study CASG 113):review of medical records of 180 subjects treated with oseltamivir, amantadine, or rimantadine

- in Europe: retrospective investigator-led study of 157 infants, mean age 6.2 months, treated with oseltamivir suspension.

In the US study, the events that occurred following receipt of an influenza antiviral medication were those that would be expected in infants with influenza disease. Furthermore, no neurologic events occurred to suggest any detrimental effect from oseltamivir and the proportion of infants with any neurological event was not statistically different between the treatment groups (p=0.13). One subject, with a history of failure to thrive, died within 30 days of beginning their antiviral medication.

In the European study, oseltamivir suspension (2 x 2 mg/kg body weight) was generally well tolerated. Predominant AEs were vomiting (n = 62 infants) and diarrhea (n = 34 infants), and were mild in intensity and did not require any medical intervention. Compared with the onset of therapy, body temperature fell to values < 37°C in the majority of infants (< 80%) within 36-48 hours.

Resistance data

Resistance data from studies

Since the last renewal application, no changes to the incidence rates arising from treatment studies have been reported. No virologic resistance to oseltamivir occurred in the few patients who became culture positive for influenza during MAH-sponsored prophylaxis studies or in Study NV20235 (seasonal prophylaxis in immunocompromised patients).

Naturally occurring baseline resistance

The MAH provided a review of the literature on resistance to oseltamivir which is summarised below.

During the 2007/2008 influenza season in the Northern hemisphere, a significant proportion of influenza virus H1N1 subtype isolates (A/Brisbane/59/2007-like virus) from untreated subjects were resistant to oseltamivir. The frequency varied widely geographically, related to the relative prevalence of influenza A/H1N1 as compared to A/H3N2 and B viruses. Briefly, 24.3% of H1N1 isolates in Europe and 12.3% of H1N1 isolates in the US contained oseltamivir-resistant viruses.

This virus strain had spread globally by the 2008/2009 season when ~96% of H1N1 viruses were oseltamivir-resistant. Baseline oseltamivir resistance in these isolates was conferred by the well-described mutation H275Y (N1 numbering, corresponding to H274Y in N2 numbering) in the neuraminidase enzyme. This mutation confers resistance in a subtype specific (N1 only) manner and compound specific (oseltamivir only) manner. The influenza A (H1N1-H275Y) viruses collected during the 2007/2008 season retained sensitivity to zanamivir. As the majority of the samples were from subjects not exposed to oseltamivir, the emergence of resistance was likely a result of antigenic drift.

Co-circulating strains of seasonal influenza A/H1N1 viruses with resistance to either oseltamivir or adamantine have been described. Testing of over 1400 seasonal influenza A/H1N1 viruses collected from the US and globally in 2008–2010 identified 28 as belonging to four distinct genotypes with resistance to both oseltamivir and adamantine in five countries (USA, Canada, China, Kenya and Vietnam).

During the latter part of 2009, the Brisbane-like H1N1 virus was replaced by the new swine-origin pandemic H1N1 2009 virus. The majority of pandemic (H1N1) 2009 influenza virus isolates are sensitive to inhibition by oseltamivir. Oseltamivir-resistant variants have been observed sporadically.

304 cases of oseltamivir resistance were reported worldwide 8/2009–8/2010. In most cases, there was a H275Y point mutation apparently induced by oseltamivir treatment. The frequency of this type of resistance was around 1%. However, in immunocompromised patients 28 % of 304 cases were resistant. Case reports of resistance selection include 10 cases in immunocompetent and 19 in immunocompromised subjects. All immunocompetent patients recovered. However, 9 of the immunocompromised patients died. A common feature in the cases was bacterial co-infection potentially contributing to prolonged virus shedding facilitating selection of resistance.

No new cases of oseltamivir-resistant influenza A/H1N1(2009) were reported between 27 July and 10 August 2011, leaving the cumulative total since April 2009 at 566.

Three assessments of resistance to oseltamivir among pandemic influenza A/H1N1 strains from 2009 to 2011 are reviewed in the Clinical overview. In one study, 23 out of 3359 isolates were resistant to oseltamivir. Most of these were paediatric or immunocompromised. In another analysis 0.7 % of pandemic viruses were resistant to oseltamivir. In Japan, all 73 pandemic influenza A/H1n1 strains in 2009-2010 were susceptible to oseltamivir.

MAH sponsored Global Resistance Investigation Study (NV20237 - IRIS)

The MAH is currently conducting a prospective, multi-centre surveillance study (Study NV20237) to examine the natural prevalence and/or emergence of resistance to antivirals among influenza virus isolates, and collect data on the clinical outcome of patients with biologically-confirmed influenza who do or do not receive any treatment for their infection. Up to the clinical cut-off date of March 22, 2010, 1073 patients were enrolled into the study in the Northern hemisphere during the first 2 seasons (2008/2009 and 2009/2010). Of those enrolled, 668 had laboratory confirmed influenza infection by RT-PCR.

Two patients (0.5%) infected with pandemic H1N1 developed resistance while receiving treatment with oseltamivir. In contrast, but in line with the published literature regarding the sensitivity of the seasonal (2008/2009) H1N1 virus strain to oseltamivir: all seasonal H1N1 samples (n=44) with phenotype data in this study during this time period were resistant to inhibition by OC, consistent with the presence of the H275Y resistance mutation.

This study has continued for a third season, and an end of Season Report have been recently submitted and is under assessment. A sub-study in investigational centres in France and the Netherlands is now collecting information in immunosuppressed patients. Patients will continue to be enrolled in this study for further influenza seasons and subsequent end of season updates will be provided when available.

Resistance Selection during Treatment of Avian Influenza Virus Infection

Oseltamivir resistance in H5N1 virus isolates has been rare. To date, the selection of oseltamivir resistant H5N1 variants in patients treated with oseltamivir has been reported in three cases, with no cases of resistance or treatment failure due to resistance being reported since 2006.

2.4.3.2. Report of post marketing experience from 21 September 2010 to 15 August 2011

In addition, the MAH submitted within the renewal dossier a PSUR Addendum Report covering the period from 21 September 2010 to 15 August 2011.

Overview of adverse drug reactions

During the reporting period of this addendum PSUR, a total of 630 medically confirmed case reports containing 1,174 AEs, of which 691 were SAEs, were received from 621 patients. It should be noted that this figure of 630 medically confirmed case reports excludes spontaneous case reports containing only non-serious listed events, of which there were 305 case reports involving 375 AEs.
Of the 630 medically confirmed case reports received during the current reporting period, 474 were from spontaneous sources, 124 from literature, and 32 from studies.

The most frequently reported AEs were categorised in the following SOCs (as % of total AEs):

- General Disorders and Administration Site Conditions (30.1%),
- Infections and Infestations (13.4 %),
- Psychiatric Disorders (9.4 %)
- Nervous System Disorders (8.3 %).

The most frequently reported SAEs were from the following SOCs (as % of total SAEs):

- General Disorders and Administration Site Conditions (28.2%),
- Infections and Infestations (21.6%),
- Psychiatric Disorders (11.3%),
- Respiratory, Thoracic and Mediastinal Disorders (5.8 %)
- Skin and Subcutaneous Tissue Disorders (5.8 %).

In comparison to the previous PSUR, the frequency of total AEs reported has increased in the General Disorders and Administration Site Conditions SOC from 16.6% of the total AEs in the previous PSUR to 30.1% of total AEs in the current addendum PSUR, and in the Infections and Infestations SOC from 9.3% of total AEs in the previous PSUR to 13.4 % of total AEs in the current addendum PSUR. The total number of AEs has decreased in the Psychiatric Disorders SOC from 13.8% of total AEs in the previous PSUR to 9.4% of total AEs in the current addendum PSUR, in Gastrointestinal Disorders from 10.7% of total AEs in the previous PSUR to 7.7% of total AEs in the current addendum PSUR. The increase of AEs in the General Disorders and Administration Site Conditions SOC can be attributed to an increase in the AEs of 'Drug Ineffective' from 57 AEs in the previous PSUR's review period to 156 during the current Addendum's review period. The majority of these events were received from literature case reports. The difference of the number of AEs received in the remaining SOCs is not attributable to a marked increase/decrease in any one specific event, but is due to a general increase/decrease in AEs across the SOCs.

Fifty four fatal case reports were received by the MAH during the reporting period. According to the MAH, no consistent causal associations between the reported fatal adverse events and the use of oseltamivir could be established due to a combination of one or more factors including underlying influenza infections, complications of influenza, significant medical history, suspect comedications or the lack of sufficient information reported in the cases.

The MAH received a total of 1,205 medically confirmed pregnancy case reports and nine non-medically confirmed pregnancy case reports concerning maternal exposure to oseltamivir. One medically confirmed pregnancy case report and two non-medically confirmed pregnancy case reports concerning paternal exposure to oseltamivir were also received during the review period of this addendum PSUR.

During the review period, one case report was received concerning neonates (birth to <1 month) and 28 case reports concerning infants (≥1 month to <2 years), 126 case reports concerning children (≥2 to <12 years) and 35 case reports concerning adolescents (≥12 to <18 years). Fifty nine case reports concerned elderly (≥65 years) patients.

2.4.3.3. Discussion and Conclusion on safety

Most of the safety related type II variations during the SBR period were recommended based on the post marketing data presented in the previous PSURs. Due to pandemic use, the patient exposure increased dramatically during the PSUR period (21 September 2009 to 20 September 2010) compared with the PSUR period (21 September 2008 to 20 September 2009), and the current Addendum period (21 Sep 2010 to June 2011) (14.7 million vs. 10.4 million vs. 6.96 million patients, respectively). Exposure in clinical studies also significantly increased during the PSUR period (21 September 2009 to 20 September 2010) compared with the PSUR period (21 September 2008 to 20 September 2009), from 39 to 1805 patients.

The safety data from clinical trials and surveillance do not indicate any new safety signals in adults, children, infants, or elderly subjects.

Considering changes in medical dictionaries, overall, the most frequently reported System Organ Classes (SOCs) during the review period of the SBR were Psychiatric Disorders (2,747 AEs), General Disorders and Administration Site Conditions (1,354 AEs), Nervous System Disorders (1,175 AEs), Gastrointestinal Disorders (1,058 AEs) and Skin and Subcutaneous Disorders (704 AEs).

Emergence of oseltamivir-resistance is of concern, especially in immunocompromised patients and children. The resistance situation of influenza viruses is variable by season, strain, and geographical region. Resistance is a clinically significant concern and the MAH should continue to monitor the development of resistance in collaboration with international health organisations. Transmission of resistant viruses has also been reported. Lack of efficacy related case reports have increased steadily since 2006 from zero (1 April 2006 to 30 September 2006) to 159 (21 September 2010 to 14 August 2011), including fatal cases. The MAH will continue close surveillance of the development of resistance. The SmPC was amended with new data on resistance during the SBR period. The following studies are ongoing and study reports are expected after completion: Study IRIS, NV20237 (a global resistance investigation study), Study NV22155 (assessment of optimal treatment and resistance selection in pandemic (H1N1) 2009) and the Study NV 20234 (immunocompromised patients).

During the Addendum period 5 cases of acute renal failure were reported of which 3 (including one renal impairment) had fatal outcome. During the previous PSUR period (September 2009-2010), a total of 16 serious acute renal failure cases were reported and two cases had a fatal outcome. Therefore, acute renal failure should also be extensively monitored.

Reports of neuropsychiatric adverse events have been declining. Neuropsychiatric events are frequently reported in children and adolescents and a significant number of ADRs were serious. This safety issue has now been addressed in the 4.4 of the EU SmPC. No mechanism for the reported neuropsychiatric events has been demonstrated. The safety information is based on spontaneous reporting which makes the evaluation of the causality very difficult. Close monitoring of central nervous system effects will continue.

Regarding the potential risk of medication errors associated with the change in formulation strength of Tamiflu oral suspension from 12 mg/ml to 6 mg/ml (see Summary of Risk Management Plan, Table 12), the communication plan and DHPC letter text as presented in Attachment 6 are considered acceptable by the CHMP.

In addition, the CHMP considered that the applicant should submit the following safety data within the next PSUR:

- The MAH should submit a Drug safety report on renal disorders including data from preclinical, clinical and post marketing experience.
- The MAH should continue the safety monitoring in patients with renal impairment
- The MAH should continue close monitoring of central nervous system effects

The MAH submitted a PSUR addendum covering the period from 21 September 2010 to 15 August 2011. The MAH submitted in December 2011 PSUR 11 covering the period from 21 September 2010 to 20 September 2011. Based on the available safety information, the CHMP considers that the MAH should continue to provide yearly PSUR. The next PSUR covering the period from 21 September 2011 to 20 September 2012 is due by December 2013.

2.5. Risk management plan

The MAH submitted a updated risk management plan, which included a risk minimisation plan.

Table 12 Summary of the risk management plan

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
Important identified risks		
Neuropsychiatric events	Close observation through routine pharmacovigilance system. Guided questionnaire to procure more detailed information on neuropsychiatric events.	Sections 4.4 and 4.8 of the SmPC describe psychiatric and nervous system disorders.
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. Guided questionnaire to procure more detailed information on liver and biliary disorders.	Described in Section 4.8 of the SmPC 'Undesirable Effects'.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
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. Clinical assessment of resistance emergence during treatment of new H1N1 infections with oseltamivir. Virologic characterization of new H1N1 viruses and new oseltamivir resistant viruses. Ongoing study NV 20237 – Influenza Resistance Information Study (IRIS) Co-operation with other organisations e.g. NISN, WHO-GISN ECDC in exchange of information regarding resistance of pandemic strain NV22155 (evaluate the efficacy of four regimens of oseltamivir in patients infected with pandemic [H1N1] 2009.) Enrolment is complete with 102 patients enrolled. A final clinical study report will be submitted by 30 April 2012	Described in Section 5.1 of the SmPC, 'Pharmacodynamic Properties'
Important potential risks		
Exposure during pregnancy	Close observation through routine pharmacovigilance system NV25577- Working with existing pregnancy registries to monitor pregnancy outcomes during H1N1 pandemic	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
Potential risk of medication errors associated with the change in formulation strength of TAMIFLU® (oseltamivir phosphate) for Oral Suspension- changing the concentration from 12 mg/ml to 6 mg/ml and the dispenser from mgs to mls.	Close observation of reported cases through routine pharmacovigilance system	Posology and method of administration described in Section 4.2 of the SmPC DHCP letter informing the HCP of the change in formulation A communication plan for the distribution of the DHCP letter regarding the change in formulation strength of TAMIFLU® (oseltamivir phosphate) for Oral Suspension is provided in Annex 8
Important missing information		

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Hepatic and renal impairment in children	Close observation of reported cases through routine pharmacovigilance system Two studies in immuno-compromised patients (NV 20234 - a treatment study, NV 20235 - a prophylaxis study) enroll patients one year of age and older. Study NV 20235 has recently been completed. Study NV20234 will also enroll patients 1 year of age and older.	EU SmPC Section 4.2 describes insufficient information in children with hepatic impairment or renal impairment. Hepato-biliary disorders reports are describes in SmPC under section 4.8
Patients receiving dialysis treatment	Routine pharmacovigilance activities: Patients on haemodialysis and/or peritoneal dialysis treatment prior to receiving Tamiflu as per new dosing recommendations will be closely monitored and relevant information will be presented in a dedicated section in the PSUR.	Dosing recommendations for dialysis patients are described in Section 4.2 of the SmPC
Treatment of influenza in immunocompromised children and adults	Close observation through routine pharmacovigilance system; clinical trial NV20234 is ongoing and the final data is expected at the end of 2016. The MAH does review and submit annually a report on safety and efficacy of oseltamivir in immunocompromised patients of this trial, up to final submission of the clinical trial NV20234 study report.	Dosing recommendations, warnings and AR reports are described in sections 4.2, 4.4 and 4.8 of the SmPC.
Children <1 year of age	Close observation of reported cases through routine pharmacovigilance system A pharmacokinetic study conducted by NIH (CASG 114) Planned epidemiological surveillance study: A prospective, non-interventional, surveillance safety study in young children with influenza receiving Tamiflu is planned in EU. Study (WP22849) is a prospective, open-labelled, multicenter trial evaluating the PK/PD and safety of oseltamivir therapy in infants less than one year of age with influenza. Available PK, efficacy and safety data collected during the H1N1 pandemic influenza, together with its full assessment to support the pandemic indication and dosing in children under 1 year of age, will be submitted by 2Q2012.	Dosing recommendations in Section 4.2 of the SmPC Discussions on special population in Sections 5.1 and 6.6 of the SmPC

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Additional pharmacovigilance activities according to CHMP July 2009 strategy paper for monitoring of Tamiflu use during pandemic	Swift signal detection for use of Tamiflu during pandemic and communication to health authorities, physician, prescribers, policy makers 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)	

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Immunocompromised patients The MAH should continue to review annually the safety and efficacy of oseltamivir in immunocompromised patients up to final submission of the clinical trial NV20234 study report (treatment) as flu and season permits.	Annually in December CSR by the end of 2016
Resistance data - The MAH should report yearly to the CHMP regarding the resistance situation of influenza viruses - In order to elucidate clinical significance of new resistance information in immuno-competent patients, the MAH should provide results and final reports from the following studies: Study IRIS (NV20237) Study NV22155 Study NV20234	Annually in December Final CSR: March 2013 April 2012 2016
Pharmacokinetics data in infants and children The MAH should provide pharmacokinetics data from CASG 114, WP22849 and any additional available pharmacokinetics data	Q2 2012
H1N1 data The MAH should submit all available PK, efficacy and safety data collected during the H1N1 pandemic influenza, together with its full assessment to support the pandemic indication and dosing in children under 1 year of age and amend the Product Information wherever needed	Q2 2012
Study NV25182 The MAH should submit the results of study NV25182 in order to provide further data on the short-term safety profile of oseltamivir when used as treatment or	December 2012

Description	Due date
prophylaxis for influenza A or B in children 24 months of age or younger.	
Pandemic Safety Report (PSR) covering 21 September 2011 to 20 March 2012	May 2012

The following additional risk minimisation activities were required

- DHPC letter to inform about the change in the concentration of the Tamiflu oral suspension and in the graduation of the syringe at launch.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk Management Plan is submitted:

- to improve the quality of the document regarding the description and follow-up of measures included in the EU-RMP pharmacovigilance plan.

2.6. Changes to the product information

The MAH proposed changes to the Product Information (PI), which were reviewed during the assessment of this renewal application.

Changes were also made to the PI to bring it in line with the current Agency/QRD template and SmPC guideline, which were reviewed by QRD and accepted by the CHMP.

In addition changes were made to the SmPC and package leaflet to improve the readability.

During the procedure, the CHMP requested additional amendments to section 4 of the Package Leaflet to better reflect the information related to neuropsychiatric events and their monitoring as presented in section 4.4 of the SmPC. Since most children and adolescents are treated at home, observation of children and adolescents for behavioural changes is considered as an essential risk minimisation measure and the package leaflet was revised as follows:

'These are reported primarily among children and adolescents and often had an abrupt onset and rapid resolution. In a very few cases resulting in self-injury, in some instances with fatal outcome. Such events have also been reported in patients with influenza who were not taking Tamiflu.

• Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

• If you notice any of these symptoms, especially in younger people, get medical help immediately.'

The MAH is recommended to consider the impact of the drug safety report on renal disorders when available on the product information. In addition, once pharmacokinetics data from the paediatric clinical studies and the analysis of the pharmacokinetics, efficacy and safety data collected during the H1N1 pandemic influenza are available, the MAH is recommended to consider the impact on the Product Information.

The MAH will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use by June 2012.

2.7. Overall conclusions and benefit risk balance

Benefits

- Beneficial effects

Most benefits on the effect of oseltamivir were already demonstrated before the first renewal. Oseltamivir has been shown to shorten the clinical course of influenza, especially influenza caused by A viruses, by approximately one day. In influenza-infected patients, oseltamivir treatment reduces upper respiratory tract infections requiring antibiotics. Prerequisites for the efficacy of oseltamivir treatment are an accurate diagnosis and early administration of the therapy. The additional analyses on ITT population provided by the MAH further confirm the treatment effect of oseltamivir.

Recent studies in dialysis patients have clarified the posology in patients with severe renal insufficiency.

Oseltamivir is also effective in preventing influenza both in the seasonal prophylaxis and in post-exposure setting. In prophylaxis, the usefulness of oseltamivir will depend on the nature of the circulating virus and on the timing of oseltamivir administration. It is reassuring that the proportion of patients with protective post-baseline antibody titres in clinical studies was equally high in oseltamivir arms as well as placebo arms, indicating that Tamiflu does not impair immune response against influenza.

The majority of pandemic (H1N1) 2009 influenza viruses were susceptible to neuraminidase inhibitors, including oseltamivir, but were resistant to adamantanes. Therefore, oseltamivir remains an option for treatment and prophylaxis of influenza.

- Uncertainty in the knowledge about the beneficial effects

The efficacy has not been confirmed in elderly patients and in patients with cardiac or respiratory disease.

After the first renewal, the use of oseltamivir was extended to younger children and infants. There is still uncertainty of the optimal posology in young children and in immunocompromised patients. Clinical studies CASG 114 and WP22849 may provide further information regarding the posology for children. Unfortunately, study WP22849 is lagging behind the schedule. Likewise, study on optimal dose in immunocompromised patients has suffered from slow recruitment.

Prevention of serious complications, such as pneumonia, and complications in patients with underlying chronic diseases, including immunocompromised patients, has not been demonstrated according to regulatory standards.

Risks

- Unfavourable effects

In general, the safety profile of oseltamivir has remained largely unchanged since last renewal. The common but rarely severe adverse reactions are nausea, vomiting and headache. Uncommon but potentially serious adverse reactions include various hypersensitivity reactions. Rare cutaneous reactions, such as angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, may be serious.

The estimated cumulative exposure to oseltamivir since 01 April 2006 via commercially obtained drug and through clinical trials until June 2011 is 42,062,464 patients. The massive use of oseltamivir during the 2009/2010 pandemic resulted in an increase of spontaneous reports of adverse events. Some possible new but rare adverse reactions have been added to the sections 4.4. and 4.8. of the Tamiflu SmPC. There is now a large database of spontaneous reports of the use of oseltamivir during

pregnancy. These data do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development.

The mechanisms of oseltamivir resistance are well known. In general, most influenza virus strains remain susceptible to oseltamivir. Nevertheless, during the 2007/2008 influenza season in the Northern hemisphere, a significant proportion of influenza virus H1N1 subtype isolates (A/Brisbane/59/2007-like virus) from untreated subjects were resistant to oseltamivir. By the 2008/2009 season ~96% of H1N1 viruses were oseltamivir-resistant. Fortunately, the majority of pandemic (H1N1) 2009 influenza viruses were susceptible to neuraminidase inhibitors, including oseltamivir, while resistant to adamantanes. The resistance/decreased susceptibility to oseltamivir is, in most cases, natural, i.e. not caused by selection pressure by oseltamivir. From clinical point of view, it is important to consider oseltamivir resistance in patients with high viral load and prolonged virus shedding, i.e. children and immunocompromised patients.

Thus, oseltamivir continues to be effective in treatment and prophylaxis provided that the prescriber takes note of available local official information on the nature and phase of the seasonal epidemics. The company should continue to collaborate worldwide with laboratories capable of monitoring resistance/reduced susceptibility of viruses to oseltamivir in isolates from patients.

- Uncertainty in the knowledge about the unfavourable effects

Neuropsychiatric ADRs have raised a lot of attention since the last renewal. Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, and self-injury have been reported and have raised a lot of public attention. The evaluation of the causality has been extremely difficult since non-clinical studies conducted by the MAH before and after the first renewal have not been able to confirm CNS effects of oseltamivir or its metabolites. In addition, controlled clinical trials do not confirm the safety signals from spontaneous reporting. Nevertheless, the current SmPC and PL contain warnings of a possible risk.

There have also been reports and publications of possible drug-drug-interactions and interference with membrane transporters. These observations have not been confirmed in company-sponsored studies. Thus, oseltamivir has only a few interactions with relevant medicinal products.

The role of oseltamivir in the treatment and prophylaxis is still somewhat controversial due to the fact that influenza seasons vary in severity and the susceptibility of viruses to oseltamivir also varies. Therefore, clinical studies conducted in the past may not be fully applicable to future epidemics. The MAH has had difficulties in addressing some crucial issues, such as prevention of complications in various sections of the population.

Post-marketing surveillance has included spontaneous reports of renal failure with oseltamivir, however, causal association has not been confirmed based on the data available. This association will be further investigated.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Although the effect of oseltamivir is considered modest, data available since the last renewal have confirmed that oseltamivir is efficacious in the prevention and treatment of influenza. Oseltamivir has been shown to shorten the clinical course of influenza, especially influenza caused by A viruses, by approximately one day. Oseltamivir is also effective in preventing influenza both in the seasonal

prophylaxis and in post-exposure setting. Furthermore, oseltamivir has been recognised as a valuable option in a potential pandemic influenza outbreak.

The overall safety profile of Tamiflu since the last renewal has remained unchanged.

- Benefit-risk balance

Benefit-risk balance of oseltamivir remains positive in the approved indications.

3. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Tamiflu in the treatment and prophylaxis of influenza remains favourable and therefore recommends the renewal of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

PSURs

The MAH will continue to submit yearly PSURs (Data Lock Point 21 September) unless otherwise specified by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall ensure that at the launch of Tamiflu 6 mg/ml powder for oral suspension, all physicians who are expected to prescribe or use Tamiflu are provided with a Direct Healthcare Professional Communication letter, the text of which is appended to the CHMP assessment report. The MAH shall agree the communication plan for the DHPC letter with the National Competent Authority in the Member States where the letter will be distributed.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented.

The Member States shall ensure that the MAH provides all physicians who are expected to prescribe or use Tamiflu a Direct Healthcare Professional Communication (DHPC) letter, the text of which is appended to the CHMP assessment report. The Member States shall agree with the MAH the communication plan for the DHPC letter.

The CHMP recommends that the renewal be granted with unlimited validity.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application, the CHMP recommends amendments to the Annexes I, II, IIIA, IIIB and 127a. These changes do not affect the risk-benefit balance of the product, which remains positive.