



27 September 2011  
EMA/CHMP/781264/2011 Rev.1  
Evaluation of Medicines for Human Use

## Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring addressed to member states for IV Tamiflu available for compassionate use

### 1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use:** Tamiflu IV
- **Active substance(s):** Oseltamivir phosphate
- **Pharmaceutical form:** Powder for solution for infusion
- **Route of administration:** Intravenous use
- **Strength:** 100mg

### 2. NAME AND CONTACT DETAILS OF THE COMPANY

F.Hoffmann-La Roche Ltd. - Pharmaceuticals Division  
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### 3. 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.

### 4. CONDITIONS FOR DISTRIBUTION

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Tamiflu IV should be prescribed only by clinicians skilled in the diagnosis and management of patients with potentially life-threatening illness.

## 5. CONDITIONS OF USE

It should be noted that the following conditions of use are based on very limited pharmaceutical, pre-clinical and clinical data provided by F. Hoffmann-La Roche, Ltd on 6 November 2009.

### 5.1 Posology

#### • 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).

#### • Treatment duration and monitoring

The duration of treatment with Tamiflu IV is 5 days

Special monitoring during the infusion

Systemic monitoring with some combination of heart rate, blood pressure and oxygen saturation (pulse oximetry), based on the age of the patient is mandatory. If there are any unexplained changes in any of these parameters, the infusion must be withheld.

Before the start of infusion: Blood pressure and heart rate for all patients.

During the infusion and for 1 hour following the infusion:

Adults and adolescents (13 years and older)

Heart rate should be monitored with audible alarm limits (alarm limits depending on pre-infusion heart rates) using continuous telemetry. Additionally blood pressure must be measured at 15, 30, 60, 90 and 120 minutes following the start of the infusion and 60 minutes following the end of the infusion (approximately 180 minutes after the start of the infusion). Pulse oximetry may also be used per investigator discretion.

Children (1 – 12 years)

Heart rate should be monitored with audible alarm limits (alarm limits depending on pre-infusion heart rates and appropriate for age of patient) using continuous telemetry. Additionally in older children, blood pressure must be measured at 15, 30, 60, 90 and 120 minutes following the start of the infusion and 60 minutes following the end of the infusion (approximately 180 minutes after the start of the infusion). In toddlers and younger children, blood pressure may be monitored at the discretion of the physician. Pulse oximetry may be used per investigator discretion.

#### Infusion Site Monitoring

The pH of the initially reconstituted solution (with 1.1 ml of Water for Injection) is about 4 (specified as 3.0 - 5.0). After further dilution with normal saline solution to 2 mg/ml the measured pH was approximately 4.6. At this dilution the medication is considered isotonic (osmolarity similar to that for 0.9% sodium chloride).

Peripheral veins with comparatively slow blood flow may be irritated by extremes of pH. Phlebitis, thrombophlebitis or infiltration of the tissues may result with loss of the vein for therapy and possibly tissue damage. When catheters are positioned in the central veins, blood flow is fast and achieves rapid dilution of injected substances

If the patient receives oseltamivir IV through a peripheral venous canula, the site of insertion of the canula must be examined periodically. If there are any reactions (thrombophlebitis, extravasation) at the site of insertion, the site of infusion must be changed.

Tamiflu IV should be administered over 2 hours. An infusion pump which can be programmed to accurately administer at the desired rate of infusion should be used. Residual oseltamivir phosphate (OP) in IV lines must be cleared gradually over several minutes (depending on the dead space of the line and the concentration of OP).

If Tamiflu IV is administered through peripheral venous access, the site of administration must be monitored frequently for extravasation, thrombophlebitis and infusion site pain. If there is any evidence for extravasation or thrombophlebitis the infusion must be stopped promptly and resumed at an alternate site.

#### Monitoring of laboratory parameters

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 determine oseltamivir and oseltamivir carboxylate concentrations.

#### • **Specific populations**

##### Children

For infants below 1 year of age, no dose recommendations can be provided, given the lack of data.

##### 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 m<sup>2</sup> (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 m<sup>2</sup> – 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 m<sup>2</sup> – adolescents aged 13 to < 18). In the event that CrCL falls below 10 ml/min/1.73 m<sup>2</sup> 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 1 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 <sup>1</sup>	40 mg over 2 hours	q 12 h	5
	10 to 30 ml/min <sup>1</sup>	40 mg over 2 hours	q 24 h	5
Intermittent Hemodialysis (HD)		40 mg over 2 hours	After each HD Session <sup>2</sup>	5
Continuous Ambulatory Peritoneal Dialysis (CAPD) <sup>3</sup>		40 mg over 2 hours	one dose <sup>4</sup>	5

<sup>1</sup> Total renal clearance of oseltamivir carboxylate should be estimated by adding together  $CL_{CRRT}$  and residual renal function ( $CL_{CRRT} + CrCl$ ).

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

**• Method of administration**

Tamiflu IV should be administered by a slow volume and time controlled infusion over 2 hours between 12h intervals.

Vascular access

A multi-port (multi-lumen) central venous line or a peripherally inserted long line (or central catheter) is ideal. Alternatively, a peripheral venous canula may be used, provided the site of infusion is clearly visible for inspection.

When administered through a peripheral venous canula, if there is any evidence of extravasation or thrombophlebitis the infusion must be immediately stopped. The infusion may be resumed at an alternate site.

Infusion Pump

An infusion pump, which can be programmed to accurately administer at the desired rate of infusion should be used. The rate of infusion should be such that each dose is administered over 2 hours. For small volumes of infusion, a piston driven syringe pump is recommended. The dead space in the IV tubing between syringe pump and patient should be as small as possible. After the infusion is completed, this dead space must be slowly cleared over several minutes.

Co-administration of Other Drugs

Tamiflu IV should be administered through one lumen alone. Co-administration of other IV drugs via other lumens of a multi-lumen port, or intravenous lines is allowed. Co-administration implies simultaneous administration of more than one drug through the same port/lumen of a vascular access. The simultaneous use of different ports in a multi-lumen central line is not considered co-administration. The only IV solution that oseltamivir has been shown to be compatible with is 0.9% sodium chloride. Tamiflu IV may therefore be co-administered with 0.9% sodium chloride.

- **Preparation of the medicinal product to be administered**

In preparing the IV solution for administration, always take care to minimize direct exposure of oseltamivir to the skin and eyes. A responsible qualified individual should dispense the correct dose according to the dosing instructions.

Tamiflu IV is supplied as a bulk supply of open-label vials containing formulation Ro 064-0796/F09-01. Each 3 ml glass vial, with a 13mm butyl rubber stopper, contains 157.6 mg of oseltamivir phosphate, corresponding to 120.0 mg of oseltamivir free base as a lyophilizate; this provides a 20% overage to compensate for the non-removable volume of reconstituted solution. The contents of the vial must be reconstituted with 1.1 ml of water for injection to make a reconstituted solution of 1.2 ml. The reconstituted solution (made with 1.1 ml of water for injection) is hypertonic (osmolality approximately 687 mosm/kg) with a pH of about 4 (specified as 3.0 - 5.0).

One (1.0) ml of this reconstituted solution contains 131.4 mg of oseltamivir phosphate corresponding to 100 mg of oseltamivir free base. This concentrated solution must be further diluted with 0.9% sodium chloride prior to administration by infusion. The final concentration of oseltamivir should not exceed 4 mg/ml.

Dilution should be as follows: dilute 1 ml of the reconstituted solution to a final volume of 100 ml with 0.9% sodium chloride. At this dilution, the drug is considered isotonic (osmolality similar to that of 0.9% sodium chloride). This results in a concentration of 1 mg/ml. In cases where the volume of infusion needs to be decreased, dilution should be as follows: dilute 1 ml of the reconstituted solution to a final volume of 50 ml with 0.9% sodium chloride. The final concentration of oseltamivir should not exceed 2 mg/ml. Under no circumstances should a concentration in excess of 4 mg/ml ever be administered.

## **5.2 Contraindications**

Hypersensitivity to the active substance or any of the excipient.

## **5.3 Special warnings and precautions for use**

Tamiflu IV must not be administered via passive drip infusion.

Tamiflu IV must not be administered by bolus ("IV push") injection.

Tamiflu IV must not be administered if the concentration exceeds 4 mg/ml.

Systemic monitoring with some combination of heart rate, blood pressure and oxygen saturation (pulse oximetry), based on the age of the patient is mandatory. If there are any unexplained changes in any of these parameters, the infusion must be withheld.

If Tamiflu IV is administered through peripheral venous access, the site of administration must be monitored frequently for extravasation, thrombophlebitis and infusion site pain. If there is any evidence for extravasation or thrombophlebitis the infusion must be stopped promptly and resumed at an alternate site.

## **5.4 Interaction with other medicinal products and other forms of interaction**

Tamiflu IV should not be used in patients on probenecid as probenecid inhibits organic anion transporters (OAT) function.

## **5.5 Pregnancy and lactation**

Pregnant patients may be considered for treatment with Tamiflu IV only if the potential benefit justifies the potential risk to the fetus.

## **5.6 Incompatibilities**

The only IV solution that Tamiflu IV has been shown to be compatible with is 0.9% sodium chloride. Other crystalloid infusion solutions (e.g. Ringer's Lactate Solution) have not been tested for compatibility.

Tamiflu IV is not compatible with reducing sugars i.e. glucose or fructose. Oseltamivir as a primary amine reacts with reducing sugars forming degradation products in situ. The reconstituted solution must not be co-administered or added to infusion solutions containing reducing sugars

Oseltamivir IV is theoretically incompatible with solutions containing calcium ions, due to the risk of calcium phosphate precipitation.

The compatibility of oseltamivir has not been evaluated with any other IV drug.

### **5.7 Overdose**

If Tamiflu IV is administered at a concentration exceeding 4 mg/ml, the medication-related adverse events should be closely monitored, especially vital signs and symptoms and infusion site side effect.

### **5.8 Shelf life**

30 months.

### **5.9 Storage conditions**

Vials of Tamiflu IV should be stored below 25°C.

### **5.10 Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **6. OTHER INFORMATION**

### **• Summary of relevant pharmacological properties**

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oral oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Recent clinical studies as well as modelling and simulation studies have predicted that twice daily administration of 100 mg of oseltamivir as I.V. infusion over 2 hour period would achieve similar Ro 64-0802 pharmacokinetic profiles achieved with oral dose of 75 mg twice daily although the concentrations of the pro-drug are 3-4 times higher for  $C_{max}$  and  $AUC_{inf}$ . 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 the clinical data is missing.

### **• Summary of relevant Clinical properties**

No clinical data on efficacy of Tamiflu IV and only very limited safety data is available for this drug. Tamiflu IV is being investigated in clinical trials.

## **7. CONDITIONS FOR SAFETY MONITORING**

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.

## **8. DATE OF CHMP OPINION**

20/01/2010