EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 September 2011
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SUMMARY ON COMPASSIONATE USE
FOR
Tamiflu IV

International Nonproprietary Name:
Oseltamivir

Procedure No. EMEA/H/K/2287/CU

CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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PRODUCT INFORMATION

Name of the medicinal product for Compassionate Use:	Tamiflu IV
Company:	F. Hoffmann-La Roche Ltd
Active substance:	Oseltamivir phosphate
International Nonproprietary Name:	Oseltamivir
Target Population:	Compassionate Use Tamiflu IV should be considered only to treat critically ill adults and children older than 1 year of age having a life-threatening condition due to suspected or confirmed pandemic (H1N1) infection or infection due to seasonal influenza A or B virus and answering to the following criteria: (1) patients not responding to either oral or inhaled authorised antiviral medicinal products, or (2) patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible. For infants below 1 year of age, no recommendation can be given at this stage due to the absence of pharmacokinetic and safety data on the use of Tamiflu IV in this very young population. Should a physician decide to treat an infant below 1 year of age, the decision should be taken based on the assessment of the benefit and risk for the individual.
Pharmaceutical form(s):	Powder for solution for infusion
Strength(s):	100 mg
Route(s) of administration:	Intravenous
Packaging:	Vials
Package size(s):	10 Vials

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

Finland notified the Agency (EMA) on 21 October 2009 and requested a CHMP opinion on the compassionate use for the above mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004), and data submitted to the Agency (EMA) by F. Hoffmann-La Roche Ltd on 6 November 2009.

The legal basis for this application refers to:
Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004)

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Janne Komi
Co-Rapporteur: Helder Mota-Filipe

1.2 Steps taken for the assessment of the product

- The timetable for the procedure was agreed-upon by CHMP on 22 October 2009.
- The dossier was received by the EMA on 6 November 2009.
- The Rapporteur's preliminary Quality Assessment Report was circulated to all CHMP members on 4 December 2009.
- The Rapporteur's updated preliminary Overview was circulated to all CHMP members on 4 December 2009.
- The PDCO provided comments on the preliminary Rapporteur's Assessment Report on 15 December 2009.
- During the meeting held in December 2009, the CHMP agreed on the consolidated List of Questions to be sent to the company. The final consolidated List of Questions was sent to the company on 17 December 2009.
- The company submitted the responses to the CHMP consolidated List of Questions on 8 January 2010.
- The PDCO provided comments on the Rapporteur's Assessment Report on 18 January 2010.
- The Rapporteur circulated an Overview on the company's responses to the List of Questions to all CHMP members on 16 January 2010.

2 GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

2.1 Manufacturing authorisation holder

Manufacturer(s) of the active substance
Name: F. Hoffmann-La Roche Ltd
Address: Grenzacherstrasse 124, CH-4070 Basel
Country: Switzerland

Name: Roche Carolina Inc.
Address: 6173 E Old Marion Hwy, Florence, SC 29506
Country: USA

A GMP (Good Manufacturing Practice) certificate for Roche Basel and a QP declaration of GMP compliance of Roche, Carolina, were provided. The re-test period of oseltamivir phosphate was extended to 8 years in 2009.

Manufacturer(s) of the finished product
Name: F. Hoffmann-La Roche Ltd
Address: Grenzacherstrasse 124, CH-4070 Basel
Country: Switzerland

Manufacturer responsible for import and batch release in the European Economic Area
Name: Roche Pharma AG
Address: Emil-Barell-Strasse 1, D-79639 Grenzach-Wyhlen
Country: Germany

2.2 Conditions of distribution

Medicinal product subject to special medical prescription.
Tamiflu IV should be prescribed only by clinicians skilled in the diagnosis and management of patients with potentially life-threatening illness

2.3 Conditions for update of Compassionate Use to be implemented by the company

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP on 20 January 2010, related to the conditions of use, distribution and targeted population of Tamiflu IV, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4 Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the company will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

The company will submit yearly all safety information on Tamiflu IV in the format of a Periodic Safety Update Report (PSUR) unless otherwise specified by the CHMP.

The company will submit all safety information on Tamiflu IV as part of the Tamiflu monthly Pandemic Safety Report as long as the phase 6 is declared by the WHO or unless otherwise specified by the CHMP.

2.5 Conditions for safety monitoring to be implemented by the Member States

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3 SCIENTIFIC DISCUSSION

3.1 Introduction

As requested by the CHMP in October 2009, the company submitted a dossier to support the compassionate use of Tamiflu IV formulation. The dossier was presented in accordance with Chapter 7 of Notice to Applicants Volume 2A, meaning according to CTD format.

Very limited amount of quality, non-clinical and clinical data were submitted as part of this dossier. It should therefore be kept in mind that the following assessment concerns exclusively the use of Tamiflu IV formulation in the context of the compassionate use in a specific targeted population.

3.2 Quality aspects

Introduction

Tamiflu IV formulation for compassionate use is a lyophilised powder, packaged in glass vials, with rubber stoppers and caps with seals.
Tamiflu 75 mg, 45 mg and 30 mg hard capsules and 12 mg/mL powder for oral suspension packaged have been already authorised.

Drug Substance

Oseltamivir phosphate, (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1), is a non-hygroscopic pro-drug of the active metabolite, oseltamivir carboxylate. It is freely soluble in water. The drug substance oseltamivir phosphate has been appropriately characterized and fully described and was already approved within the Tamiflu 75 mg capsules marketing Authorization Application.

- Manufacture

The manufacturing process comprises the same 4 steps and process controls are the same as in the current dossier of Tamiflu 75 mg capsules. Starting materials as well as synthetic intermediates were described in sufficient detail. The critical process parameters of all stages with appropriate justification have been described.

- Specification

The drug substance specification includes tests for appearance and colour, identification, specific optical rotation, water content, heavy metals, assay, organic impurities and residual solvents.
The specifications are previously assessed and approved and therefore considered to be justified.

- Stability

The proposed re-test period has been approved in connection with Tamiflu 75 mg capsules and testing of three production batches will be continued up to the end of the re-test period.
A complete stability program at 25°C/60% RH with 3 batches has been initiated in 2005. The samples will be tested annually until 8 years.

Drug Product

- Pharmaceutical Development

Oseltamivir phosphate is a pro-drug which is converted to the active metabolite oseltamivir carboxylate via hepatic decarboxylases. Oseltamivir phosphate has already been available as oral capsules and oral suspension and the IV-formulation was developed for treatment of severe cases of influenza that can no longer be treated orally. The oseltamivir pro-drug was chosen over the active metabolite oseltamivir carboxylate as the drug substance for the intravenous formulation because it has a longer half-life compared with oseltamivir carboxylate following direct IV administration. Early clinical investigations with an IV formulation of oseltamivir phosphate showed that the half-life of the active metabolite oseltamivir carboxylate is comparable to the oral administration of the oseltamivir and it was well tolerated. Additionally, oseltamivir phosphate is an approved drug substance and does not require a prolonged technical development program.
The drug product is a lyophilised powder in a glass vial with a rubber stopper and a cap with seal and is manufactured by standard manufacturing processes. The only critical issue in the manufacture is sterility which is ensured by aseptic processing and by setting a low bioburden limit before sterile filtration. Stability studies with oseltamivir phosphate have shown that the drug substance is very stable in solid state but undergoes relatively rapid degradation in aqueous solution. A freeze-dried formulation was developed to improve the stability. The PK results for the active metabolite confirmed that 100 mg administered intravenously was equivalent to 75 mg orally, although the PK results for oseltamivir, but not oseltamivir carboxylate, were significantly different to that seen with the oral formulation. A 100 mg formulation to be reconstituted as 50 mg/mL in a 6 mL vial was developed for the clinical study WP20727. In order to increase the lyophilisation capacity another 100 mg formulation to be reconstituted as 100 mg/mL and packaged in a 3 mL vial was developed for use during the pandemic. The vials contain an overage of 20% to compensate for the non-removable volume of reconstituted solution. The required dose withdrawn from the reconstituted contents is further diluted to achieve a concentration of not exceeding 4 mg/mL oseltamivir (free base) prior to IV administration by infusion.
The stability of the reconstituted solution was determined with the clinical formulation Ro 064-0796/F08-01 (50 mg/mL) in the upright position No degradation was observed after 48 hours at ambient condition and the stability of the reconstituted solution is limited only by microbiological considerations to 24 hours. Leaching studies of the reconstituted solution in the upside-down position were considered irrelevant since the drug product is a lyophilised powder and after reconstitution, the drug product is stored in the upright position when the solution is not in contact with the closure.
The stability of the pandemic formulation (100 mg/mL) is considered to be the same.
The compatibility of the reconstituted solution with 0.9% NaCl solution has been demonstrated. Other saline infusion solutions (e.g. Ringer's Injection) have not been tested for compatibility. It is

conceivable that infusion solutions containing Ca ions or reducing sugars may not be compatible due to precipitation of calcium phosphate or formation of degradation products in a Maillard type reaction.

- Adventitious Agents

Neither the excipients nor the active substance is derived from human or animal origin.

- Manufacture of the Product

The drug product is manufactured by standard manufacturing processes. Sterility is ensured by sterilisation of primary packaging elements, aseptic techniques and sterile filtration. Process simulating media fill runs were performed before starting the production.

- Product Specification

The specifications of the drug product were set according to current guidelines and contain all the relevant tests and limits for a product of this type. Tests include appearance of vial content (visual), identification (IR, HPLC), oseltamivir content per vial (HPLC), degradation products, uniformity of dosage units (Ph.Eur), water content (Karl Fischer), bacterial endotoxins (Ph.Eur) and sterility (Ph.Eur). In addition tests and limits for clarity, colour, pH (potentiometric), and visible and sub-visible particles (light obscuration) of the reconstituted solution are included in the specification.
Batch analysis results for one laboratory scale batch and one production scale batch conformed to the specification.

- Stability of the Product

Stability of the drug product has initially been examined on the clinical formulation and the pandemic formulation. Both batches were manufactured at the same manufacturing site on laboratory scale equipment. Stability data was available at 25°C/60% RH over 12 months for both batches and over 24 months for the clinical batch. Accelerated stability data at 40°C/75% RH was collected for both batches over 6 months. The clinical batch was additionally tested at 30°C/75% RH at time points 12 and 24 months. The technical batch was tested at 30°C/75% RH at time points 6 and 12 months.
The approved re-test period of oseltamivir phosphate is 8 years and the approved shelf-lives of Tamiflu capsules and oral suspension are 7 years and 2 years, respectively. The powder for solution for infusion is a lyophilised powder containing essentially no excipients. The stability of oseltamivir phosphate is good and it can be expected that the iv formulation is very stable too.
Additional stability data on two pilot batches of Tamiflu 100 mg vials have been provided to support an extension of the shelf life from 24 months to 30 months. Real time stability data on the pilot scale batches are available up to 24 months and up to 18 months, respectively (Table 1).

Table 1. Stability data available

Batch	**Stability data available**		
	40 °C/75 %RH	30 °C/75 %RH	25 °C/60 %RH
Clinical, pilot scale	6 months	24 months	24 months
Technical, lab scale	6 months	36 months	36 months
Clinical, pilot scale	6 months	18 months	18 months

No significant differences in stability are seen between the two pilot batches. Appearance and colour of the freeze-dried powder stay unchanged during storage time of 18 / 24 months. Clarity and pH of constituted solution do not change during the testing periods. Water content increases slightly up to 0.41% / 0.49% at 25°C/60% and up to 0.65% / 0.75% at 30°C /75% after 18 / 24 months. No actual decrease is seen in assay results. Amount of total degradation products is slightly increasing up to 0.32%/ 0.28% at 25°C/60% and up to 0.41% / 0.38% at 30°C/75%. Maximum level of total unspecified degradation products seen at real time conditions is 0.17%. Colour of the constituted solution is changing from initial almost colourless to slightly coloured after 3 months at each storage condition. No significant change in discolouration can be seen during storage period from 6 months to 18 / 24 months.

Based on the additional stability results provided the CHMP concluded that extension of the shelf life of Tamiflu 100 mg vials from 24 months to 30 months with storage conditions "store below 25°C" is approvable.

The CHMP also recommended that the cause of the change in colour of the constituted solution should be studied more comprehensively if intensifying of the colour is seen during stability follow-up.

Discussion on chemical, pharmaceutical and biological aspects

All relevant information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were no unresolved quality issues, which could have a negative impact on the Benefit Risk balance of the product.

3.3 Non-clinical aspects

Introduction

For Tamiflu IV, Roche has decided to use oseltamivir phosphate, the pro-drug of the active metabolite oseltamivir carboxylate, since the half-life of the carboxylate metabolite is only 2 hours after its direct IV-dosing compared to 8 hours after oral administration of oseltamivir phosphate. Early clinical investigations using IV oseltamivir phosphate also showed that the half-life of the active metabolite is comparable to oral administration of oseltamivir.

To support this dossier for compassionate use of the IV formulation of oseltamivir phosphate, the company provided information elucidating the tolerability and safety of oseltamivir phosphate after IV dosing.

Non-Clinical studies performed with IV dosing

- *Non-Clinical data submitted*

Four (4) studies were submitted elucidating tolerability and safety of oseltamivir phosphate and oseltamivir carboxylate when administered intravenously for 14 days to rats and marmosets.

These studies are the following:

1) Ro 64-0796/002 (oseltamivir phosphate): A 14 day rat study by the intravenous route. Roche Report 1001809, 2000.
2) Ro 64-0802/002: A 2 week intravenous toxicity and toxicokinetic study in the rat (Study No SAR691). Roche Report W-142938, 1999.
3) Ro 64-0796/002: A 2-week intravenous toxicity and toxicokinetic study in the marmoset (study no. SAP718). Roche Report 1002143, 2000.
4) Ro 64-0802/002: A 14 day intravenous repeated dose toxicity study of Ro 64-0802/002 in male marmosets (study no. SBL 71-51). Roche Report W-142940, 1998.

1) Ro 64-0796/002 (oseltamivir phosphate): A 14 day rat study by the intravenous route. Roche Report 1001809, 2000.
In the study, groups of rats received oseltamivir phosphate intravenously at doses 10, 50 or 100 mg/kg/day free base for 14 days. The doses were given once daily by infusion over 50 seconds. Additional groups of rats were used to toxicokinetic analysis to ensure exposure of the drug during the study period.

Systemic exposure was dose-proportional for both pro-drug and the active metabolite. Exposure to the latter was almost twice that to the former compound.

One female rat in the high dose group was found dead on day 11; no cause of death could be determined by histopathology. All other animal showed excellent systemic and local injection site tolerance to the IV formulation of oseltamivir phosphate.

2) Ro 64-0802/002: A 2 week intravenous toxicity and toxicokinetic study in the rat (Study No SAR691). Roche Report W-142938, 1999.
In this study, Ro 64-0802/002 (the active metabolite of oseltamivir) was administered by bolus injection to groups of male rats for 2 weeks at doses of 6.8, 27.2 and 136 mg/kg/day as hemitartrate salt equivalent to 5, 20 and 100 mg/kg/day of free base. Full in-life, laboratory and terminal

investigations were made. Toxicokinetic monitoring was performed on an additional subset of animals following dosing on day 1 and sacrificed on day 2.

The pharmacokinetics following a single IV dose at 6.8, 27.2 and 136 mg/kg were approximately linear, although a slight decrease in clearance at the high doses is suggested by the data. Treatment was well-tolerated at doses up to 27.2 mg/kg/day with no adverse treatment related findings. Three (3) animals, all given 136 mg/kg/day of the test compound had alveolitis in the lung. In 2 rats, only a small focus of inflammation was found, and one had more extensive hemorrhagic inflammation. It was concluded that IV-dosing of Ro 64-0802/002 was well tolerated in male rats with no adverse effects at doses of 6.8 or 27.2 mg/kg/day. At the highest dose of 136 mg/kg/day some laboratory findings showed marginal changes in urine volume and electrolytes. One (1) male had moderate to extensive hemorrhagic alveolitis in the lungs. The NOAEL in this study was 27.2 mg/kg/day of Ro 64-0802/002 equivalent to 20 mg/kg/day free base.

3) Ro 64-0796/002: A 2-week intravenous toxicity and toxicokinetic study in the marmoset (stuy no. SAP718). Roche Report W-1002143, 2000.
In the study described in the Roche Report 1002143, 2000, Ro 64-0796/002 (oseltamivir phosphate) was administered intravenously for 2 weeks to groups of 3 male and 3 female marmosets at doses 10, 25 and 50 mg/kg/day (free base) or saline control. In-life investigations included clinical observations, body weights, urinalysis, biochemistry and toxicokinetic evaluations. Post mortem examinations included weighing organs and recording macroscopic and microscopic changes. There were no adverse effects observed in any of these parameters, although some, statistically insignificant changes were found in liver weight in all groups but no histopathological findings or in liver enzymes to suggest liver toxicity. The systemic exposure of the drug was dose-dependent for the active compound, and slightly less for the pro-drug.

4) Ro 64-0802/002: A 14-day intravenous repeated dose toxicity study of Ro 64-0802/002 in male marmosets (study no. SBL 71-51). Roche Report W-142940, 1998.
In the study described in the Roche Report W-142940, 1998, Ro 64-0802/002 (the active metabolite) was administered at dose levels 5, 15 and 50 mg/kg/day to 3 male marmosets per dose group for a 14 days period. The control group received vehicle. Additionally, toxicokinetic evaluation was done in subset of animals at the end of the study period. The pharmacokinetics following the initial intravenous dose of Ro 64-0802/002 was found to be essentially linear, although a slight decrease in clearance was observed at the 50 mg/kg dose. There were no deaths during the dosing period. No test compound-related abnormalities were noted in clinical signs, food and water consumptions, body weights, urinalysis, haematology, serum biochemistry, gross pathology or in histopathological examinations in any animal groups. It was concluded that Ro 64-0802/002 cause no systemic or local toxic effects in marmosets at any dose level studied.

- *Conclusions on Non-Clinical studies with IV dosing*

Oseltamivir phosphate was well-tolerated in adult rats in doses from 10 mg/kg/day to 100 mg/kg/day (free base) given as intravenous infusion over 50 seconds once daily for 14 days, since no systemic or local intolerance was noted. Doses of 132 mg/kg/day (given as bolus) for 14 days of Ro 64-0802/002 were associated with alveolitis in male rats wherefore the NOAEL was considered to be 27.2 mg/kg/day. Although the alveolitis was considered mild, the observation might still be clinically relevant if the drug is given at extremely high doses.

Oseltamivir phosphate is well tolerated also in marmosets when given intravenously for 14 days at doses up to 50 mg/kg/day (free base). The pharmacokinetics of oseltamivir is closer to humans than in rats, and the results are thus clinically more relevant. The active metabolite of Tamiflu was also found to be well tolerated in marmosets when given intravenously at doses up to 50 mg/kg/day for 14 days.

Other animal studied submitted, performed with oral dosing

- *Data submitted*

1) In the study report 1029359, pharmacokinetics of oseltamivir phosphate and its metabolite oseltamivir carboxylate was investigated after single oral doses (by gavage) of 763 mg/kg and 1000 mg/kg (free base). Pharmacokinetic parameters were evaluated in plasma, brain and CSF. Mean maximum plasma concentrations were found at 6 and 2 h post-dose, respectively. Maximum concentrations of oseltamivir carboxylate were found at 8 h post-dose. The maximum brain concentrations of oseltamivir phosphate were approximately 12-14 % of those found in plasma. The

calculated brain/plasma exposure ratios were approximately 0.12 for oseltamivir phosphate and 0.01 for oseltamivir carboxylate. The calculated CSF/plasma exposure ratios were approximately 0.07 for oseltamivir phosphate and 0.007 for oseltamivir carboxylate. The study describes basic pharmacokinetics of oseltamivir phosphate and oseltamivir carboxylate after single oral administration. It also shows that relatively small amounts of the parent compound and the metabolite penetrate into the CNS.

2) The study report 1029346 contains data on the effect of oseltamivir phosphate in the modified Irwin test and of effect on body temperature following single oral administration in the rat. The company has previously reported as part of safety pharmacology studies (Roche report number W-142972) that oseltamivir phosphate up to doses (as phosphate salt) 1000 mg/kg as a single oral dose did not have any observable effects in male Sprague Dawley rats. Furthermore, oseltamivir phosphate had no effects on Irwin test, locomotor activity, and in other studies involving CNS function in CD-1 mice following the same dose levels (W-142690, W-142691, W-142971). In the present study report, the purpose of the study was to further evaluate possible effects of oseltamivir phosphate on CNS function as indicated by changes in behaviour, motor activity and coordination, sensory/motor reflex responses, or autonomic profile including the body temperature effects following a single oral administration in rats (500 mg/kg, 763 mg/kg and 1000 mg/kg free base). D-amphetamine (10 mg/kg p.o.) was used a positive control substance. Oseltamivir phosphate did not induce any effects on behaviour, motor activity and coordination, or sensory/motor reflex responses in male Sprague-Dawley rats. A slight transient dose independent decrease in the body temperature was noted one hour post dosing; this was not considered relevant. Therefore, the no-observed adverse effect level (NOAEL) is considered to be equal to or greater than 1000 mg/kg per os.

3) In the study described in the study report Gilead study no 96-TOX-4104-003, Ro 64-0796 was given orally for 28 days at 0, 2 x 50, 2 x 150 or 2 x 500 mg/kg/day for one month to marmoset monkeys. A subset of animals was also followed 14 days after treatment. All animals survived the experimental period. Ro 64-0796 afforded high levels of the active drug, Ro 64-0802, within 3 hours of dosing. Exposure of the active drug was 5-20 times that of the prodrug. It was concluded that oral administration of Ro 64-0796 to marmosets at doses up to 2 x 500 mg/kg/day for one month did not lead to any major clinical toxic effects, and there were no adverse clinical pathological or histopathological changes at any doses.

- *Conclusions on preclinical studies with oral dosing*

Basic pharmacokinetics of oseltamivir and oseltamivir carboxylate after single oral administration in rats has been provided. It was shown that relatively small amounts of the parent compound and the metabolite penetrate into the CNS. Based on the reported effects of oseltamivir phosphate in rats, given as single oral doses up to 1000 mg/kg free base, in the modified Irwin test, oseltamivir phosphate does not seem to induce CNS-related behavioural, sensory or motor effects in the rat. This is consistent with the known pharmacological effect of the main active metabolite oseltamivir carboxylate, as a specific and selective inhibitor of the influenza virus neuraminidase. Long term exposure in rats has shown that oseltamivir phosphate given orally up to doses 2 x 500 mg/kg/day for one month is well tolerated and no toxicity was observed.

Juvenile rat studies performed with oral and subcutaneous dosing

- *Data submitted*

1) In the study described in the Roche Report 1027696, the toxicity of oseltamivir phosphate was investigated in juvenile (on postnatal day 7; PND) and compared to adult rats. Oseltamivir phosphate was given as a single oral administration. Oseltamivir phosphate was given orally to juvenile rats at doses 300, 500, 600, 700, 850 and 1000 mg/kg (free base) or deionised water as a control. There were no test item-related mortality or moribundity for juvenile rats at 300 mg/kg, or in adults in the 1000 mg/kg group. A dose related increase in test item-related mortalities was observed for juvenile rats at 500 mg/kg and above. Animals at 600 mg/kg and above had several behavioural findings including low arousal, tremors, convulsions, alterations in general body posture, respiration and hypoactivity showing toxicity of the test drug in juvenile rats. The NOEL of oseltamivir phosphate, when administered as a single oral dose to juvenile rats (PND 7), was 300 mg/kg (free base), and at least 1000 mg/kg for young adults (PND 42).

2) In the study described in the Roche Report 1029873, blood and brain concentrations of Ro 0840802-002 (active metabolite) were determined in juvenile rats after single subcutaneous injection

of this test compound at doses 25 mg/kg and 50 mg/kg. The rats were at the age of PND 7 (as in the above study and same strain, crl:CD(SD) rats). The pharmacokinetic parameters were analysed in plasma and in the brain. Subcutaneous administration of the test compound up to dose 50 mg/kg was well tolerated and did not induce any gross behavioural changes or clinical signs of overt toxicity in juvenile rats. Mean maximum plasma concentration were 44800 and 88900 ng/mL after 25 and 50 mg/kg doses, respectively. Brain penetration was low as indicated by brain/plasma ratios for Cmax and AUC (0-24h) of approximately 0.03 and 0.09, respectively.

- *Conclusions on preclinical studies with juvenile rats with oral and subcutaneous dosing*

Oseltamivir phosphate seems to be clearly more toxic in juvenile rats when compared to adult animals. This may be partly due to a lower conversion of the parent drug into the active form oseltamivir carboxylate than in adult animals. The NOEL-dose is 300 mg/kg orally as a single dose. Therefore, care must be followed when Tamiflu is given to neonate in clinical settings although the doses used in the present study are exceeding clinical doses by at least one order of magnitude. When single doses of the active metabolite were administered to juvenile rats subcutaneously, the active metabolite of oseltamivir was well tolerated when given at doses up to 50 mg/kg. The brain penetration was low.

Overall conclusion on non-clinical aspects

The non-clinical data provided by Roche supports that the compassionate use of intravenous Tamiflu with appropriate safety margins in adults. In adult animal studies, no toxicity has been observed at levels of oseltamivir which are 126- and 11-fold higher, based on Cmax and AUC, respectively, than for the IV dose of 100 mg in human adults. This margin is expected to be similar for children ≥ 1 year of age.

3.4 Clinical aspects

Introduction

To support the application of compassionate use of Tamiflu IV formulation, the company submitted the following clinical data:
- Four (4) pharmacokinetic studies with intravenous and oral administrations,
- Some data on clinical pharmacology,
- No efficacy data, as no studies have been conducted using the IV formulation to date,
- Four (4) clinical safety studies.

Pharmacokinetics

- Data submitted

To support the application of compassionate use of oseltamivir phosphate IV formulation 4 pharmacokinetic studies with intravenous and oral administrations have been presented (Table 2).

Table 2. Overview of submitted clinical studies

Study Number	Study Objectives	Study Design	Dosage, Route, Regimen	Country for Study Conduct
NP15718	To investigate the routes and rates of elimination of orally-dosed radiolabelled OP and IV-dosed OC	Open-label, single center, parallel group in 12 healthy male subjects	• Single 75 mg ^{14}C-labelled OP PO • Single IV infusion over 1 h of 75 mg ^{14}C-labelled OC	UK
NP15719	To determine the absolute bioavailability of the active species, OC, from OP after oral administration of OP	Open-label, single center, randomized, two-way cross-over study in 13 healthy male subjects	• Single 150 mg OP PO • Single IV infusion over 3 h of 150 mg OC	France
PP16361	To determine the PK of OP and its active metabolite, OC, in relationship to nausea and vomiting in healthy volunteers	Randomized, double-blind, placebo-controlled, single ascending dose study in 32 healthy male volunteers	• Single IV infusion over 1 h of 15 mg, 45 mg, and 105 mg OP • Single IV infusion over 1 h of 150 mg OC	UK
WP20727	To examine the pharmacokinetics, safety and tolerability of three single IV infusion doses of Ro 64-0796/F08 (100, 200 and 400 mg each infused over 2h) and a single PO dose of Tamiflu 75 mg.	Single dose, open-label, randomized, two-sequence study in healthy male and/or female volunteers	• Single 75 mg PO • Single 100 mg IV infusion over 2 h • Single 200 mg IV infusion over 2 h • Single 400 mg IV infusion over 2 h	France

OP, oseltamivir phosphate; OC, oseltamivir carboxylate; PO, per os; h, hour.

Oseltamivir carboxylate (Ro 79-0802), the active metabolite of oseltamivir (also called oseltamivir phosphate, Ro 64-0796) has poor bioavailability and is therefore used as the pro-drug. The pro-drug oseltamivir phosphate is converted by hepatic carboxylesterase-1 (HCE1) to oseltamivir carboxylate and the drug is excreted renally mainly as the active metabolite.

The analytical methods and the methods for pharmacokinetic data analysis have been assessed during the evaluation of the documentation for oral formulation and will not be discussed in this assessment report. The pharmacokinetic data have been presented by listing and descriptive summary statistics.

- **Study NP15718**

Total recovery of radioactivity in urine was approximately 74 % over a 7-day period after single oral dose of 75 mg of ^{14}C-labelled oseltamivir phosphate (Table 3). About 17 % of oseltamivir phosphate dose was recovered in faeces. After intravenous administration of 75 mg of ^{14}C-labelled oseltamivir carboxylate (the active metabolite) over 1 hour the recovery of total radioactivity in urine was 97.2 % (Table 4). No metabolites besides the active moiety were found. Active metabolite was the major radioactive component found in plasma, with a small contribution of unchanged pro-drug.

Table 3. Mean pharmacokinetic parameters of total radioactivity, oseltamivir and oseltamivir carboxylate after administration of a single oral dose of approximately 75 mg of ^{14}C-labelled oseltamivir phosphate (50µCi).

Parameter	**Total radioactivity**	**Oseltamivir Ro 64-0796**	**Oseltamivir carboxylate Ro 64-0802**
C_{max} (ng/mL)	357 (67)	45.7 (19.0)	252 (58)
T_{max} (h)	3.50 (0.55)	1.01 (0.44)	4.17 (0.98)
AUC (ng*h/mL)	5290 (959)	84.1 (13.4)	2870 (519)
$t_{1/2}$ (h)	9.02 (2.19)	1.01 (0.55)	6.34 (1.20)
% Excreted urine	73.6 (3.0)	4.75 (0.47)	80.6 (2.3)
Cl_r (L/h)	-	44.7 (9.5)	20.6 (3.7)
% Excreted faeces	17.2 (2.4)	-	-

Table 4. Mean pharmacokinetic parameters of total radioactivity and oseltamivir carboxylate after administration of a single intravenous dose of approximately 75 mg of oseltamivir carboxylate containing 25µCi of ^{14}C-labelled oseltamivir carboxylate

Parameter	**Total radioactivity**	**Oseltamivir Ro 64-0796**	**Oseltamivir carboxylate Ro 64-0802**
C_{max} (ng/mL)	2590 (522)	-	2290 (488)
T_{max} (h)	0.92 (0)	-	0.94 (0.07)
AUC (ng*h/mL)	4520 (1370)	-	3920 (1150)
$t_{1/2}$ (h)	1.13 (0.28)	-	1.11 (0.21)
% Excreted urine	97.2 (2.4)	-	99.9 (4.0)
Cl_r (L/h)	-	-	19.7 (6.78)
% Excreted faeces	0.30 (0.14)	-	-

- **Study NP15719**

The absolute bioavailability of oseltamivir carboxylate from oseltamivir phosphate was determined based on oral administration of 150 mg oseltamivir phosphate and intravenous infusion of 150 mg oseltamivir carboxylate over 3 hours. The absolute bioavailability of oseltamivir carboxylate was 79.0 % based on AUC comparison from plasma and 80.1 % based on urinary excretion data.

- **Study PP16361**

The pharmacokinetics of oseltamivir and oseltamivir carboxylate in relationship to nausea and vomiting was assessed after intravenous infusion of the pro-drug oseltamivir phosphate (15 mg, 45 mg, 105 mg) for 1 hour and intravenous infusion of 105 mg of the metabolite oseltamivir carboxylate for 1 hour.

The C_{max} and AUC_{inf} of oseltamivir following 15 mg and 45 mg of oseltamivir phosphate over 1 hour were similar to those following oral administration of 75 mg and 200 mg of oseltamivir phosphate. Mean half-lives, apparent clearance, renal excretion and renal clearance of oseltamivir carboxylate were similar to those after oral administration. The clearance and V_{ss} tended to increase with increasing dose. Intravenous infusion of 150 mg oseltamivir carboxylate delivered a mean C_{max} of 5090 ng/mL that is higher than the C_{max} associated with 1000 mg oral dose of oseltamivir phosphate.

It was concluded that nausea and vomiting were associated with oral administration of oseltamivir phosphate due to local gastrointestinal effect.

- **Study WP20727**

Table 5. Summary of Study design WP20727

Period	Sequence 1 (n=12)	Sequence 2 (n=12)
A1	PO 75 mg SD	I.V. 100 mg /2 h SD
A2	I.V. 100 mg/2 h SD	PO 75 mg SD
A3	I.V. 200 mg/2 h SD	I.V. 200 mg/2 h SD
A4	I.V. 400 mg/2 h SD	I.V. 400 mg/2 h SD

Oseltamivir phosphate is extensively converted to the active metabolite oseltamivir carboxylate (Ro 64-0802) by hepatic carboxylesterase-1 (HCE1) (over 90 %). The pharmacokinetic parameters of the active metabolite Ro 64-0802 after infusion of 100 mg of the pro-drug oseltamivir phosphate (Ro 64-0796) for 2 hours were similar to the 75 mg dose given orally (Table 6). Geometric mean maximum concentrations of 215 ng/mL and 240 ng/mL were attained after a median time of 5.0 and 4.0 h for the 75 mg PO and 100 mg/2h IV treatments, respectively. The primary PK parameters of Ro 64-0802 C_{12} and $AUC_{0-\infty}$ were also similar for these treatments although exposures were marginally higher following the 100 mg/2 h IV treatment than after the oral administration.

Comparison of the three IV dose regimens (100, 200 and 400 mg IV) through graphical exploration of their PK parameters showed that there was a dose linearity in the exposure to Ro 64-0802 between the 3 dose regimens.

Table 6. Summary of the pharmacokinetic parameters of the active metabolite oseltamivir carboxylate (Ro 64-0802) after oseltamivir phosphate (Ro 64-0796) oral or IV for 2 hours (mean ± SD) in study WP20727

	75 mg PO N = 24	100 mg IV N = 24	200 mg IV N = 23	400 mg IV N = 22
C_{max} (ng/mL)	215 (22.8)	240 (20.4)	478 (21.8)	977 (19.9)
C_{min} (ng/mL)	104 (16.9)	131 (16.7)	265 (16.5)	551 (14.0)
AUC_{inf} (ng•h/mL)	3060 (19.4)	3840 (17.0)	7860 (15.1)	16200 (14.9)
T_{max} (h) *	5	4	4	5
$t_{½}$ (h)	7.73 (29.4)	8.81 (22.1)	9.05 (20.5)	9.00 (20.0)

Exposure to oseltamivir (Ro 64-0796) after IV administration of 100 mg/2h was approximately 3.1-fold higher for C_{max} and 3.9-fold higher for $AUC_{0-\infty}$ when compared to the oral 75 mg oseltamivir dose (Table 7). This is because oseltamivir is extensively metabolized by hepatic carboxylesterase and, when oseltamivir is given intravenously, first pass metabolism is avoided.

Table 7. Summary of Oseltamivir Geometric Mean Pharmacokinetic Parameters (CV%) by Dose Regimen.

	75 mg PO N= 24	100 mg IV N= 24	200 mg IV N= 23	400 mg IV N= 22
C_{max} (ng/mL)	84.1	263 (23.6)	548 (28.2)	1100 (20.2)
AUCinf (ng•h/mL)	140	540 (27.1)	1150 (32.7)	2360 (28.3)
$t_{½}$ (h)	1.7	1.54 (33.3)	1.76 (32.6)	1.82 (57.0)

- Absorption:

The absolute bioavailability of the metabolite oseltamivir carboxylate has been analysed based on treatment with oseltamivir phosphate orally and oseltamivir carboxylate intravenously. Oseltamivir phosphate is a highly bioavailable pro-drug with absolute bioavailability of about 80 % to the metabolite oseltamivir carboxylate.

- Distribution:

Volume of distribution, V_{ss}, of oseltamivir phosphate was 95.8 L (42.5), 116 L (12.8) and 144 L (43.7) after 15mg, 45 mg and 105 mg of oseltamivir intravenously for one hour, respectively (Report PP16361). After oral administration of 75 mg of oseltamivir the distribution, V/F, value of oseltamivir was 1320 L (Report WP20707).
Volume of distribution, V_{ss}, of oseltamivir carboxylate (Ro 64-0802) was 25.6 L (6.22) following intravenous dose of 150 mg of Ro 64-0802 over 1 hour.

- Elimination:

The mean half-live values of oseltamivir phosphate after IV and oral administrations were similar. The mean half-life varied between 1.5 h and 1.8 h after 100-400 mg of oseltamivir compared to 1.7 h after 75 mg of oseltamivir orally. (Report WP 20727)
Mean half-life of the metabolite oseltamivir carboxylate was 7.7 h after oral dose of 75 mg of the pro-drug oseltamivir phosphate and 8.8 h, 9.1 h and 9.0 h after intravenous infusion for 2 hours after 100 mg, 200 mg and 400 mg of oseltamivir, respectively. (Report WP20727)
The elimination half-life of oseltamivir carboxylate following IV administration of Ro 64 0802 (1-2 h) was shorter than the half-life following oral administration of oseltamivir (6-10 h).

- Excretion:

Excretion of oseltamivir has been studied. Subjects received either a single dose of 75 mg of ^{14}C-labelled oseltamivir phosphate (50 µCi) orally or an intravenous dose of 25 mg of ^{14}C-labelled oseltamivir carboxylate (Ro 64-0802) (25 µCi) over 1 hour. Each dose was received by six subjects. (Report NP15718)
Excretion into urine was rapid after the oral dose. Most of the radioactivity of oseltamivir phosphate was recovered in urine during the first 24 hours and total recovery into urine was approximately 74 % of dose over a 7-day period. About 17 % of the dose was excreted into faeces. No metabolites besides the active moiety were found in urine. The primary components of the radioactivity were the active metabolite oseltamivir carboxylate and oseltamivir.
Excretion of the radioactivity after intravenous dose was rapid and most of the radioactivity appeared in urine within 8 hours after dosing. Total recovery in urine was 97.2 % of the dose. Only 0.30 % of the dose was found in faeces. The elimination rate of oseltamivir carboxylate is more rapid following intravenous infusion compared to its elimination when oseltamivir phosphate is give orally.
Urinary excretion has also been determined after single intravenous dose of 150 mg of oseltamivir carboxylate over 3 hours (Report NP15719). Excretion of oseltamivir carboxylate into urine was 93 %.
The studies show that renal excretion is the main elimination pathway. Renal secretion of oseltamivir carboxylate occurs via organic anion transporters (OAT).

- <u>Interconversion:</u>

No interconversion of oseltamivir carboxylate to oseltamivir is likely to occur as oseltamivir concentrations were not measurable after 75 mg of Ro 64-0802. (Report NP 15718).

- Dose proportionality:

The results of the single dose pharmacokinetic study (WP20727) show that the pharmacokinetics of oseltamivir, Ro 64-0796, and its metabolite Ro 64-0802 are linear after ascending IV doses of oseltamivir between 100 mg and 400 mg for 2 hours. The metabolite Ro 64-0802 concentrations are similar after 100 mg of Ro 64-0796 IV for 2 hours compared to a single oral dose of Ro 64-0796 (75 mg). The result for dose proportionality is consistent with oral administration of oseltamivir.

- Special populations:

    - Renal impairment and renal replacement therapy

Since renal impairment maybe a significant element in critically-ill influenza patients, the company has provided dosing instructions for these situations.

As oseltamivir is mainly excreted via kidneys in urine the proposed IV dosing in patients with severe renal impairment (CrCL between 10 to 30 mL/min/1.73 m^2) should be decreased to 40 mg intravenously over 2 hours once daily. In patients with moderate renal impairment (CrCL between 30 to 60 mL/min/1.73 m^2) the proposed dosing should be decreased to 40 mg intravenously over 2 hours twice daily.

For patients with renal impairment, creatinine clearance (CrCL) should be estimated using the modified Schwarz equation for adolescents and children, and the Cockcroft-Gault method for adults (see appendix 1 for the calculation of creatinine clearance).

There are currently limited data to recommend dosing regimens for oral oseltamivir for patients undergoing routine haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) treatment with end-stage renal disease (ESRD).

The proposed IV dose for patients undergoing routine haemodialysis (HD) is 40 mg infused over 2 hours following each routine HD session and for patients on continuous ambulatory peritoneal dialysis (CAPD) a single 40 mg IV dose infused over 2 hours for the full 5 day treatment period is suggested.

The company provided justification for IV dose in HD and CAPD patients based on the data submitted to support the revision of the oral formulation dosing recommendations in renally impaired patients (please refer to variation II-86 for Tamiflu). In the frame of this procedure, the MAH provided the data from two clinical studies (studies PP15974 and NP16472). Study PP15974 was a single oral dose, multi-centre, open label study of the pharmacokinetics, safety and tolerability of oseltamivir in end-stage renal disease subjects on hemodialysis and peritoneal dialysis. Study NP16472 was a single centre, open label multiple dose oral oseltamivir suspension study in end-stage renal disease patients on haemodialysis and continuous ambulatory peritoneal dialysis (CAPD).
It was found in the study assessing the pharmacokinetics and safety of a single 75 mg OP dose in HD and CAPD patients (study PP15974) that OC levels increased in both patient-groups to the levels where the amount of safety information is still not sufficient. Therefore, this dosing regimen was not recommended. Study NP16472 provided valuable clinical data of the long-term use of OP in HD and CAPD patients both in treatment and prevention of influenza. The results showed that an oral dose of 30 mg OP administered once weekly in CAPD patients delivers the OC levels found efficient in prevention of influenza (32 ng/mL) during the whole 6.5 week study period. The same 30 mg OP dose was estimated adequate also for 5-day treatment of influenza in CAPD patients although the mean OC concentration at 120 hours post dose (147 ng/mL) was just under the mean trough concentration of the 75 mg twice daily regimen in previous studies treatment studies of healthy subjects (153 ng/mL). Based on this study, the dosing regimen used in CAPD patients (oral dose of 30 mg once weekly) was estimated as adequate and safe for both treatment and prevention of influenza.
In subjects with normal renal function 100 mg IV provides similar OC exposure as 75 mg PO (~30% increase in dose for IV). Therefore, a 40 mg IV dose of oseltamivir in patients on CAPD would be expected to deliver similar OC exposure as 30 mg PO. This can be considered appropriate.
The study did not however give the answer whether the patients on automated peritoneal dialysis (APD) should follow the same treatment regimen as the CAPD patients. Therefore, the MAH has been requested to include a statement in relation to PD patients that available data is derived from the studies done in CAPD patients and the clearance of OC is probably higher when APD mode is used and therefore the treatment mode can be switched from APD to CAPD during the OP treatment if considered necessary by nephrologists. In addition, the MAH has proposed to collect clinical PK data in subjects on APD in order to evaluate any changes in OC clearance. This data can be used to determine if an alternate dosing regimen is necessary for patients on APD.

According to the study NP16472, the 30 mg OP oral dose administered after alternate dialyses in HD patients provided an exposure to OC which was, just as in CAPD patients, well above the plasma concentrations shown clinically effective for prevention of influenza in other patient groups. The drug was relatively well tolerated despite the relatively high AUC values. The dosing regimen of the study was considered adequate and safe for the prevention of influenza in HD patients. The MAH also developed a population pharmacokinetic model to predict plasma concentrations of oseltamivir and the active metabolite oseltamivir carboxylate (OC) which was based on the data from traditional frequent-sampling pharmacokinetic studies on 65 healthy subjects and 15 subjects with renal impairment. Based on the report of pharmacokinetic modelling and simulation, the dosing regimen of 30 mg after every dialysis for treatment of influenza in HD patients was considered appropriate. Therefore, the corresponding intravenous dose of 40 mg after every dialysis session was considered adequate by the CHMP.

Very limited clinical data are currently available following oral oseltamivir administration in patients undergoing Continuous Renal Replacement Therapy (CRRT). The extrapolation to CRRT patients is based on one continuous venovenous hemofiltration (CVVH) in vitro study (Gruber et al, 2007, International Journal of Antimicrobial Agents 30 (2007) 93–100) where the results suggest that clearance of oseltamivir can be estimated from the ultrafiltration rate. Several different kinds of CRRT exist, including CVVH, continuous arterio-venous hemofiltration (CAVH) or hemodiafiltration (CVVHDF or CAVHDF). Drug clearance differences are generally not clinically significant between different types of CRRT at the same total effluent (dialysate + formed ultrafiltrate) rates. The total effluent rate can therefore be used to approximate the OC clearance by CRRT (CLCRRT). Depending on the type of CRRT, the effluent rate can range from approximately 10 to 50 ml/min with the target dose of delivered therapy being 35 ml/h/kg (approximately 35 ml/min). Any residual renal function the patient has can be estimated and added to CLCRRT to estimate total renal clearance. It is assumed that the contribution of active tubular secretion to OC renal clearance would be negligible in these patients. Based on this range, the proposed recommendations for dosing in patients on CRRT are:
- 40 mg over 2 hours twice daily for patients with an estimated CrCl > 30 ml/min
- 40 mg over 2 hours once daily for patients with an estimated CrCl between 10-30 ml/min

Further to the assessment of the limited data submitted for this special population the CHMP concluded the following for the compassionate use of Tamiflu IV formulation:

- Patients with renal impairment

In case of renal impairment, special dosing instructions must be followed. No dose adjustments/modifications are required for patients whose creatinine clearance (CrCL) is > 60 ml/min (adults) or > 60 ml/min/1.73 m2 (adolescents aged 13 to < 18) In adults and adolescents, the dose and frequency of administration should be decreased to 40 mg IV over 2 hours twice daily in patients with moderate renal impairment (CrCl 30 to 60 ml/min – adults or 30 to 60 ml/min/1.73 m2 – adolescents aged 13 to < 18). In adults and adolescents, the dose and frequency of administration should be decreased to 40 mg IV over 2 hours once daily in patients with severe renal impairment (CrCl 10 to 30 ml/min – adults or 10 to 30 ml/min/1.73 m2 – adolescents aged 13 to < 18). In the event that CrCL falls below 10 mL/min/1.73 m^2 and the patient is receiving renal replacement therapy, see below.
If the investigator feels that renal function is compromised, dosing may be decreased to 40 mg once daily or withheld until CrCL results (measured or calculated) are available. Dosing may then be resumed, as appropriate, based on CrCL. However, it is vital that dosing not be inappropriately withheld for extended periods of time especially in the first 3 days of treatment when viral titers may be high.
CrCL should be estimated using the modified Schwarz equation for adolescents and the Cockcroft-Gault method for adults

- Renal Replacement Therapy

Adolescents and adults > 13 years of age

The IV doses derived below for patients undergoing routine haemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) treatment with end-stage renal disease (ESRD) and patients undergoing continuous venovenous hemofiltration (CVVH) are based on limited data from two oral pharmacokinetic studies. The recommendations are based on a 5 day treatment period. If required the drug may be given to cover a 10 day treatment period but patients should not be dosed for a period greater than 10 days. In these patients, the drug continues to accumulate with each dose administered.

Table 8 Dosing in Adults and Adolescents (13 years of age and older) with Moderate/Severe Renal Impairment, on CRRT, Intermittent Hemodialysis or Continuous Ambulatory Peritoneal Dialysis

Type of Patient		Dose (mg)	Frequency	Duration (Days)
Severe/Moderate Renal Impairment (CrCl)	> 30 to 60 ml/min	40 mg over 2 hours	q 12 h	5
	10 to 30 ml/min	40 mg over 2 hours	q 24 h	5
	< 10 ml/min	Not recommended (no data available)		
CRRT	> 30 ml/min[1]	40 mg over 2 hours	q 12 h	5
	10 to 30 ml/min[1]	40 mg over 2 hours	q 24 h	5
Intermittent Hemodialysis (HD)		40 mg over 2 hours	After each HD Session[2]	5
Continuous Ambulatory Peritoneal Dialysis (CAPD)[3]		40 mg over 2 hours	one dose[4]	5

[1] Total renal clearance of oseltamivir carboxylate should be estimated by adding together CL_{CRRT} and residual renal function (CL_{CRRT} + CrCl).
[2] Hemodialysis – The first 40 mg dose should be administered within 96 hours of onset of symptoms, then administer a 40 mg dose 1 hour after each HD session during the 5-day treatment period.
[3] Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.
[4] A single 40 mg intravenous dose of oseltamivir is expected to provide therapeutic exposure for the full 5-day treatment period.

Children and adolescents less than 13 years

No dosing recommendations are available for this age group.

Clinical pharmacology

When oseltamivir phosphate is administered intravenously to healthy volunteers over 1 hour the exposure to oseltamivir is significantly higher than that achieved orally, the exposures being comparable between 15mg IV and 75mg PO as well as between 45 mg IV and 200mg PO. This is due to the lack of first pass metabolism which is dominant after oral dosing. The elimination half-life of oseltamivir is similar after oral and IV dosing (1.5-1.7h). If the active metabolite is given IV the half life is much shorter after IV (1-2 h) than after oral dosing (6-10h). Therefore, for IV dosing, the use of the pro-drug oseltamivir phosphate intravenously is justified. However, oseltamivir carboxylate should be considered as a useful compound for development as an IV-formulation for critically ill infants.
Recent clinical studies as well as modeling and simulation studies have predicted that twice daily administration of 100 mg of oseltamivir as IV infusion over 2 hour period would achieve similar Ro 64-0802 pharmacokinetic profile (Figure 1) as that achieved with an oral dose of 75 mg twice daily although the concentrations of the pro-drug are 3-4 times higher for C_{max} and AUC_{inf} (Figure 2). The high concentration of the pro-drug may be a significant safety concern especially in babies and small children, since increased toxicity have been observed in young animals and clinical data is not available.

Figure 1. Mean Plasma Concentration-time Profiles of Ro 64-0802 after Single Doses of 100 mg IV vs. 75 mg PO Oseltamivir

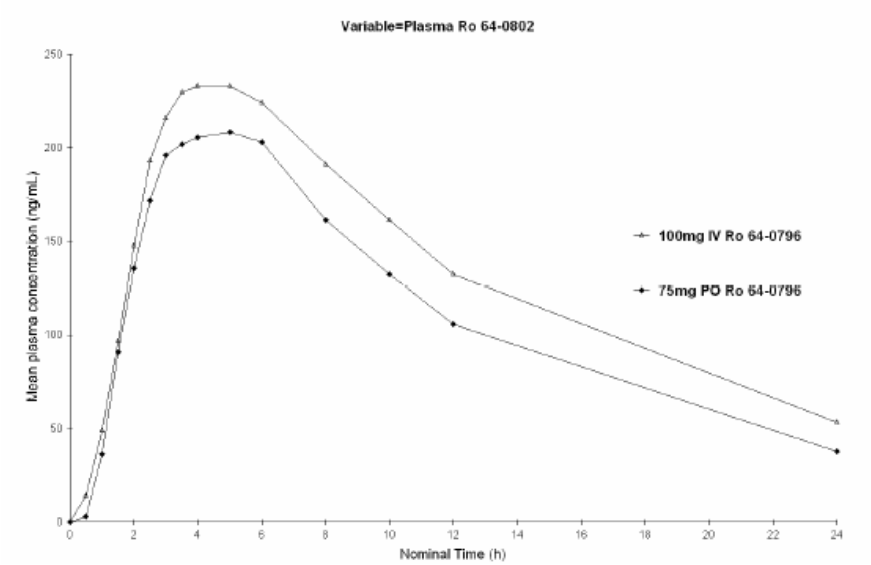
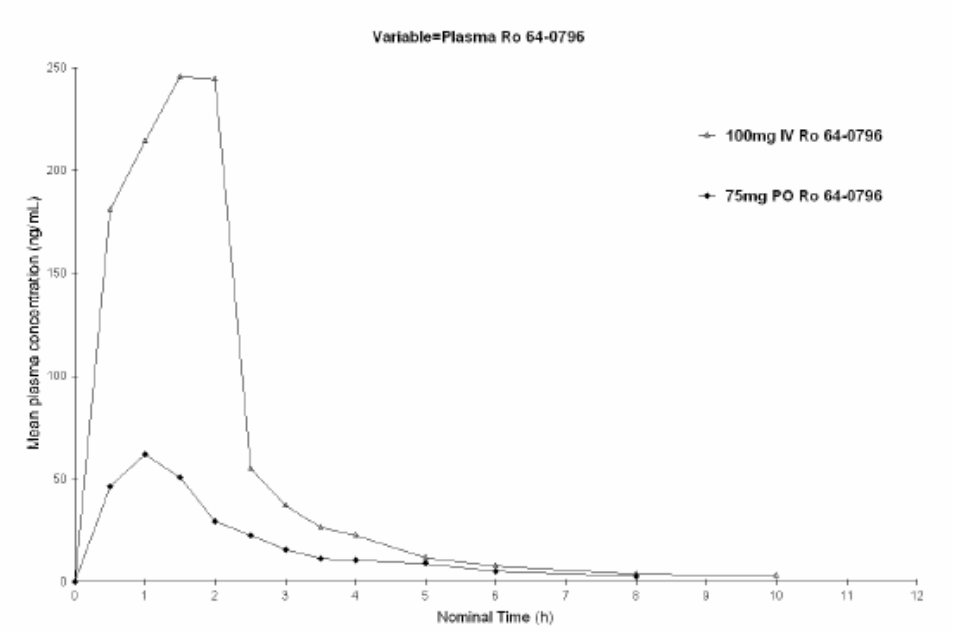


Figure 2. Mean Plasma Concentration-time Profiles of Ro 64-0796 after Single Doses of 100 mg IV vs. 75 mg PO Oseltamivir



When submitting the dossier to support this compassionate use, the company proposed the following dosing recommendations:

Adolescents and adults > 13 years

100 mg IV BID (twice daily) infused at a constant rate over 2 hours

Children 1 to 12 years

Must be infused at a constant rate over 2 hours
Weight ≤ 23 kg: 3 mg/kg BID (twice daily)
Weight > 23 to 40 kg: 2.5 mg/kg BID (twice daily)
Weight > 40 kg: same as adults – 100 mg BID (twice daily)

Infants birth to 1 year post natal age

No recommendations possible.

The doses recommended for children greater than 1 year of age were justified based on exposure data from adults comparing 100 mg/2 hours dose to the 75 mg oral dose. A similar adjustment in dose has been made for children when going from oral to IV administration. In study WP20727 75 mg PO and

100 mg/2h IV gave similar OC levels in healthy adults and, therefore, it can be estimated that 1.33 x the oral dose should be given IV. Based on the current oral dosing in children over 1 year of age, the 1.33 x-dosing would be: between 2.7-4 mg/kg when weight is ≤15kg, between 2.6-4 mg/kg when weight is ≤23 kg, between 2.0-3.5mg/kg when weight is > 23 to 40 kg and below 2.5mg/kg when weight is > 40 kg. Therefore, the dosing proposal can be justified. However, a twice daily dosing is advised.

A dose recommendation for children under 1 years of age has not been provided by the company. No recommendations are possible at this stage given the absence of data on safety and pharmacokinetics in this very young population following Tamiflu IV.
However, and for information only, the CHMP decided that the doses that are to be investigated in a planned paediatric clinical study should be included in the adopted conditions for use.

The company has proposed IV dosing of oseltamivir phosphate 100mg/2h BID for compassionate use for adults and adolescents (>13 years). The dosing proposal has also been made for children over 1 year of age and for patients with renal impairment. The dose recommendations are acceptable based on estimates of exposures compared to approved oral dosing.

The recommended dosages adopted by the CHMP in the context of this compassionate use of Tamiflu IV are as follows:

- **Dosing recommendations**

Adolescents and adults > 13 years
100 mg IV BID (twice daily) infused at a constant rate over 2 hours.

Children 1 to 12 years
Weight ≤ 23 kg: 3 mg/kg
Weight > 23 to 40 kg: 2.5 mg/kg
Weight > 40 kg: same as adults – 100 mg
The doses listed immediately above should be infused at a constant rate over 2 hours BID (twice daily).

Infants < 1 year post natal age
For infants below 1 year of age, no recommendations can be given at this stage due to the absence of pharmacokinetic and safety data on the use of intravenous oseltamivir in this very young population. Should a physician decide to treat an infant below 1 year of age, the decision should be taken based on assessment of benefit and risk for the individual.

For the purposes of information only, the following doses are to be investigated in clinical study NP25138 for infants with post natal age less than 1 year, who were born with a gestational age of ≥ 37 weeks as calculated from menstrual dates:
- Age 91 to < 365 days: 3 mg/kg
- Age 31 to 90 days: 2.5 mg/kg
- Age 0 to 30 days: 2 mg/kg

The doses listed immediately above should be infused at a constant rate over 2 hours BID (**twice daily**). These doses were selected based upon preliminary results from modeling and simulation.

The usual duration of oseltamivir treatment is 5 days. If the investigator believes that the duration of treatment should be extended, this will be at the discretion of the treating clinician.

Premature infants
The dosing information provided above is not intended for premature infants with a gestational age of less than 37 weeks (by menstrual date).

Clinical efficacy

No efficacy studies have been conducted using the IV formulation to date. The company has provided two references as for Critical review of available authorised methods of prevention, medical diagnosis or treatment and justification as to why the target patients can not be treated satisfactorily by the methods reviewed, supported by clinical information or scientific literature. The article below reports that in serious cases antiviral treatment may be of clinical benefit.

- Jain S, Kaminoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med. 2009;361. [This article (10.1056/NEJMoa0906695) was published on October 8, 2009, at NEJM.org.]

The company has concluded that currently, there remains an unmet medical need for an intravenous (IV) neuraminidase inhibitor to treat influenza in patients who cannot tolerate, swallow or absorb orally administered medications. The company's suggestions for these situations where patients are likely to benefit from an IV neuraminidase inhibitor over a systemically available, oral formulation include:

• critically ill patients (e.g. impaired conscious level, intubated, or those experiencing other complications of influenza such as encephalitis)
• where concern exists that poor/erratic absorption is possible (e.g. diarrhoea, vomiting, ileus)
• non-critically ill patients unable to tolerate, or swallow medications (e.g. due to disease, concurrent surgical procedure, anaesthesia)

The CHMP is of the view that in the frame of its compassionate use, Tamiflu IV should be considered only to treat critically ill adults and children older than 1 year of age having a life-threatening condition due to suspected or confirmed pandemic (H1N1) infection or infection due to seasonal influenza A or B virus and answering to the following criteria:

(1) patients not responding to either oral or inhaled authorised antiviral medicinal products, or
(2) patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.

For infants below 1 year of age, no recommendation can be given at this stage due to the absence of pharmacokinetic and safety data on the use of Tamiflu IV in this very young population. Should a physician decide to treat an infant below 1 year of age, the decision should be taken based on the assessment of the benefit and risk for the individual.

Clinical safety

- Patient exposure

	Study number	Patients exposed
Placebo-controlled	PP16361	6 (15mg IV), 6 (45mg IV,) 6 (105 mg IV)
		6 (150mg IV oseltamivir carboxylate)
	NP15718	
		6 (75mg IV oseltamivir carboxylate)
Open studies	NP15719	13 (150mg IV oseltamivir carboxylate)
	WP20727	6 (100mg), 6 (200mg), 6 (400mg)

- Adverse events (AEs)

Adverse events were collected from the 4 following safety studies:

Study NP15718 (6 males, 75mg 14C-labelled oseltamivir carboxylate IV, 1h infusion)

No difference was demonstrated in the incidence of adverse events between the p.o. group and the IV group. All of the adverse events in the IV group were considered to be unrelated to treatment. The injection site inflammation reported in the p.o. group was considered to be unrelated to treatment; the other adverse events in the p.o. group were considered to be remotely related. Two subjects, both in the IV group, reported adverse events during the 'off treatment' period (those occurring later than 2

days after the end of study treatment). Only headache and nausea were considered to be remotely related, the other two were unrelated.

Study NP15719 (13 males, 150mg oseltamivir carboxylate IV, 3 h infusion)
No deaths or Serious Adverse Events (SAE) were reported. The majority of adverse events were graded as mild in intensity. The only adverse events considered by the investigator to be possibly related to treatment were headache and flatulence. A number of subjects displayed levels of bilirubin above the upper limit of the standard reference range. Fasting conditions may have been a contributing factor.

Study PP16361 (Ascending dose study: 6 males 15mg IV, 6 males 45mg IV, 6 males 105 mg IV over 1 h infusion OP, 6 males 150mg OC).
One (1) subject in the placebo group had low then high phosphate levels during the study. At follow up the value was normal. One (1) subject in the 45 mg IV infusion study had high phosphate and another had low platelets. Both abnormalities returned to normal. Two (2) subjects in the 150 mg IV oseltamivir carboxylate group experienced hypotension with an attendant cluster of symptoms (dizziness, sweating, blurred vision, nausea, and feeling hot). Hypotension was not observed with IV infusions of oseltamivir phosphate.

Study WP20727
There were no deaths in the study. The incidence of adverse events throughout the study was low. The overall incidence of adverse events was higher in the 400 mg IV group (59%) compared with the 75 mg oral (8%), 100 mg IV (17%), and 200 mg IV (13%) groups, primarily due to the incidence of infusion site pain, which was reported only in the former group (50%). The 400 mg IV dose equates to an oseltamivir concentration of 8 mg/mL. The company proposed a warning statement in the conditions for use that OP must never be reconstituted to a concentration greater than 4 mg/mL. This warning has been agreed by the CHMP and has been introduced in the adopted conditions for use under "Special warnings and precautions for use".

The incidence of adverse events was higher in sequence 1 than in sequence 2 (Table 9) although review revealed no indication of a sequence effect. AEs remotely related to study drug were dyspepsia (at 100 mg IV), ventricular extrasystoles and mild sleep disorder (single nightmare) (at 200 mg IV), and skin reaction (reaction to sticking plaster, at 400 mg IV). There were only possibly related AEs which were abdominal pain (75 mg PO) and headache (400 mg IV), and no probably related AEs for the 75 mg PO, 100 mg IV or 200 mg IV dose regimens.

Table 9. Overview of adverse events in study WP20727

	Sequence 1	Sequence 2
Total No. of AEs	14	12
No of Subjects with any AE	9	6
Severe AEs	1	-
Life threatening AEs	-	-
Related AEs	10	9
Serious AEs	-	-
Deaths	-	-
Premature Withdrawals for AEs and laboratory adverse events	-	1

One (1) subject was withdrawn prematurely from the study due to an adverse event (subject 107067/1011 withdrew due to ventricular extra-systoles in Period 3), following the 200 mg IV dose of Ro 64-0796 (OP). The patient presented with premature ventricular contractions for which an external cardiologist diagnosed as pre-existing ventricular extra-systoles. This event was mild in intensity and was considered as remotely-related to treatment by the investigator.

No subject had their dose modified for AEs or laboratory abnormalities. However one subject had the dosing schedule delayed by approximately 6 hours to accommodate additional safety results due to suspicion of thrombocytopenia, with no dose modification. One (1) subject had a markedly low platelet count on Period 2 Day 5 after treatment with 75 mg Ro 64-0796 PO.

There were no clinically significant or dose-dependent (group mean) changes from baseline (defined as Day 1 pre-dose within each period) in electrocardiogram parameters in any dosing group. There was no individual QT, QTcB or QTcF value > 500 milliseconds (ms) and no individual change from baseline in QT or QTcB of > 60 ms. There were 3 subjects with QTc readings within the 450 to 500 ms range, none of these QTc values were considered as being clinically significant by the investigator. One (1) subject exhibited an increase from baseline of > 30 ms (but less than 55 ms) in QTcF, 4 hours after the administration of 400 mg IV Ro 64-0796 in Period 4 only. QTcF remained elevated up until follow-up (approximately 3 days post-dose) although the plasma concentrations of both Ro 64-0796 and its Ro 64-0802 would be expected to be minimal within 48 hours of the last dose. There were no changes in vital signs at doses of 75 mg Ro 64-0796 PO or from the three Ro 64-0796 IV.

- Discussion on clinical safety

In studies NP15718, NP15719 and PP16361, IV administration of oseltamivir phosphate and oseltamivir carboxylate were well tolerated. The incidence of adverse events was similar in the oral and IV dose groups in studies NP15718 and NP15719. Headache and gastrointestinal events were the most common adverse events in studies NP15719 and PP16361.

When oseltamivir carboxylate 150mg was given IV in Study PP16361, 2 subjects experienced hypotension concomitantly with a cluster of symptoms (dizziness, sweating, blurred vision, nausea, and feeling hot). However, slower oseltamivir carboxylate infusions did not induce hypotension (150 mg IV infused over 3 hours in study NP15719 or 75 mg oseltamivir carboxylate infused over 1 hour in study NP15718). IV infusions of oseltamivir phosphate did not induce hypotension in study PP16361. Previously, hypotension has not been observed with oral oseltamivir administration of therapeutic or high doses.

In study WP20727, overall incidence of adverse events was (59% in 400 mg IV group, 13% in 200 mg IV group, 17% in 100 mg IV group) more common during IV administration compared with the 75 mg oral administration (8%). A single case of ventricular extrasystoles (VES) was reported in a subject (200 mg IV dose, study WP20727) with a family history of VES. A relationship to test drug could not be ruled out, although a cardiologist did not consider the event to be related to the test drug. The applicant has discussed acute toxicity of oseltamivir in the Clinical Overview. In earlier studies with mice, a bolus injection of 100 mg/kg of oseltamivir has resulted in death of some mice but the same dose at a slower infusion rate was well tolerated. This has been thought to be related to the rate of IV infusion of the prodrug and maximum plasma concentrations. Therefore, the 3- to 4-fold higher oseltamivir concentrations and exposures achieved with the proposed 100mg IV/2h dosing compared to approved 75mg po dosing, may have relevance in humans. Especially, rapid injection/infusion of oseltamivir phosphate is considered a potential risk for humans as well until more safety data will be provided. The company provided appropriate warning statements that oseltamivir phosphate should be administered over 2 hours, residual oseltamivir phosphate in IV lines must be cleared gradually over several minutes (depending on the dead space of the line and the concentration of oseltamivir), and that oseltamivir must never be administered by bolus ("IV push") injection. These warnings have been introduced in the adopted conditions for use under "Special warnings and precautions for use".

The increased exposure of oseltamivir (pro-drug) after IV administration (due to lack of first pass effect) has been discussed by the MAH from a safety perspective. IV dosing of oseltamivir phosphate (400mg in 2 hours) produced 4 times higher oseltamivir exposures than a dose of 100 mg/2 hours IV. This exposure was well tolerated. However, infusion site pain was very common (50%). Oral administration of oseltamivir phosphate (1000mg) in six subjects resulted in 3 times higher oseltamivir exposures than a dose of 100 mg/2 hours IV. This exposure induced nausea and vomiting. CHMP concluded that high exposure to oseltamivir in adults has not revealed any major safety signal. However, the safety of high oseltamivir concentration in small infants is uncertain. Therefore, the MAH has not made dose recommendations for children under 1 years of age for compassionate use.

In study WP20727, infusion site pain was reported in half of the patients in the 400 mg IV group when the oseltamivir concentration was 8mg/mL. The company has discussed local tolerance in the Clinical Overview. In studies with rabbits, the administration of oseltamivir phosphate at oseltamivir concentrations of 4 and 8 mg/mL by perivenous injection was well tolerated. However, administration of 16 mg/mL by perivenous injection was associated with erythema, discoloration, and an increased incidence of severity of haemorrhage at the injection site. If oseltamivir phosphate is administered through peripheral venous access, the company proposed that the site of administration must be monitored frequently for extravasation, thrombophlebitis and infusion site pain. If any inexplicable changes in these parameters are observed, the infusion must be withheld. A warning statement that OP must never be reconstituted to a concentration greater than 4 mg/mL has also been included.

These warnings have been introduced in the adopted conditions for use under "Treatment duration and monitoring" and "Special warnings and precautions for use".

- Conclusions on clinical safety

Significant safety concerns may be related to potential acute toxicity associated with fast infusion times (less than 2 hours), because of resulting high oseltamivir concentration. Infusion site symptoms may be related to high concentration (over 8mg/mL) of oseltamivir in the infusion. The company proposed adequate monitoring measures and warnings, which have been introduced in the adopted conditions for use under "Treatment duration and monitoring" and "Special warnings and precautions for use".
The CHMP concluded that high exposure to oseltamivir in adults has not revealed any major safety signal, although the data is very limited. However, the safety of high oseltamivir concentration in small infants is uncertain. Therefore, the MAH has not made dose recommendations for children under 1 years of age for compassionate use.

3.5 Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for Tamiflu IV formulation as follows:

Conditions for safety monitoring to be implemented by the company
In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the company will ensure that these pharmacovigilance rules and responsibilities are fulfilled.
The company will submit yearly all safety information on Tamiflu IV in the format of a Periodic Safety Update Report (PSUR) unless otherwise specified by the CHMP.
The company will submit all safety information reported into the Roche safety database on Tamiflu IV as an attachment to the Tamiflu monthly Pandemic Safety Report as long as the phase 6 is declared by the WHO or unless otherwise specified by the CHMP.

Conditions for safety monitoring to be implemented by the Member States
In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

Additionally, in the dossier submitted, the company proposed a "Tamiflu IV End of Treatment Form" (see appendix 2).

This form, despite not compulsory, is recommended by the CHMP in order to collect data and allow a better assessment of the use of this Tamiflu IV formulation. This form contains:

- Information on underlying diseases / conditions (e.g., ventilation support)
- Information on dosing
- Adverse events
- Laboratory parameters such as blood leukocytes, haemoglobin, thrombocytes, C-reactive protein, liver and renal function tests, electrolytes and glucose as well as laboratory confirmation of influenza should be included in routine monitoring during treatment with Tamiflu IV. Furthermore, it can be considered to withdraw 2 blood samples between dosing from each patient to eventually determine oseltamivir and oseltamivir carboxylate concentrations
- Outcome

3.6 Risk/benefit assessment and recommendation

Risk-benefit assessment

The A(H1N1)v-pandemic has reached its peak in several EU Member states. In spite of its relatively mild clinical presentation, there are severe cases, including previously healthy children and young adults who need intensive care. In such cases, per oral antiviral therapy may not always be feasible. Thus, there is a medical need for parenteral antiviral therapy.

Oseltamivir phosphate IV development program is ongoing for the treatment of influenza. No efficacy data are yet available from the studies conducted with this formulation.

The development strategy is to apply an IV dosing of oseltamivir that gives a comparable exposure of the active metabolite oseltamivir carboxylate as the standard oral dose of Tamiflu, which should allow building a bridge to the efficacy and safety of Tamiflu. A single 100mg/2h oseltamivir phosphate dose IV has been shown to give similar exposures to the active metabolite oseltamivir carboxylate as 75 mg taken orally, which is the approved dose for adults. Up to 400 mg of oseltamivir phosphate IV has been given to healthy humans with no significant safety concerns. However, the IV dosing gives 3-4 times higher exposures to oseltamivir after single doses and there are no data from repeated dosing. In addition, there are non-clinical findings suggesting that juvenile rats are more sensitive to oseltamivir. No human studies with IV oseltamivir are available from children or neonates.

IV dosing of oseltamivir phosphate (400 mg in 2 hours) has produced 4 times higher oseltamivir exposures than a dose of 100 mg/2 hours IV. This exposure was well tolerated. However, infusion site pain was very common (50%). Oral administration of oseltamivir phosphate (1000 mg) in 6 subjects has resulted in 3 times higher oseltamivir exposures than a dose of 100 mg/2 hours IV. This exposure induced nausea and vomiting.

The proposed compassionate use IV regimen of 100 mg of oseltamivir phosphate should not be given in infusions less than 2h duration, since oseltamivir phosphate concentration may become high very rapidly and may cause local intolerance.

Since renal impairment may be a significant element in critically-ill influenza patients, the applicant has provided dosing instructions for health care professionals for these situations. However the doses in these patients are supported by limited data.
Thus, there are potential significant benefits to a very limited group of critically ill adults and children older than 1 year of age having a life-threatening condition due to suspected or confirmed pandemic (H1N1) infection or infection due to seasonal influenza A or B virus and answering to the following criteria:

(1) patients not responding to either oral or inhaled authorised antiviral medicinal products, or
(2) patients for whom drug delivery by a route other than IV (e.g. oral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.

To treat this targeted population, the recommended doses are the following:

- Adolescents and adults > 13 years

100 mg IV BID (twice daily) infused at a constant rate over 2 hours.

- Children 1 to 12 years

Weight ≤ 23 kg: 3 mg/kg
Weight > 23 to 40 kg: 2.5 mg/kg
Weight > 40 kg: same as adults – 100 mg
The doses listed immediately above should be infused at a constant rate over 2 hours BID (twice daily).

For infants below 1 year of age, no recommendation can be given at this stage due to the absence of pharmacokinetic and safety data on the use of Tamiflu IV in this very young population. Should a physician decide to treat an infant below 1 year of age, the decision should be taken based on the assessment of the benefit and risk for the individual.
For information only, the following doses, selected based upon preliminary results from modelling and simulation, are to be investigated in a planned paediatric clinical study:

- Age 91 to < 365 days: 3 mg/kg
- Age 31 to 90 days: 2.5 mg/kg

- Age 0 to 30 days: 2 mg/kg

The doses listed immediately above should be infused at a constant rate over 2 hours BID (**twice daily**).
In the context of the compassionate use of Tamiflu IV formulation for the above-mentioned targeted population and according to the conditions adopted by the CHMP, the CHMP considered that the benefits outweigh the risk.

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for Tamiflu IV available for compassionate use.

4 APPENDICES

1 Calculation of creatinine clearance.

2 Tamiflu IV End of Treatment Form.

Appendix 1

Calculation of creatinine clearance

Calculation of Creatinine Clearance

Note that glomerular filtration rate (GFR) is taken to be equal to creatinine clearance (CrCL).

Conversion Factor for Serum Creatinine:

Conventional Units (mg/dL) = SI Units (μmol/L) ÷ 88.4

Age = number of years (12 years 11 months = 12 years)

Estimated Creatinine Clearance (CrCL) according to Cockcroft-Gault (for patients ≥ 18 years):

1. Males

CrCL (mL/min) = [(140 – age) x Body Weight (kg)] ÷ [72 x **Serum Creatinine** (mg/dL)]

2. Females

CrCL (mL/min) = above equation X 0.85

Estimated Glomerular Filtration Rate according to Modified Schwartz equation (for patients < 18 years):

GFR (mL/min/1.73 M^2) = 39.1[height (m)/**Serum Creatinine** (mg/dL)]$^{0.516}$

x [1.8/cystatin C (mg/L)]$^{0.294}$[30/BUN (mg/dL)]$^{0.169}$[1.099]^{male}[height (m)/1.4]$^{0.188}$

The following approximation will give a good estimation of GFR:

GFR (mL/min/1.73 M^2) = 0.413*[Height (cm)/**Serum Creatinine** (mg/dL)]

Appendix 2

Tamiflu IV End of Treatment Form

Tamiflu IV End of Treatment Form

PLEASE COMPLETE IN BLOCK CAPITAL LETTERS

Data collection form at the end / discontinuation of treatment

To be filled in by a healthcare professional and returned by fax to: XXXXXXXX

Physician

- Name: ……..
- Signature: ……
- Hospital/Clinic ……..
- Date: DAY/MONTH/YEAR……
- Patients initials:…….

Patient details

Patient details

Age (years): _____ Gender: _____

Height (cm): _____ Weight (kg): _____

Please specify any important underlying diseases / conditions:

_____
_____
_____
_____

Ventilation support No ☐ Yes ☐

If YES: Number of days ventilated: _____

Tamiflu IV dosing:

Dose / infusion (mg): _____

Frequency / day: _____

Duration of treatment (days): _____

Adverse Event (AE)

Did the patient experience an adverse event during the treatment Yes ☐ No ☐
If YES, please fill in an AE form

Influenza Details

Date of first influenza symptom onset: _____
dd/mm/year

Laboratory confirmation of influenza (if available): No ☐ Yes ☐

If yes, please specify: _____

_____

_____

Laboratory parameters before and after oseltamivir treatment:

	_____ dd/mm/year	_____ dd/mm/year
haemoglobin	_____	_____
thrombocytes	_____	_____
leukosytes	_____	_____
creatinine	_____	_____
albumin	_____	_____
CRP	_____	_____
alanine transferase	_____	_____
sodium	_____	_____
potassium	_____	_____
glucose	_____	_____
other:		
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Note:
2 blood samples should be taken between dosing from each patient to determine drug concentrations (consult Roche for further details for sampling and immediate determination)

Oseltamivir and oseltamivir carboxylate blood concentration samples taken:

_____ _____
dd/mm/year dd/mm/year

Disease and Outcome

1	☐	Recovered / Resolved - i.e. discharged from hospital
2	☐	Not recovered/not resolved - i.e. remains in hospital
3	☐	Death - complete the adverse events collection form

Premature Discontinuation of Intravenous Treatment

☐ Switch to oral Tamiflu

☐ Patient declined further treatment

☐ Adverse event – please complete the “adverse Events notification form”

☐ Treatment failure = lack of anticipated antiviral effect by physician - please complete the “adverse Events notification form”

☐ Diagnosis of influenza excluded

☐ Pregnancy – please complete the “pregnancy report form” (discontinuation / risk assessment)

☐ Death – the direct cause of death must be reported as SAE via AE form

☐ Other reason (please specify):_____