



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2015
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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 Zanamivir available for compassionate use

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use:** IV Zanamivir
- **Active substance(s):** zanamivir
- **Pharmaceutical form:** solution for infusion
- **Route of administration:** Intravenous use
- **Strength:** 10 mg/ml

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

Compassionate Use IV zanamivir should be considered only to treat critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic influenza virus 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, or
3. Patients infected with documented influenza virus resistant to other antiviral agents and not suitable for therapy with inhaled zanamivir



4. CONDITIONS FOR DISTRIBUTION

IV Zanamivir 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 GlaxoSmithKline Research & Development Limited on 7 December 2009 and 29 October 2014.

5.1 Posology

▪ Dosing recommendations

Initiation of treatment

Empiric antiviral treatment of hospitalised patients with life-threatening illness due to suspected or confirmed influenza should not be delayed. Treatment with IV zanamivir should therefore be initiated as soon as possible in appropriate patients.

Adults

The standard dose of IV zanamivir for adults (age ≥ 18 years) with normal renal function is 600 mg given twice daily.

Children and adolescents

Paediatric subjects with normal renal function for age will receive a weight-based dose intended to provide comparable systemic exposures to 600 mg in adults. Dosing recommendations for infants and children are based upon modelling. There are currently limited data in the paediatric population.

Age Range	Weight-based Dosage Regimen
< 1 month:	8 mg/kg twice daily
1 month to < 3 months:	10 mg/kg twice daily
3 months to < 6 months:	12 mg/kg twice daily
6 months to < 6 years (if ≤ 43 kg): (if > 43 kg):	14 mg/kg twice daily 600 mg twice daily
≥ 6 years (if < 50 kg): (if ≥ 50 kg):	12 mg/kg twice daily 600 mg twice daily

Premature infants

Proposed doses only apply to term neonates. No dose recommendations are available for preterm neonates.

Patients with Renal impairment

Subjects with renal impairment should receive an initial dose equal to that for subjects with normal renal function followed by an adjusted dose based on calculated creatinine clearance (CL_{cr}). Patients must therefore have creatinine clearance determined prior to dose calculation and first administration. For patients with severe renal insufficiency, the twice-daily maintenance regimen should be initiated 24 to 48 hours after the initial dose (Table 1).

Table 1 Initial Dose Amounts and Twice Daily Maintenance Dose Regimens of IV Zanamivir for Subjects with Renal Impairment

ADULTS¹ (≥ 18 years)	Initial Dose	Maintenance Dosing (given q12 hours)				
		CLcr or CLCRRT (mL/min)				
		≥ 80	50 to < 80	30 to < 50	15 to < 30	< 15
		Begin twice-daily (q12h) maintenance dosing 12 hours after the initial dose			Begin twice-daily (q12h) maintenance dosing 24 hours after the initial dose	Begin twice-daily (q12h) maintenance dosing 48 hours after the initial dose
	600 mg	600 mg	400mg	250 mg	150 mg	60 mg
ADOLESCENTS (13 to <18 yr)	Initial Dose	Maintenance Dosing (given q12 hours)				
		CLcr or CLCRRT (mL/min)				
		≥ 80	50 to < 80	30 to < 50	15 to < 30	< 15
		Begin twice-daily (q12h) maintenance dosing 12 hours after the initial dose			Begin twice-daily (q12h) maintenance dosing 24 hours after the initial dose	Begin twice-daily (q12h) maintenance dosing 48 hours after the initial dose
≥50 kg body weight	600 mg	600 mg	400mg	250 mg	150 mg	60 mg
<50 kg body weight	12 mg/kg	12 mg/kg	8 mg/kg	5 mg/kg	3 mg/kg	1.2 mg/kg
CHILDREN (6 yr to <13 yr)	Initial Dose	Maintenance Dosing (given q12 hours)				
		CLcr or CLCRRT (mL/min/1.73 m²)				
		≥ 80	50 to < 80	30 to < 50	15 to < 30	< 15
		Begin twice-daily (q12h) maintenance dosing 12 hours after the initial dose			Begin twice-daily (q12h) maintenance dosing 24 hours after the initial dose	Begin twice-daily (q12h) maintenance dosing 48 hours after the initial dose
≥50kg body weight	600 mg	600 mg	400mg	250 mg	150 mg	60 mg
<50kg body weight	12 mg/kg	12 mg/kg	8 mg/kg	5 mg/kg	3 mg/kg	1.2 mg/kg
INFANTS and CHILDREN (6 mo to <6 yr)	Initial Dose	Maintenance Dosing (given q12 hours)				
		CLcr or CLCRRT (mL/min/1.73 m²)				
		≥ 80	50 to < 80	30 to < 50	15 to < 30	< 15
		Begin twice-daily (q12h) maintenance dosing 12 hours after the initial dose			Begin twice-daily (q12h) maintenance dosing 24 hours after the initial dose	Begin twice-daily (q12h) maintenance dosing 48 hours after the initial dose
>43 kg weight	600 mg	600 mg	400mg	250 mg	150 mg	60 mg
≤43 kg weight	14 mg/kg	14 mg/kg	9.3 mg/kg	5.8 mg/kg	3.5 mg/kg	1.4 mg/kg

¹ Adult subjects with body weight <50 kg should receive the recommended dose for adults.

Notes:

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- CL_{CRRT} = Clearance while receiving continuous renal replacement therapy (see section below regarding renal replacement therapies).
- Infants <6 months will have CL_{Cr} < 80 mL/min/1.73m², which is normal renal function for their age, and this is taken into account in the normal doses. For infants <6 months of age with additional renal impairment, no dose recommendations can currently be given.

Dosage adjustment in adults with renal impairment

All adults will receive the same initial 600 mg dose and then receive twice-daily maintenance dosing according to their renal function. Subjects with severe renal impairment and CL_{Cr} from 15 to <30 mL/min will begin the twice-daily dosing at 24 hours after the initial dose and those with CL_{Cr} <15 mL/min will start the twice-daily maintenance dosing at 48 hours after the initial dose.

Dosage determination for paediatrics

There are limited pharmacokinetic data available after intravenous administration of zanamivir in the paediatric population. Standard weight-based (mg/kg) doses for paediatric subjects are based on age and were derived using a modelling approach that characterised glomerular filtration rate (GFR) in paediatric subjects of all ages based on body size and age-related maturation in GFR [Rhodin, 2009]. The paediatric doses were selected to provide similar AUCs (area under concentration-time curve) during twice-daily maintenance dosing to those for adults with normal renal function.

As for adults, all children will receive an initial dose corresponding to the standard mg/kg dose for children with normal renal function and then start the appropriate twice-daily maintenance dosing according to their renal function (Table 1). Infants <6 months of age will typically have calculated CL_{Cr} less than 80 mL/min/1.73m² which is normal renal function for their age. This is taken into account in the dose recommendation for normal renal function.

Renal function assessment in adults and adolescents

For adults and adolescents, creatinine clearance (CL_{Cr}, in mL/min) may be calculated from age, body weight, serum creatinine and gender, according to the Cockcroft-Gault equation [Cockcroft, 1976; Pierrat, 2003]. Because of the small difference (6%) in serum creatinine (Scr) results in adults [Levey, 2007], the equation is also acceptable for Scr determined by either isotope dilution mass spectrometry (IDMS) traceable or non-IDMS traceable assays:

For serum creatinine in units of **mg/dL**:

$$CL_{Cr}(mL / \min) = \frac{(140 - AGE) \bullet WT}{72 \bullet Scr} \quad (\times 0.85 \text{ for females } *)$$

where AGE = age in years, WT = body weight in kg, and Scr = serum creatinine in mg/dL.

For serum creatinine in units of **micromoles/liter**:

$$CL_{Cr}(mL / \min) = \frac{(140 - AGE) \bullet WT}{0.81 \bullet Scr} \quad (\times 0.85 \text{ for females } *)$$

where AGE = age in years, WT = body weight in kg, and Scr = serum creatinine in μM.

For **pregnant women**, pre-pregnancy body weight should be used in the calculation.

For adult and adolescent subjects with **actual body weight greater than 100 kg or with body mass index (BMI) >30 kg/m²**, the following estimate for lean body weight (LBW) [Janmahasatian, 2005] should be used in place of actual weight (WT) in the above equations.

$$LBW_{male} = \frac{9270 \cdot WT}{6680 + 216 \cdot BMI}, \text{ where BMI = body mass index (in kg/m}^2\text{)}$$

$$LBW_{female} = \frac{9270 \cdot WT}{8780 + 244 \cdot BMI}$$

N.B. For obese females, when LBW is used in place of actual body weight (WT) in the Cockcroft-Gault equation, then the multiplier of 0.85 shown above should NOT also be used.

Renal function assessment in infants and children <13 years of age

a. Non-IDMS traceable method of Scr determination

The original Schwartz equation [Schwartz, 1987] for determination of creatinine clearance (CL_{Cr}, in mL/min/1.73m²) should only be used in conjunction with serum creatinine measured from a non-IDMS traceable method:

For serum creatinine in units of mg/dL:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{k \cdot HT}{Scr}$$

where HT = height in cm, Scr = serum creatinine in mg/dL, and where

- k = 0.55 for infants and children ≥ 1 year of age,
- = 0.45 for full term infants <1 year with normal weight for gestational age, and
- = 0.33 for low birth weight infants <1 year of age.

For serum creatinine in units of micromoles/litre:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{k \cdot HT}{Scr}$$

where HT = height in cm, Scr = serum creatinine in μM, and where

- k = 48.6 for infants and children ≥ 1 year of age,
- = 39.8 for full term infants <1 year with normal weight for gestational age, and
- = 29.2 for low birth weight infants <1 year of age.

b. IDMS traceable method of Scr determination

For children more than 1 year of age, the original Schwartz equation was revised for creatinine determined by IDMS traceable methods [Schwartz, 2009]. The revised equation, with corresponding adjustments for infants <1 year of age as indicated below, should be used in conjunction with serum creatinine measured from an IDMS traceable method.

For serum creatinine in units of **mg/dL**:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{k \bullet HT}{Scr}$$

where HT = height in cm, Scr = serum creatinine in mg/dL, and where

- k = 0.41 for infants and children ≥ 1 year of age,
- = 0.34 for full term infants <1 year with normal weight for gestational age, and
- = 0.25 for low birth weight infants <1 year of age.

For serum creatinine in units of **micromoles/litre**:

$$CL_{Cr}(mL/min/1.73m^2) = \frac{k \bullet HT}{Scr}$$

where HT = height in cm, Scr = serum creatinine in μM, and where

- k = 36.5 for infants and children ≥ 1 year of age,
- = 29.9 for full term infants <1 year with normal weight for gestational age, and
- = 21.9 for low birth weight infants <1 year of age.

Normal weight for gestational age means that the patient is a term infant (≥ 38 weeks gestational age) and weighed ≥2500 g at birth.

Low birth weight refers to an infant who weighs <2500g at birth, and includes both term and premature infants.

Dosage determination for patients receiving renal replacement therapy

There are no data currently available on removal of zanamivir by renal replacement therapies. However, because of its low molecular weight, small volume of distribution and low protein binding, zanamivir elimination is expected to be affected by renal replacement therapies.

For subjects on intermittent haemodialysis or intermittent peritoneal dialysis, the schedule should be arranged so that the recommended dose of zanamivir, as determined by calculated CL_{Cr}, is given after completion of the dialysis session.

Doses for renally impaired subjects receiving continuous renal replacement therapy (CRRT) are based on published drug dosing recommendations depending on CRRT modality [Joy, 1998]. The zanamivir dose should be selected using the appropriate CRRT clearance in place of calculated creatinine clearance. Values for CL_{CRRT} should be converted, as necessary, to units of mL/min for adolescents and adults, and to units of mL/min/1.73m² for paediatric patients less than 13 years of age.

For slow continuous ultrafiltration (SCUF) or
for continuous arterio-venous hemofiltration (CAVH) or
for continuous veno-venous hemofiltration (CVVH):

$$CL_{CRRT} = Q_f$$

For continuous arterio-venous hemodialysis (CAVHD) or
for continuous veno-venous haemodialysis (CVVHD):

$$CL_{CRRT} = Q_d$$

For continuous arterio-venous hemodiafiltration (CAVHDF) or
for continuous veno-venous hemodiafiltration (CVVHDF):

$$CL_{CRRT} = Q_f + Q_d$$

where Q_f = ultrafiltration rate and Q_d = dialysate flow rate.

For subjects receiving sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD), or sustained low-efficiency daily dialysis (SLEDD), the standard dose corresponding to normal renal function should be given during the dialysis procedure and the dose corresponding to calculated CL_{Cr} should be given when not receiving the procedure.

If the patient has any residual renal function while on CRRT, an estimate of the patient's renal clearance should be added to CL_{CRRT} in order to estimate total clearance before using Table 1.

Drug clearance in patients on CRRT may be affected by multiple variables, including type of filter, dialysate flow, ultrafiltration rate, blood flow, replacement solution rates and residual renal function. Drug dosing may need to be adjusted as appropriate taking into account these parameters. Consultation with the health care provider managing the CRRT is recommended in order to accurately estimate zanamivir clearance on a case-by-case basis.

Dosing in patients receiving other supportive measures

There is very little information available regarding zanamivir exposure or pharmacokinetics specific to patients receiving extracorporeal membrane oxygenation (ECMO).

Special Populations

Zanamivir is eliminated by renal clearance, therefore the dose of zanamivir when administered intravenously must be reduced in patients with renal impairment (see above for dosage adjustments in patients with renal impairment). Elderly patients (≥ 65 years) are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients.

▪ **Treatment duration and monitoring**

The duration of treatment with IV Zanamivir is 5 days. Treatment beyond 5 days may be considered depending on the patient's clinical presentation, including ongoing critical illness (e.g., respiratory failure, multi-organ failure, intensive care unit setting, severe underlying immunosuppression), continued viral shedding, or unresolved clinical influenza illness.

Renal function

Serum creatinine and calculated creatinine clearance should be assessed daily during treatment to determine if any dose modifications are required due to changes in renal function or emergent renal insufficiency. Similarly, dose modifications should be made if warranted by changes made in filtration or dialysate flow rates affecting CL_{CRRT} or by initiation or termination of SLED and related renal replacement therapies.

Routine monitoring

The prescribing health care provider and/or designee is/are responsible for the reporting of serious adverse events according to local regulatory requirements.

Until a larger safety database is available for treatment with IV zanamivir at the recommended dose and duration, the following procedures should be considered for monitoring patients during treatment (Table 2):

Table 2 Patient Monitoring Recommendations

Assessment	Laboratory Parameter
Complete blood count with differential and a basic metabolic profile	glucose, calcium, sodium, potassium, chloride, serum bicarbonate, and blood urea nitrogen, white blood cell count, haemoglobin, platelets and leukocyte differential (lymphocytes, basophils, eosinophils, monocytes and neutrophils)
Liver associated tests	alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin and total and direct bilirubin
Urinalysis	If significant proteinuria develops while on therapy then appropriate further evaluation including laboratory testing, 24-hour urine collection and possible nephrology consultation should be considered -
Assessment of renal function	serum creatinine
Vital Signs	body temperature, non-invasive blood pressure, heart rate, respiratory rate, and oxygen saturation, ECG
Site of administration monitoring	The site of administration should be monitored for severe events such as extravasation, septic phlebitis and infusion site pain on each dosing administration
Viral response and resistance monitoring	Viral load assessment, susceptibility testing
Pregnancy	Urine or serum pregnancy test. Any reports of pregnancy should be followed up until outcome of the pregnancy is known wherever possible.
Adverse Events	Adverse events should be followed until resolution.

- Patients with abnormal laboratory parameters should have careful monitoring and follow-up and, at a minimum, repeat assessment within 1 to 2 weeks of the conclusion of therapy to assess normalization
- Patients with significant or serious metabolic abnormalities should be assessed regularly with regard to the risks and potential benefits of continued IV zanamivir therapy.

▪ **Method of administration**

IV zanamivir may be administered as supplied or diluted in 0.9% sodium chloride solution and administered at a constant rate over approximately 30 minutes (e.g., at an infusion rate of 500 ml/hr for a 250 ml infusion volume) for adults and paediatric population.

IV zanamivir should be administered only as an intravenous infusion and not as an intramuscular or bolus injection.

Heparin lock

Before infusion of zanamivir via a heparin lock, the port should be flushed with 3-5 mLs of sterile saline. After the infusion of zanamivir is complete, the port should be flushed again with sterile saline and then heparin can be added to maintain patency of the catheter.

Single or multilumen catheter

To the extent possible, a separate IV line or separate IV lumen in a multi-lumen catheter is recommended for infusion of zanamivir. If other medications are also administered via a single lumen catheter or a single lumen of a multi-lumen catheter, at least 10 mLs of sterile saline should be administered between the infusion of any other medication and the administration of zanamivir to assure that all medication is flushed from the catheter tubing before zanamivir is administered

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

The volume of drug product and total volume for infusion will depend on patient age, weight and renal function (see dosing recommendations).

The dose can be infused as supplied or diluted to a concentration greater than or equal to 0.2 mg/mL. Each vial is for single use only; once the seal has been broken, the remaining volume must be discarded.

How to prepare the infusion:

- Use **aseptic techniques** throughout preparation of the dose.
- Calculate the required dose and volume of zanamivir aqueous solution.
- Decide on the volume of 0.9 % sodium chloride (saline) for infusion.
- Using a sterile needle and syringe, withdraw and discard a volume of saline (equal to the volume of zanamivir).
- Infusion bags may have a further overage of saline included – this can also be removed if considered necessary.
- Using a sterile needle and syringe withdraw the volume of zanamivir aqueous solution from the vial(s) and add to the infusion bag.
- Discard any unused portion of the vial.
- The infusion bag should be gently manipulated by hand to ensure it is mixed thoroughly.
- The dose should be administered immediately whenever possible
- If not administered immediately after preparation, the infusion bag should be refrigerated.
- If refrigerated, the infusion bag should be removed from the refrigerator and brought up to room temperature before use.
- Any unused diluted solution must be discarded after 24 hours.

5.2 Contraindications

Hypersensitivity to the active substance or any of the excipients.

5.3 Special warnings and precautions for use

There have been very rare reports of patients being treated with inhaled zanamivir who have experienced bronchospasm and/or decline in respiratory function, which may be acute and/or serious. No data are available on bronchospasm with IV zanamivir. Some of these patients did not have any previous history of respiratory disease. Any patients experiencing such reactions should discontinue zanamivir and seek medical evaluation immediately.

Neuropsychiatric events of seizures, delirium, hallucination and abnormal behaviour have been reported during administration of inhaled zanamivir in patients with influenza, especially in children

and adolescents. Therefore, patients should be closely monitored for behavioural changes and the benefits and risks of continuing treatment should be carefully evaluated for each patient

Vasovagal-like reactions have been reported in patients with influenza symptoms, such as fever and dehydration, shortly following inhalation of zanamivir.

Allergic-like reactions, including anaphylactic and anaphylactoid reactions, facial and oropharyngeal oedema, serious skin reactions (including rash, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), have been reported with use of RELENZA (zanamivir powder for inhalation). IV zanamivir should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

Zanamivir is eliminated by renal clearance, therefore the dose of zanamivir when administered intravenously must be reduced in patients with renal impairment. Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients.

Reports have been received of hepatic events, which may be severe, in patients with severe influenza receiving IV zanamivir. In the majority of patients, these findings are confounded by the severity of the influenza-related disease or underlying concurrent medical conditions and a causal relationship to treatment with IV zanamivir has not been confirmed. Patients in whom elevation of liver function tests are noted should be closely monitored and the potential benefit of continued treatment weighed against the potential risks.

5.4 Interaction with other medicinal products and other forms of interaction

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely.

5.5 Pregnancy and lactation

The safe use of zanamivir during pregnancy has not been established. IV zanamivir should be given to pregnant women only when the potential benefit is believed to outweigh the potential risk to the foetus.

5.6 Incompatibilities

The compatibility of IV zanamivir with intravenous solutions and medications other than 0.9 % sodium chloride is not known. There are no data to support dilution of zanamivir with dextrose containing solutions or solutions containing electrolytes other than sodium chloride.

IV zanamivir should not be administered simultaneously with another intravenous medication or prepared in solutions containing dextrose or other electrolytes.

5.7 Overdose

No cases of overdose have been reported with IV zanamivir.

As zanamivir has a low molecular weight, low protein binding, and small volume of distribution, it is expected to be removed by haemodialysis. Therefore, this may be considered a management option in the event of symptomatic overdose.

5.8 Shelf life

60 months

5.9 Storage conditions

Vials of Zanamivir should be stored below 30°C. Do not freeze.

From a microbiological point of view, intravenous zanamivir should be used immediately once prepared. If not used immediately, in-use storage times of the preparation and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C.

This medicinal product is for single use. After use, vials and any remaining contents should be discarded.

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

Zanamivir is a selective inhibitor of neuraminidase, the influenza virus surface enzyme.

Neuraminidase inhibition occurred *in vitro* at very low zanamivir concentrations (50 % inhibition at 0.64 nM – 7.9 nM against influenza A and B strains). Viral neuraminidase aids the release of newly formed virus particles from infected cells, and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. The inhibition of this enzyme is reflected in both *in vitro* and *in vivo* activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication occurs in the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. To date, virus with reduced susceptibility to zanamivir has not been detected in samples obtained pre and post treatment from patients in clinical studies.

Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated *in vitro*. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

▪ Summary of relevant Clinical properties

Very limited clinical data on efficacy of IV Zanamivir and only very limited safety data are available for this drug [Marty, 2014]. Zanamivir IV is being investigated in clinical trials.

▪ References

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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

26/02/2015