ZANAMIVIR AQUEOUS SOLUTION FOR COMPASSIONATE USE IN SERIOUS INFLUENZA ILLNESS

IMPORTANT INFORMATION

INITIAL SUPPLY OR RESUPPLY is only available between certain times.
PLEASE CONTACT GSK Clinical Support Help Desk (CSHD):
AFTER 7AM OR BEFORE 6PM WEEKDAYS*
AFTER 7AM OR BEFORE 2PM WEEKENDS*

Supply cannot always be guaranteed on the same day, particularly if requests are not received between the times stated above.
Please allow up to 2 hours before the end of the daily supply period if possible, if same day supply is required.

PLEASE NOTE THE TREATING CONSULTANT NEEDS TO COMPLETE ALL THE INFORMATION IN THE PATIENT MEDICATION REQUEST FORM (INCLUDES DOSAGE CALCULATION).

THIS FORM MUST THEN BE FAXED BACK TO GSK AND GSK MUST BE CALLED TO CONFIRM THE FAX HAS BEEN SENT

Contact number:
00800 2468 3579 (Freephone) or 0208 990 4855 (if Freephone is not available) - 24 hours per day/365 days per year

Fax number:
0207 192 6397

** If you already have been supplied with zanamivir aqueous solution, and your call is urgent (such as issues related to a serious adverse event/safety issue, or other urgent matter requiring contact with a GSK physician), you may call at any time using the contact numbers above*

NB: In order to discuss patient eligibility for named patient supply, a GSK UK Physician must be able to speak to the patient's treating Consultant

REQUESTS FOR RE-SUPPLY OF ZANAMIVIR AQUEOUS SOLUTION:

If requesting re-supply, please ensure you have available the initial supply number for the patient. This number takes the form: REL113375/xxxUK and was sent via email to the requesting treating physician on initial supply for the patient.

PHYSICIAN'S GUIDANCE DOCUMENT

ZANAMIVIR AQUEOUS SOLUTION FOR COMPASSIONATE USE IN SERIOUS INFLUENZA ILLNESS

Table of Contents

1. BACKGROUND

Zanamivir aqueous solution is available on a compassionate use basis for the treatment of serious influenza illness. Currently, zanamivir solution is not approved for use in any country. Zanamivir solution may be administered via inhaled nebulized or intravenous (IV) routes. However, data on safety and efficacy via these routes of administration are limited.

Nebulized administration: In several early phase clinical trials, a total of 126 patients received zanamivir solution administered via nebulization at doses of up to 16mg four times daily for 5 days. Additionally, 80 patients received nebulized zanamivir in a compassionate use program conducted during 1999-2002, at doses up to 24mg four times daily for 10 days. In general, zanamivir aqueous solution administered via nebulization was well tolerated.

Intravenous administration: In 10 Phase I clinical studies, zanamivir solution has been administered to 193 subjects by IV administration, at doses up to 600mg twice daily for 5 days. A total of 201 subjects were treated with IV zanamivir in the open-label Phase II study NAI113678, including 14 adolescents (age 13 to <18 years), 57 pediatric subjects (6 months to <13 years), 3 pregnant and one immediate post-partum subjects. Additionally, NAI114373, a double-blind, double-dummy Phase III study completed enrolment with 626 subjects randomized to either 300mg or 600mg IV zanamivir twice daily or oral oseltamivir 75mg twice daily. Furthermore, as of 30 April 2015 (an arbitrary cut-off date for analysis), 2393 patients have received zanamivir solution via nebulized or IV administration as part of this ongoing compassionate use program.

An overview of the clinical development program for IV zanamivir, and available safety data from Phase I, Phase II and Phase III studies and the ongoing compassionate use program are provided in Appendix 6 and 7, respectively.

2. OBJECTIVES

- To provide a mechanism to supply zanamivir aqueous solution on a named patient compassionate use basis for treatment of individuals with serious influenza infection.
- To obtain, where possible, limited safety and medical data in an anonymised way from patients treated with zanamivir aqueous solution when administered by inhaled nebulized or IV route.

3. PATIENTS

3.1. Inclusion Criteria

Patients will be eligible for treatment if ALL the following apply:

- Hospitalized patients severely ill with influenza infection.
- Patients not responding to either oral or inhaled authorised antiviral medicinal products , *OR* 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* Patients infected with documented influenza virus resistant to other antiviral agents and not suitable for therapy with inhaled zanamivir.

- The patient/legal guardian or representative has given informed consent to treatment prior to administering nebulized or intravenous zanamivir.

3.2. Exclusion Criteria

Patients will not be eligible for treatment if **ANY** of the following apply:

- Females who are pregnant, unless the expected benefit to the patient is thought to outweigh any possible risk to the foetus.

  Note: While zanamivir has been used to treat a limited number of pregnant women, the safety of zanamivir when used during pregnancy has not been established. Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer or teratogenicity in humans.

- Patients who are known or suspected to be hypersensitive to zanamivir.

4. PROCESS OVERVIEW FOR REQUESTING ZANAMIVIR AQUEOUS SOLUTION

The requesting physician will be put in contact with the GSK Clinical Support Helpdesk (CSHD). The CSHD will process requests with PPD, the contract research organisation (CRO) administering the programme on behalf of GSK. The overall process is summarised in Appendix 1 as a quick reference guide. The requesting physician completes a Medication Request Form provided by the CSHD which summarises the patient's demographics and overall medical condition including recent clinical course, brief medical history, confirmation of influenza illness, details of renal function and name and address for delivery of drug supplies (see Appendix 3). If required PPD Pharmacovigilance Group will provide support for completion of the request form. Once all relevant approvals, including regulatory and import, are in place the completed Medication Request Form should be submitted to the CSHD who will then initiate accelerated drug shipment to the requestor.

The GSK CSHD will then send the requestor notification of dispatch of investigational IV zanamivir treatment, an example informed consent form (ICF) for sharing medical data with GSK, as well as Serious Adverse Events reporting instructions and form.

NOTE: it is the responsibility of the treating physician to obtain separate informed consent from the patient or legal guardian before the administration of unlicensed zanamivir aqueous solution, along with ethics and regulatory approvals, if required, in accordance with local regulations.

GSK is not providing an example ICF for consent to treatment with IV zanamivir. Consent to treatment is distinct from the consent that must be obtained from the patient or legal guardian for sharing medical data with GSK; an example ICF for sharing data is provided in Appendix 2. Consent to share data with GSK is not a prerequisite for supply of zanamivir in this compassionate use program**.**

The treating physician is requested to collect safety and clinical follow-up information on a Case Report Form (CRF). Patient consent and, where relevant, local regulatory and ethics approval requirements will need to be followed for obtaining patient data. Further details on patient data collection are provided in Section 8.

5. DOSAGE AND ADMINISTRATION

5.1. Route of Administration

For each patient, the method of administration (i.e., IV or nebulized) will be agreed upon prior to dispatch of medication. While the treating physician will ultimately employ his/her medical judgment in choosing the most appropriate route of administration, the following factors should be considered:

- age of the patient.
- current pulmonary function and status, including:
    - ventilator status (some settings will prohibit nebulized administration)
    - presence of fluid in lungs (may require IV zanamivir to maximize drug exposure in lower airways)
    - low tidal volume capacity (may require IV zanamivir to maximize pulmonary drug distribution and exposure)
    - underlying airways disease (IV administration is recommended).

5.2. Treatment Duration

The duration of treatment for both IV and nebulized zanamivir is 5 days. Treatment beyond 5 days may be considered depending on the patient's clinical status, including ongoing critical illness (e.g., respiratory failure, multi-organ failure, intensive care unit setting, severe underlying immune-suppression), continued viral shedding, or unresolved clinical influenza illness.

5.3. Dosage Regimens

5.3.1. Nebulized Administration

The dosage for administration by nebulizer is 25mg four times daily. No dosage adjustment is required based on age, weight or renal function.

Use of aseptic techniques is required throughout preparation of the dose. Withdraw 2.5mL zanamivir (10mg/mL) from the vial using a sterile syringe and transfer to the nebulizer chamber, immediately prior to administration. The solution should be nebulized to dryness.

5.3.2. IV Administration

Zanamivir is eliminated from the body as unchanged drug by renal elimination, and adjustments to IV dosing are made according to renal function. In addition, doses in children and infants are based on age and body weight.

5.3.2.1. Dosing recommendations

Initiation of treatment

Empiric antiviral treatment of hospitalized 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 adolescents with body weight ≥ 50kg and for all adults (age ≥ 18 years) with normal renal function is 600 mg given twice daily. Subjects with renal impairment should receive reduced doses as described below (see the section on renal impairment).

Infants, children and adolescents

Pediatric 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 pediatric population. Dosage adjustments for subjects with renal impairment are described below in the section on renal impairment.

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:	14 mg/kg twice daily
≥ 6 years (if < 50kg):	12 mg/kg twice daily
≥ 6 years (if ≥ 50kg):	600 mg twice daily

Premature infants

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

Dosage adjustment for 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 (CLcr). Patients must therefore have creatinine clearance determined prior to dose calculation and first administration.

Renal function assessment in adults and adolescents:

The relationship between zanamivir clearance and renal function determined in Phase I studies and used to develop IV zanamivir dosage adjustments was based on measured creatinine clearance (CLcr). Accordingly, use of the Cockcroft-Gault

equation [Cockcroft, 1976] which estimates CLcr is appropriate for assessment of renal function. The equation is also appropriate for use in adolescents [Pierrat, 2003]. Although many laboratories have moved over recent years to the more specific IDMS traceable serum creatinine assays than those used when the Cockcroft-Gault equation was developed, the difference appears to be only about 6% in adults [Levey, 2007]. Thus, for adults and adolescents, use of the Cockcroft-Gault equation remains appropriate for renal function assessment and zanamivir dose determination of IV zanamivir.

For adults and adolescents, creatinine clearance (CLcr, in mL/min) may be calculated from age, body weight, serum creatinine and gender, according to the Cockcroft-Gault equation:

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

$$CLcr\,(mL/\min) = \frac{(140 - AGE) \bullet WT}{72 \bullet Scr} \qquad (x\ 0.85\ for\ females\ *)$$

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:**

$$CLcr\,(mL/\min) = \frac{(140 - AGE) \bullet WT}{0.81 \bullet Scr} \qquad (x\ 0.85\ for\ females\ *)$$

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/m^2**, the following estimate for lean body weight (LBW) [Janmahasatian, 2005] should be used in place of actual weight (WT) in the above equations.

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

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

* **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.

Subjects with severe renal impairment and CLcr from 15 to <30 mL/min will begin the twice-daily dosing at 24 hours after the initial dose and those with CLcr <15 mL/min will start the twice-daily maintenance dosing at 48 hours after the initial dose (see Table 1).

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

For children with renal impairment, doses are adjusted based on calculated CLcr (in mL/min/1.73m^2 using the Schwartz equations) and scaled as for renally-impaired adults. Unlike published data for adults, there appears to be a significant difference in

creatinine values between older methods of determination and more recent IDMS traceable methods. Accordingly, it is important to know the method of creatinine determination at the lab for use of appropriate Schwartz equations in assessing renal function in this pediatric population.

a. Non-IDMS traceable method of Scr determination

The original Schwartz equation [Schwartz, 1987] for determination of creatinine clearance (CLcr, in mL/min/1.73m^2) should only be used in conjunction with serum creatinine measured from a non-IDMS traceable method:

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

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

where HT = height in cm, Scr = serum creatinine in mg/dL, and where
k = 0.55 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/liter**:

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

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**:

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

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/liter**:

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

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 ≥2500g at birth.

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

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 CLcr less than 80 mL/min/1.73m^2 which is normal renal function for their age. This is taken into account in the dose recommendation for normal renal function.

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

ADULTS [1] (≥ 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 m^2**)				
		≥ 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 m^2**)				
		≥ 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
>42.8 kg weight	600 mg	600 mg	400mg	250 mg	150 mg	60 mg
≤42.8 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.

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 (see Table 1).

Infants, children and adolescents with renal impairment

There are very few pharmacokinetic data available from IV administration of zanamivir in the pediatric population. Standard weight-based (mg/kg) doses for pediatric subjects are based on age and were derived using a modelling approach that

characterised glomerular filtration rate (GFR) in pediatric subjects of all ages based on body size and age-related maturation in GFR [Rhodin, 2009]. The pediatric 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.

Patients receiving renal replacement therapy

There are currently no data 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 CLcr, 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 (CL_{CRRT} in mL/min) in place of calculated creatinine clearance.

For slow continuous ultrafiltration (SCUF) or for continuous arterio-venous hemofiltration (CAVH) or for continuous veno-venous hemofiltration (CVVH):	**CL_{CRRT} = Qf**
For continuous arterio-venous hemodialysis (CAVHD) or for continuous veno-venous hemodialysis (CVVHD):	**CL_{CRRT} = Qd**
For continuous arterio-venous hemodiafiltration (CAVHDF) or for continuous veno-venous hemodiafiltration (CVVHDF):	**CL_{CRRT} = Qf + Qd**

where **Qf** = ultrafiltrate outflow rate and **Qd** = dialysate outflow 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 CLcr 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 extracorporeal membrane oxygenation

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

Elderly patients

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.

5.3.2.2. 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.

Preclinical results from IV zanamivir administration in dogs and rats provide sufficient toxicologic data to support administration to humans at doses up to 600 mg twice daily for up to 14 days. In the compassionate use program some physicians have chosen to treat severely ill patients with IV zanamivir for longer periods of time based on the patient's clinical status and the physician's assessment of potential benefit vs. risk; however safety data for this extended period of treatment is not available.

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, blood urea nitrogen, white blood cell count, hemoglobin platelets and leukocyte differential (lymphocytes, basophils, eosinophils, monocytes and neutrophils)
Liver associated tests	alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, 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, systolic and diastolic 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 (where available)	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.

5.3.2.3. 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).

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 mL 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 mL 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 (see section 9.1.1 – Incompatibilities).

5.3.2.4. 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 section 5.3.2.1). The total volume for infusion can be adjusted, but the infusion should be given over approximately 30 minutes.

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.

6. PHARMACEUTICAL INFORMATION

6.1. Presentation

Zanamivir aqueous solution 10mg/mL is supplied as a sterile clear, colourless or pale yellow preparation made isotonic with saline and presented in 20mL clear glass vials closed with rubber stoppers. Each vial contains 200mg zanamivir. Store unopened vials at up to 30°C (do not freeze) (see Section 10, Storage conditions) See Appendix 4 and Appendix 5 for number of vials of zanamivir solution required for 5-day treatment course of IV zanamivir in adolescents (weight ≥ 50kg) and adults (age ≥ 18 years) and number of vials of zanamivir solution required for 5-day treatment course of IV zanamivir in infants, children and adolescents (weight < 50kg) respectively.

7. DRUG ACCOUNTABILITY

The physician requesting compassionate use supply or the site-designated pharmacist is responsible for ensuring that all the zanamivir supplies are received, dispensed and destroyed. Upon receipt of the drug supplies, centres will be required to conduct an inventory, review the materials shipment form, and retain and/or forward the form to GSK as directed. All unused supplies should be destroyed.

NOTE: It is important that drug is dispensed to the patient for whom the supplies were requested and to no other patient in order to comply with the regulatory requirements for compassionate use.

8. DATA COLLECTION

Collection and analysis of medical information, and especially of safety information, is an important part of this compassionate use program that allows timely analysis of data on zanamivir aqueous solution by GSK. In order to obtain consistent baseline and follow-up data on these patients, as well as maintain a register of all patients treated with zanamivir on a compassionate use basis, limited medical and safety information is requested on the CRF provided.

NOTE: please ensure that the patient or legal representative provides informed consent to share medical data in an anonymised manner using the example consent form provided. The completed consent form does not need to be returned to GSK but should be kept with the patient's hospital records.

Following the end of treatment, the completed CRF should be returned to the GSK e-mail address or fax number detailed on the front cover of the CRF.

8.1. Safety Evaluations

8.1.1. Adverse Event Definitions

8.1.1.1. Definition of an Adverse Event (AE)

Adverse event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease

temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse reaction of an investigational medicinal product: all untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting physician, or in the case of a clinical study the investigator or the sponsor, as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey in general that there is evidence or argument to suggest a causal relationship.

8.1.1.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.2. Recording of Adverse Events.

All adverse events meeting the criteria and definition of a SAE in patients who received at least one dose of zanamivir should be documented and reported to GSK, in addition to local ethics committees and regulatory agencies. All SAEs should be reported on the SAE form provided, from the time of first dose of zanamivir until up to 14 days after completing treatment. In addition, non serious adverse events are also requested to be reported in the CRF provided.

8.1.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

9. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

There have been very rare reports of bronchospasm and/or decline in respiratory function, which may be acute and/or serious, in patients being treated with inhaled, dry-powder, lactose-containing zanamivir formulation, and a small number of reports of bronchospasm in IV zanamivir clinical trials in hospitalised patients. Some of the patients treated with zanamivir 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. No new important safety information which would change the risk to benefit balance of IV zanamivir has been identified from the compassionate use program or ongoing Phase II and Phase 3 studies to date, and the risk/benefit profile of IV zanamivir for the treatment of influenza infection under the compassionate use program continues to be favourable. Ongoing collection of data from patients treated in the compassionate use program continues to be monitored and assessed on a regular basis.

9.1. 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.

9.1.1. Incompatibilities

The compatibility of IV zanamivir with IV 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.

9.2. Overdose

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 case of adverse events suspected to be related to overdose.

10. STORAGE CONDITIONS

Zanamivir aqueous solution should be stored in a secure location at temperatures between 2 ºC and 30 ºC. The product may be refrigerated but should not be frozen. However, if freezing has inadvertently occurred, the vials should be inspected as a precipitate may be observed. If this occurs the vial should be brought up to room temperature and be gently shaken to re-disperse the precipitate.

The solution should be clear before it is used to make up an infusion. If a clear solution is not observed the vial(s) should be discarded.

From a microbiological point of view, IV 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.

10.1. Special precautions for disposal

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

11. REFERENCES

Cockcroft DW, Gault MH. Prediction of dreatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.

EMA: Opinion of the Committee for Medicinal Products for human Use of, the condition for distribution and patients targeted for compassionate use for IV Zanamivir: http://www.ema.europa.eu/pdfs/human/compassionate_use/11092010en.pdf

Englund J et al. MMWR Weekly Dispatch, August 14, 2009. Weblink: http://www.cdc.gob/mmwr/preview/mmwrhtml/mm58d0814a1.htm?s_cid=mm58d0814a1_e

Janmahasation S, Duffull SB, Ash S et al. Quantification of lean body weight. Clin Pharmacokinet 2005; 44:1051-1065.

Joy MS, Matzke GR, Armstrong DK, Marx MA, Zarowitz BJ. A primer on continuous renal replacement therapy for critically ill patients. *Ann Pharmacother* 1998;32:362-375.

Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007;53:766-72

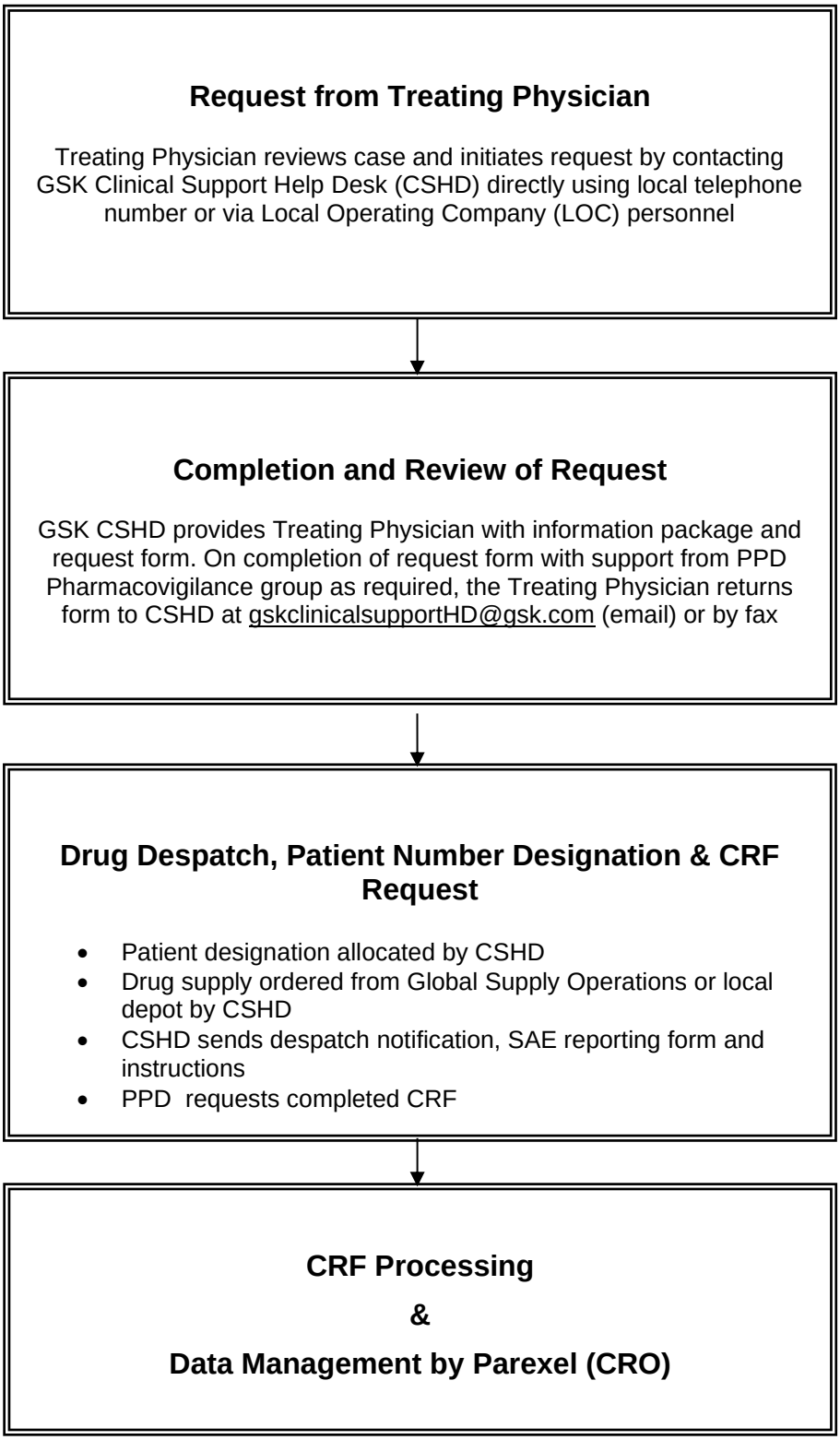
Pierrat A, Gravier E, Saunders C, et al. Predicting GFR in children and adults: A comparison of the Cockcroft-Gault, Schwartz, and Modification of diet in Renal disease formulas. *Kidney International* 2003; 64:1425-1436.

Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol* 2009; 24:67-76.

Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatric Clinics of North America 1987; 34:571-590.

Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J. Am. Soc. Nephrol. 2009; 20(3):629-637.

APPENDIX 1: Global* Process Overview for Responding to Requests in Zanamivir Compassionate Use Program REL113375



***VARIATIONS IN THE PROCESS MAY OCCUR IN INDIVIDUAL COUNTRIES ACCORDING TO LOCAL LOGISTICAL AND/ OR REGULATORY NEEDS.**

APPENDIX 2: Example Informed Consent Form for Sharing Clinical Data with GlaxoSmithKline

Zanamivir Aqueous Solution for Compassionate Use in Serious Influenza Illness
Consent for Data Sharing with GlaxoSmithKline

Patient Initials: _____ Year of birth: _____

WHAT IS THE REASON FOR THIS FORM?

You have (or recently had) serious influenza (flu) illness and you are going to be (or have been) treated with an experimental drug called zanamivir aqueous solution. Although an inhaled powder form of this drug is approved for treatment of the flu, the aqueous (liquid) form you received is not approved for use. It is being provided as part of a "compassionate use" program, which means that the drug is being (or was) made available to you because of the seriousness of your flu illness. If you have any questions about your treatment, you should talk to your doctor.

The purpose of this form is to ask for permission to release personal medical information about your recent flu illness and treatment to GlaxoSmithKline, the makers of zanamivir. GlaxoSmithKline may use your medical information for research reasons to try to better understand the use of zanamivir aqueous solution for treating serious flu illness.

Your decision to release medical information to GlaxoSmithKline is completely voluntary. If you decide not to share this information, your current and future medical care will not be affected in any way and you will not lose any benefits to which you are entitled.

WHAT IS MEANT BY "MEDICAL INFORMATION?"

The personal medical information that will be given to GlaxoSmithKline will include details about whether you are male or female, your age, year of birth, medical conditions, medications, facts about your flu illness, and any adverse events (bad effects) you might have had. Your name or address will not be given to GlaxoSmithKline.

WHAT ARE MY CONFIDENTIALITY AND PRIVACY RIGHTS?

Your right to keep your medical data private is protected by law. Keeping patient information confidential is very important to GlaxoSmithKline. Your information will be identified only by a number. Your name will not be known to GlaxoSmithKline and will not be mentioned in any publication or report.

You have the right to ask your doctor about the personal information being collected about you, to see the data, and to ask that any needed corrections are made. You can withdraw this permission at any time by notifying your doctor. If you withdraw your permission, no new information will be collected unless the information concerns an

adverse event (a bad effect) related to this program. It is possible that your medical information may be sent to regulatory agencies who monitor the safety of drugs.

DECLARATION OF PERMISSION

I understand the reason for this form is to give permission to release information about my medical condition to GlaxoSmithKline to better understand if zanamivir aqueous solution might be helpful in treating serious flu illness.

I have been given time to think about this form and to ask questions. All questions have been answered in a way that I understand. If I wanted to do so, I was able to have a member of my family or a friend with me while I was told about this permission process.

I understand that the personal information obtained by my signature on this form will only be used for research purposes and not for any other reasons.

By signing below I give permission of my own free will and understand that my decision either to release or not release my medical information will ha**v**e no impact on my current or future medical care:

- I agree to release to GlaxoSmithKline anonymous personal medical information

Patient/Parent/Legal Guardian/Legal Representative Name : (please print)		
Signature		Date

Name of Witness : (please print)		
Witness Signature :		Date
Name of Person Obtaining Permission (if not physician): (please print)		
Signature of Person Obtaining Permission		Date
Physician Name : (please print)		
Physician Signature :		Date

APPENDIX 3: MODEL MEDICATION REQUEST FORM

ZANAMIVIR AQUEOUS SOLUTION (AN UNLICENSED PRODUCT) REL113375

This form must be completed by the treating physician, who must also read the declaration at the end of this form, sign and email to: gskclinicalsupportHD@gsk.com **or fax to XXXX XXX XXXX**

ALL fields must be typed or handwritten IN BLOCK CAPITALS to ensure this request can be processed. Failure to do so will delay the request process

DATE & LOCAL TIME	

PHYSICIAN CONTACT INFORMATION		
Name of requesting physician		
	mobile telephone	
	e-mail	
Name of physician in overall charge of patient		☐ **Check box if same as requesting physician**
	mobile telephone	
	e-mail	
DELIVERY DETAILS		
Name of receiving healthcare professional		
Hospital/Institution Department (e.g. ITU/pharmacy) Address Town / City Postcode Country		
Telephone		
e-mail		

INCLUSION CRITERIA	**PLEASE CHECK ALL THAT APPLY**
Hospitalized patient severely ill with influenza infection	☐
Patient not responding to either oral or inhaled authorised antiviral medicinal products, **OR** Patient 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** Patient infected with documented influenza virus resistant to other antiviral agents and not suitable for therapy with inhaled zanamivir.	☐ ☐ ☐
Patients will be eligible for treatment if **ALL** the above apply	

EXCLUSION CRITERIA	
Females who are pregnant, unless the expected benefit to the patient is thought to outweigh any possible risk to the foetus.	☐ **Does not apply**
Patients who are known or suspected to be hypersensitive to zanamivir.	☐ **Does not apply**
Patients will not be eligible for treatment if **ANY** of the above apply	

PATIENT DETAILS		
Is this is new request or a re-supply request? If this is a re-supply request state unique patient ID assigned previously	☐ **New request** ☐ **Re-supply request** **REL113375/**_ _ _ _ _ _ _	
Sex*	☐ Male	☐ Female
*If female, is patient pregnant?		☐ Pregnant ☐ Not pregnant
*If pregnant does perceived benefit outweigh any possible risk to the foetus? (**Note**: not eligible for treatment if "No")		☐ Yes ☐ No
Year of Birth (e.g 1998)		
Weight (Kg)		
Date of laboratory confirmation of influenza infection (if available)		

History of present illness (e.g. days since onset, temperature, ventilation status, O_2 saturation x-ray findings).	
Other Medical History	

RENAL FUNCTION Please refer to page 9 of The Physician's Guidance document for calculation of CL_{CRRT} (CL_{CRRT} =clearance whilst receiving continuous renal replacement therapy)					
Is Renal function (creatinine clearance) normal?	☐ Yes	☐ No			
Is patient on continuous renal replacement therapy (CRRT) [1]?	☐ Yes	☐ No			
If renal function is abnormal, what is creatinine clearance (CLcr) or CL_{CRRT} (ml/min)[1]?					
	CLcr or CL_{CRRT} (ml/min)[1]				
Please select one value:	≥ 80	50 to <80	30 to <50	15 to <30	<15

DOSAGE Refer to the Physician's Guidance Document recommendations on dosage determination: Adults (pgs 7 & 8), Infants (pg 7 & 8), nebulised administration (pg 7)		
Check route of administration	☐ **iv**	☐ **nebulised**
Dose of zanamivir	Initial dose (mg) ☐	25mg four times daily
	Maintenance dose (mg) ☐	
No. of vials requested for 5-day treatment course according to age/weight and renal function **Please refer to Appendix 4 and 5 of the Physician's Guidance Document to calculate number of vials required**		

DECLARATION BY TREATING PHYSICIAN

1. I have requested the supply of zanamivir aqueous solution ("the Drug") for the purpose of treating my named patient.
2. I understand this Drug is unlicensed globally but have requested supply of this Drug as I consider there are no other treatment options available for this patient.
3. I understand that completing this form does not guarantee supply.
4. I understand that the Drug is supplied solely for administration to the named patient and for no other purpose. The intellectual property claiming and/or covering the Drug to be supplied is the property of GlaxoSmithKline (GSK) and/or its group companies, and/or is licensed to GSK and/or its group companies, and supply to the named patient and/or his or her physician shall not operate to confer any right, title or interest in or to that intellectual property.
5. I understand that I, as the patient's treating physician, am fully responsible for screening, eligibility evaluation, dosage calculation and administration, following the patient through therapy, and managing any side effects should they occur.
6. I will take responsibility for compliance with all local and national regulatory and ethical requirements relating to the supply of unlicensed relevant medicinal products for individual patients
7. I confirm that prior to administration of the Drug, I will explain to my named patient and/or their legal guardian the fact this drug is unlicensed, the potential risks and benefits and take responsibility to obtain written consent to treatment from the patient or their legal guardian.
8. I understand that GSK reserves the right to temporarily suspend or terminate this named patient supply at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance.
9. I will promptly report all serious adverse events (SAEs), adverse events (AEs) and pregnancies to GSK and to relevant regulatory authorities as required by local regulations.
10. I agree to keep confidential any information provided by GSK in relation to this supply and to limit disclosure of such information to those members of the clinical team who require the information for the purpose of providing the medical treatment for the named patient and who have been made aware of the confidential nature of the information.

Signature: _____	**Date:**
Name (PRINT):	

This form must be completed by the treating physician, who must also sign the declaration above.

Once completed fax to: XXXX XXX XXXX and call GSK Clinical Support Helpdesk on XXXX XXX XXXX to confirm receipt of fax or email to gskclinicalsupportHD@gsk.com. Failure to do so may delay delivery.

APPENDIX 4: Number of Vials of Zanamivir Solution Required for 5-Day Treatment Course of IV Zanamivir in Adolescents (Weight ≥ 50kg) and Adults (Age ≥ 18 Years)

Population	CLcr or CL_{CRRT} (mL/min)	# Vials
All subjects ≥ 18 years of age and all adolescents ≥ 50kg body weight	≥ 80	30
	50 - <80	21
	30 - <50	21
	15 - <30	11
	<15	9

APPENDIX 5: Number of Vials of Zanamivir Solution Required for 5-Day Treatment Course of IV Zanamivir in Infants, Children and Adolescents (Weight < 50kg)

Age Range	CLcr or CL_{CRRT}	Weight Range (kg)	# Vials
6 yr - < 18 yr	≥ 80	≥33.3	30
		16.7 - <33.3	20
		<16.7	10
	50 - <80	≥33.3	21
		25 - <33.3	20
		16.7 - <25	11
		<16.7	10
	30 - <50	≥40	21
		33.3 - <40	12
		16.7 - <33.3	11
		<16.7	10
	15 - <30	≥33.3	11
		16.7 – <33.3	10
		<16.7	9
	<15	≥33.3	9
		16.7 – <33.3	8
		<16.7	7
6 mo - < 6 yr	≥ 80	≥28.6	30
		14.3 - <28.6	20
		<14.3	10
	50 - <80	≥28.6	21
		21.5 - <28.6	20
		14.3 - <21.5	11
		<14.3	10
	30 - <50	≥34.5	21
		28.6 - <34.5	12
		14.3 - <28.6	11
		<14.3	10
	15 - <30	≥28.6	11
		14.3 - <28.6	10
		<14.3	9
	<15	≥28.6	9
		14.3 - <28.6	8
		<14.3	7
< 6 mo	≥ 30	all	10
	15 - < 30	all	9
	< 15	all	7

APPENDIX 6: Summary of Clinical Development Program For IV zanamivir

An overview of the Clinical Development Program of IV zanamivir from Phase I Studies, Phase II / Phase III studies and the Compassionate Use Program.

1.0. Clinical Pharmacology Phase I Studies

IV zanamivir has been evaluated in 10 Phase I trials. In these studies, 193 adult subjects received single doses ranging from 1mg to 600mg, and another 85 adult subjects received multiple doses of IV zanamivir up to 600mg IV twice daily for five days. Brief summaries of key studies of IV zanamivir are described below.

1.1. Pharmacokinetic Studies (C92-083, NAIB1008, NAIB1009)

The pharmacokinetics (PK) of IV zanamivir were studied in healthy volunteers after single escalating doses of 1 to 16mg (Study C92-083) and 50 to 600mg (Study NAIB1008), and repeated doses of 600mg twice daily (BID) for 5 days (Study NAIB1009) [Cass, 1999a]. No accumulation of zanamivir in serum was evident with 600mg BID dosing. Dose proportional increases in zanamivir AUC and Cmax were demonstrated. The volume of distribution of zanamivir was about 16L, which approximates the volume of extracellular water. This finding is consistent with its physicochemical characteristics as a polar compound with low protein binding. Zanamivir is excreted in the urine as unchanged drug. Additionally, chromatographic profiling showed no evidence of biotransformation. These findings indicate that the drug does not undergo metabolism. Given its low protein binding and elimination primarily by passive renal filtration of unchanged drug, it is unlikely that zanamivir would affect the elimination of other concurrently administered compounds or, conversely, that other agents would affect the elimination of zanamivir.

1.2. Human Challenge Study in Healthy Volunteers (NAIA1010)

Study NAIA1010 was a double blind, randomized trial to examine the prophylactic antiviral activity and efficacy of repeat dose IV zanamivir compared to placebo in healthy male volunteers against infection from inoculation with Influenza A/Texas/91 (H1N1) virus [Calfee, 1999]. Subjects were randomized to receive either IV zanamivir 600mg every 12 hours for 5 days or placebo every 12 hour for 5 days. Subjects received Influenza A/Texas/91 (H1N1) virus suspension (~10^5 $TCID_{50}$) intranasally four hours after the first dose of IV zanamivir or placebo. Serial nasal washings for viral load measurements, hemagglutinin antibody titres, and symptom assessment scores were evaluated.

IV zanamivir was well tolerated in this study. In addition, IV zanamivir had a significant prophylactic effect against an experimental challenge with influenza A as demonstrated by the low infection rate (14% vs. 100 % positive serology in placebo group), isolation of virus (0% vs. 100% in placebo group), as well as reductions in fever (14% vs. 88% in placebo group), upper respiratory tract illness (0% versus 100% in placebo group) and total symptom scores (1 vs. 44 median score in placebo group).

1.3. Bronchoalveolar Lavage (BAL) Study (NAI106784)

Study NAI106784 was an investigation of zanamivir serum and pulmonary PK following administration of IV and oral inhaled zanamivir to healthy adult subjects [Shelton, 2011]. The study included separate cohorts (6 subjects each) who received two doses 12 hours apart of IV zanamivir 100mg, 200mg or 600mg, or of oral inhaled zanamivir 10mg. Blood samples were collected for zanamivir PK in serum and to quantify urea concentrations in blood. BAL samples were collected at 12 hours after the second IV or inhaled dose to measure pulmonary exposure. Following bronchoscopy, four consecutive BAL samples were collected; the first aspirate (BAL1) was kept separate and the latter three were combined (BAL2). Pulmonary concentrations of zanamivir were calculated based upon relative urea concentrations in BAL supernatant vs. serum and recovered volume of BAL aspirate to derive a concentration in epithelial lining fluid (ELF).

Key PK findings of the human BAL study were:

- Median ELF zanamivir trough concentrations (12-hour post-dose; BAL2 samples) from 100mg, 200mg and 600mg IV doses were 74, 146 and 419 ng/mL, respectively, reflecting approximate dose proportionality. These trough concentrations are many fold in excess of reported mean zanamivir IC50 values for influenza virus neuraminidases, which are typically in the range of <1 to 4ng/mL.
- For the 100mg, 200mg and 600mg IV zanamivir dose cohorts, median within-subject ELF to simultaneous serum trough concentration ratios were 0.73, 0.55 and 0.79, respectively, indicating good distribution of zanamivir into the pulmonary compartment throughout the dosing interval.
- Following orally inhaled zanamivir 10mg, serum zanamivir trough concentrations were below the limit of detection and the median ELF trough concentrations were 891 ng/mL (BAL1) and 326 ng/mL (BAL2).

Results from this study demonstrate that the pulmonary penetration of zanamivir from IV administration supports clinical investigation of this formulation for treatment of influenza in patients for whom oral or inhaled product formulations are not appropriate. Data are summarized on the GSK Clinical Study Register at the following link:

http://www.gsk-clinicalstudyregister.com/study/106784?study_ids=NAI106784#rs

1.4. Renal Impairment Study (NAI108127)

Study NAI108127 evaluated safety and PK following administration of single IV doses of zanamivir 100mg to subjects with impaired renal function (mild, moderate and severe) as well as normal renal function. This study was designed to provide additional PK information at a higher dose of zanamivir compared to prior data from lower doses (2-4mg) administered to subjects with renal impairment [Cass, 1999b].

Results demonstrated that renal impairment has a significant effect on zanamivir PK and that dosage adjustment would be required for administration of IV zanamivir in patients with significant renal impairment [Weller, 2010]. Zanamivir total clearance (mL/min) was highly correlated with creatinine clearance (mL/min) after IV administration:

$$CL \cong 7.08 + 0.826 \bullet CLcr \qquad (r^2 = 0.89)$$

Taken together with the results of the previous renal impairment study, this study provides data to support recommendations for appropriate dose adjustments in renally impaired patients that deliver systemic zanamivir exposure comparable to that from the dose selected for subjects without renal impairment. Data are summarized on the GSK Clinical Study Register at the following link:

http://www.gsk-clinicalstudyregister.com/study/108127?study_ids=108127#rs

1.5. Drug Interaction Study with Oseltamivir (NAI112977 / SEA003)

Study NAI112977 (SEA003), a collaborative effort between GSK and the Southeast Asia Influenza Clinical Research Network, was an open-label, repeat-dose, 4 period crossover, drug interaction study conducted in Thailand [Pukrittayakamee, 2011]. Both intermittent (600mg BID) and continuous infusion (50mg/hour) administration of IV zanamivir were evaluated alone and in combination with oseltamivir 150mg BID in healthy Thai adult subjects.

In this study the PK properties of IV zanamivir and oral oseltamivir, whether administered alone or in combination, were generally similar to those observed in previous studies of the individual drugs. There were no SAEs reported during the study and no AEs considered attributable to IV zanamivir. There was no evidence for a clinically significant PK interaction between the two drugs, and results suggest IV zanamivir and oral oseltamivir can safely be administered concurrently.

1.6 Thorough QTc Study (NAI114346)

Study NAI114346, a randomized, single-dose, 4-way crossover study was conducted to evaluate the effect of IV zanamivir on cardiac conduction as assessed by continuous 12-lead electrocardiogram monitoring in healthy volunteers [Lou, 2013]. IV zanamivir 600 mg, a supratherapeutic dose of 1200mg IV zanamivir, a positive control with oral moxifloxacin 400mg and placebo were evaluated in approximately 40 healthy adult male and female subjects. Key findings from the study were as follows:

Key findings from the study were:

- Single therapeutic (600 mg) and supratherapeutic (1200mg) doses of IV zanamivir were well-tolerated in this study of healthy subjects
- Zanamivir PK from IV administration demonstrated low inter-subject variability (12-19%) and was dose proportional from the 600 mg and 1200mg doses.
- The study was sufficiently sensitive to detect the effect of moxifloxacin, the positive control on QTcF, confirming that this study was valid for assessing the effects of IV zanamivir on cardiac repolarization.
- IV zanamivir had no effect on cardiac repolarization at either the anticipated therapeutic dose (600 mg) or supratherapeutic (1200mg) dose.

Data are summarized on the GSK Clinical Study Register at the following link:

http://www.gsk-clinicalstudyregister.com/search?study_ids=114346#rs

2.0 Phase II Study in Hospitalized Subjects (NAI113678)

Protocol NAI113678 was an open-label, Phase II, multi-centre, international, single arm study to evaluate the safety, tolerability and PK of IV zanamivir 600mg twice daily for 5 days in hospitalized adult and pediatric subjects with laboratory confirmed influenza infection Target enrolment in the study was 200 subjects, to include approximately 150 adult (≥18 years of age) and adolescent (13 to <18 years of age) subjects and approximately 50 pediatric subjects (6 months to <13 years of age). Enrolment for adults was completed in September 2011 with 130 subjects. Results from the adult subjects are reported separately from the pediatric and adolescent subjects [Marty, 2014]. Enrolment of 57 pediatric (6 months to <13 years) and 14 adolescent (13 to <18 years) subjects was completed in February 2015. Countries participating in the study were Australia, Brazil, Canada, France, Hong Kong, Japan, Norway, Russia, Spain, South Africa, Thailand, UK, and US.

Statistical analysis is ongoing for the pediatric/adolescent cohorts. Final data for the adult cohort and preliminary data for pediatric/adolescent cohorts are summarized on the GSK Clinical Study Register at the following link:

http://www.gsk-clinicalstudyregister.com/study/113678?study_ids=113678#rs

Sixty percent of enrolled subjects were male, 40% were female, and 72% were Caucasian. Median ages for the adult and adolescent/pediatric cohorts were 47.5 and 7 years, respectively. At baseline 77% of the adult subjects had at least one chronic underlying medical condition, the most common of which were asthma and diabetes mellitus (18% each). For the adolescent/pediatric cohort (56% with baseline underlying chronic illness) asthma (30%) and seizure disorder (11%) were most common.

Following IV administration, zanamivir PK in hospitalized adult subjects was generally consistent with expectations based on experience from Phase I studies. Zanamivir clearance after the initial 600mg loading dose appeared to be reasonably well approximated by estimated creatinine clearance, such that the dosage adjustments for subjects with renal impairment resulted in generally similar AUCs over a 12-hour dosing interval for twice daily maintenance dosing. PK parameters for subjects who received CRRT and/or extracorporeal membrane oxygenation ECMO appeared similar to those for subjects not receiving these procedures. PK data for the adolescent/pediatric subjects are not available at this time.

A rapid antiviral effect was observed. In subjects who were PCR positive at Baseline, viral load decreased 1.42 $\log_{10}$ copies/ mL in adults and 1.84 $\log_{10}$ copies/mL in adolescents/pediatrics after 2 days of treatment with IV zanamivir despite starting treatment a median of 4.5 days (adults) or 4.0 days (adolescents/pediatrics) after symptom onset and high incidence of previous oseltamivir use (80% of adult subjects and 69% of adolescent/pediatric subjects prior to study entry).

No safety signals or clinically significant trends in laboratory values, vital signs or ECGs that were considered attributable to the administration of IV zanamivir were identified in the adult cohort or, based on preliminary analysis, in the adolescent/pediatric cohort (see section 2.4, Appendix 7).

3.0. Phase III Study in Hospitalized Subjects (NAI114373)

Protocol NAI114373 was an international Phase III, double-blind, double-dummy, 3-arm study to evaluate the efficacy, antiviral activity and safety of 600mg IV zanamivir compared to oral oseltamivir, or 600mg IV zanamivir compared to 300mg IV zanamivir given twice daily for 5-10 days in hospitalized adults and adolescents with influenza infection.

Enrolment into the study is complete, but data analysis is ongoing. The study enrolled a total of 626 subjects between January 2011 and February 2015 from the following 26 countries: Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hong Kong, Hungary, India, South Korea, Mexico, Netherlands, New Zealand, Norway, Poland, Czech Republic, Russia, Slovakia, Spain, South Africa, Taiwan, UK, and US.

Although statistical analysis is ongoing a summary of key findings are summarised below. Preliminary results are also summarized on the GSK Clinical Study Register at the following link:

http://www.gsk-clinicalstudyregister.com/study/114373?study_ids=114373#rs

Preliminary key findings:

- **Population:** 626 subjects were randomized into the study of which 615 received at least one dose of investigational product and comprised the ITT-E and Safety Populations. The primary analysis population for efficacy was the confirmed Influenza Positive Population which comprised 488 subjects (78% of the overall population).
- **Demographics:** 54% of the study population was male; mean age was 56 years and 76% were Caucasian. The demographic characteristics were generally well matched across all treatment groups. However, there were more female subjects (57%) in the oseltamivir arm compared with the IV zanamivir arns (41% each).
- **Efficacy:** The study did not meet its pre-specified primary endpoint of achieving superiority of 600mg IV zanamivir to oral oseltamivir, or to 300mg IV zanamivir on the primary endpoint of time to clinical response (resolution of vital signs or hospital discharge). The results showed that a higher proportion of subjects treated with IV zanamivir achieved clinical response relative to oseltamivir and demonstrated a 0.48 day difference in median time to clinical response in favor of 600 mg IV zanamivir versus oseltamivir, with a confidence interval of -2.11, 0.97. Results from secondary clinical endpoints and virologic outcomes were generally similar across treatment arms.
- **Safety:** Adverse events were similar across all three treatment arms (see Section 2.5, Appendix 7).

4.0. Compassionate Use Program

4.1. Program Summary

This ‘named patient’ compassionate use program commenced in May 2009 in response to the emergent influenza A/ H1N1 pandemic. On the 18th of February 2010, the European Medicines Agency’s (EMEA’s) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the compassionate use

of IV zanamivir for groups of patients, under Article 83 of regulation (EC) 726/2004 [EMEA, 2010]. CHMP's opinion provides recommendations to all EU Member States and is not mandatory.

As of 30 April 2015, 2393 patients had been treated with zanamivir aqueous solution in the compassionate use program, 2335 of whom received zanamivir via the IV route, 48 of whom received aqueous zanamivir for nebulized administration. Nine patients received zanamivir by both routes and one unspecified. The majority of patients treated were from the UK (866), USA (600), Germany (233), France (83), Australia (77), Spain (65), and Canada (58),). Ages range from <1 month to 92 years, including 2114 adults ≥18 years of age, 65 adolescents 13-17 years of age, and 209 pediatric patients ≤13 years of age. Of the pediatric patients, 4 were <6 months old, 30 were aged 6 months to <1 year, 29 were 1 to<2 years, 79 were 2-5 years, and 67 were 6 -12 years. Age was not specified for 8 patients. Fifty five patients received zanamivir either during pregnancy or postpartum (up to 6 month of age).

GSK requests that treating physicians complete brief CRFs for patients from whom consent to share data has been obtained. It is important to note that data collected within this program are not quality assured and must be considered incomplete. The CRFs collect top-line demographic information, concurrent medical conditions, ventilatory status, influenza symptoms, and limited clinical outcome data. Up to the cut off date 30 April 2015, 690 CRFs were provided.

While limited information is available on clinical outcomes in these patients, clinical improvement has been reported in a number of patients. A number of case reports describing treatment of seriously ill patients with zanamivir aqueous solution in the compassionate use program have been published [Anraku 2009; Bhatt 2015; Busani 2010; Da Dalt 2010; Dohna-Schwake 2010; Dulek 2010; Englund 2009; Fraaij 2011;Gaur 2010; Ghedin 2011; Ghosh 2012; Gristina 2010; Härter 2010; Kidd 2009; Nguyen 2010; Ridwan 2010; Shayegi 2011; Speers 2010; Turner 2011; van der Vries 2010; Wijaya 2011;Wolfe 2010; Wolfe 2011]. Chan-Tack et al. [Chan-Tack, 2013 and Chan-Tack, 2015] have also published reports describing FDA's clinical experience with the IV zanamivir Emergency Investigational New Drug Application (EIND) program in the US for two cohorts from April 2009 to April 2011 and from May 2011 to June 2014. Data collection continues as new patients are treated within the program.

4.2 Medical Record Review for Pediatric, Adolescent and Pregnant Patients treated in the Compassionate Use Program

To obtain further safety information from the CUP, GSK also commissioned a non-interventional retrospective chart review for a large cohort of paediatric and pregnant patients treated under the program from May 2009 up to 31 January 2011 (Study NAI115008) so called Tier 1 patients. This study was extended to include a chart review of other patients treated at the same sites (Tier 2). Data were collected from 113 patients from 34 sites. Of these patients 61 were in Tier 1, 50 paediatric, 11 pregnant or postpartum and 52 were Tier 2 adults treated at the same sites

The majority of patients in this retrospective chart review study were infected with influenza A/H1N1pdm2009. Nearly all patients, including pregnant patients, required admission to ICU, and the majority (>80%) required endotracheal mechanical ventilation. No safety signals attributable to zanamivir were identified in this study. However, determination of causality is confounded by the severity of influenza-related illness and underlying medical conditions.

Appendix 6 References

Anraku M, Husain S, Mazulli T, Pierre AF. Peri-operative novel 2009 H1N1 influenza virus infection successfully treated with oseltamivir and zanamivir in a lung transplant recipient. *J Heart Lung Transplant.* 2011; 30(3):354.

Bhatt R, Hasan M, Karki A, Shalonov A, MD; Bagheri F. Usual Presentation of Influenza Requiring an Unique Management Strategy: A Case Report. 111TH International Conference of the American Thoracic Society (ATS), 2015.

Busani S, Girardis M, Biagioni E, Pasetto A, Sambri V. Surfactant therapy and intravenous zanamivir in severe respiratory failure due to persistent influenza A/H1N1 2009 virus infection. *Am J Respir Crit Care Med*. 2010;182(10):1334.

Calfee D, Peng A, Cass L, et al. Safety and efficacy of intravenous zanamivir in preventing experimental influenza a virus infection. *Antimicrob Agents Chemother* 1999; 43(7): 1616-1620.

Cass LMR, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. *Clin Pharmacokinet* 1999a; 36(Suppl 1): 1-11.

Cass LMR, Efthymiopoulos C, Marsh J, Bye A. Effect of renal impairment on the pharmacokinetics of intravenous zanamivir. *Clin Pharmacokinet* 1999b; 36(Suppl 1): 13-19.

Chan-Tack KM, Gao A, Himaya AC, et al. Clinical experience with intravenous zanamivir under an Emergency Investigational New Drug program in the United States. J *Infec Dis* 2013; 207: 196-198.

Chan-Tack KM, Kim C, Moruf A, et al. Clinical experience with intravenous zanamivir under an Emergency Investigational New Drug program in the United States. A*ntiviral Therapy* 2015; Date published online: 10 February 2015

Da Dalt L, Calistri A, Chillemi C, et al. Oseltamivir- resistant pandemic (h1n1) 2009 treated with nebulized zanamivir. *Emerg Infect Dis.* 2010;16(11):1813-1815.

Dohna-Schwake C, Schweiger B, Felderhoff-Műser U. Severe H1N1 infection in a pediatric liver transplant recipient treated with intravenous zanamivir: efficiency and complications. *Transplantation* 2010; 90(2):223-224

Dulek DE et al. Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immunosuppressed child infected with 2009 pandemic influenza A (H1N1) Virus. *Clin Inf Dis* 2010; 50(11): 1493–1496.

EMEA. Document EMA/CHMP/32815/2010; 2010

Englund J, Zerr D, Heath J, et al. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients - Seattle, Washington, 2009. *Morb Mortal Wkly Rep.* 2009 Aug 21;58(32):893-896.

Fraaij PLA, van der Vries E, Beersma MFC, et al. Evaluation of the antiviral response to zanamivir administered intravenously for treatment of critically ill patients with pandemic Influenza A (H1N1) infection. *J Infect Dis*. 2011;204:777–782.

Gaur A, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 Influenza. *N Engl J Med* 362;1 nejm.org January 7, 2010. Available at: http://content.nejm.org/cgi/content/full/NEJMc0910893

Ghosh S, Adams O, Schuster FR, et al. Efficient control of pandemic 2009 H1N1 virus infection with intravenous zanamivir despite the lack of immune function. *Transpl Infect Dis 2012*: 14 (6): 657–659. doi: 10.1111/tid.12004

Gristina G, Nardi G, Orazi D, et al. Prone positioning and intravenous zanamivir may represent effective alternatives for patients with severe ARDS virus A (H1N1) related pneumonia in hospitals with no access to ECMO. *Crit Care Res Pract.* 2010. Article ID 146456. Doi:10.1155/2010/146456. Available at: http://downloads.hindawi.com/journals/ccrp/2010/146456.pdf. Accessed 07 Nov 2011.

Härter G et al. Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus. *Clin Inf Dis* 2010; 50(9): 1249–1251.

Kidd IM, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet.* 2009;374(9694):1036.
Published online at www.thelancet.com/infection; Sept 4, 2009

Lou Y, Gan J, Peppercorn A, Gould E, Weller S, Piscitelli SC, Patel P. Effect of intravenous zanamivir on cardiac repolarization. *Pharmacotherapy* 2013; 33(7):701-709.

Marty FM, Man CY, van der Horst C, et al. Safety and pharmacokinetics of intravenous zanamivir treatment in hospitalized adults with influenza: An open-label, multicenter, single-arm, Phase II study. *Journal Infect Dis* 2014; 209(4):542-550.

Nguyen HT, Fry AM, Loveless PA, Klimov AI, Gubareva LV. Recovery of a multidrug-resistant strain of pandemic influenza A 2009 (H1N1) virus carrying a dual H275Y/I223R mutation from a child after prolonged treatment with oseltamivir. *Clin Infect Dis.* 2010;51(8):983-984.

Pukrittayakamee S, Jittamala P, Stepniewska K, et al. An open-label crossover study to evaluate potential pharmacokinetic interactions between oral oseltamivir and intravenous zanamivir in healthy Thai adults. *Antimicrob Agents Chemother* 2011; 55(9): 4050-4057.

Ridwan BU, Goekoop GJD, Muijsken MA, Tacx AN, van de Visse EP. Intravenous zanamivir treatment of an obese patient with severe pandemic H1N1 2009 influenza. Scientific Spring Meeting of the Dutch Society for Medical Microbiology. 19th – 21st April 2010; Papendal, the Netherlands. (Poster 058).

Shayegi N, Schweiger B, Duwe S, et al. Antiviral treatment of Influenza A (H1N1-09) guided by molecular resistance testing in aplasia after allo-SCT. *Bone Marrow Transplant* .2011;46(1):1-3. Available at: http://www.nature.com/bmt/journal/vaop/ncurrent/pdf/bmt2010331a.pdf. Accesse d 07 Nov 2011.

Shelton MJ, Lovern M, Ng-Cashin J, et al. Zanamivir pharmacokinetics and pulmonary penetration into epithelial lining fluid following intravenous or oral inhaled administration to healthy adult subjects. *Antimicrob Agents Chemother* 2011, 51(11): 5178-5184.

Speers DJ et al. Oseltamivir-resistant pandemic (H1N1) 2009 influenza in a severely ill patient: the first Australian case. *Med J Australia* 2010; 192(3): 166-168. Available at: http://www.mja.com.au/public/issues/192_03_010210/spe11148_fm.html

Turner D, Rudd C, Pham J, Wolfe C, Cheifetz I. Intravenous zanamivir for pandemic H1N1 influenza infection. Pediatr Crit Care Med. 2011;12(3):A47.

Van der Vries E, Stelma FF and Boucher CA. Emergence of a multi-drug resistant pandemic influenza A (H1N1) virus. *New Engl J Med* 2010; 363 (14); 1381-82.

Weller S, Jones LS, Lou Y, Peppercorn A, Ng-Cashin J. Pharmacokinetics of intravenous zanamivir in subjects with renal impairment. Infectious Diseases Society of America 48th Annual Meeting. Oct 2010. Presentation #767.

Wijaya L, Chua YY, Cui L, Chan K, Tan BH. Intravenous zanamivir in critically ill patients due to pandemic 2009 (H1N1) influenza A virus. Singapore Med J**.** 2011;52(7): 481.

Wolfe C, Greenwald I, and Chen L. Pandemic (H1N1) 2009 and oseltamivir resistance in Hematology/ Oncology Patients. Emerging Infectious Diseases. www.cdc.gov/eid. Vol. 16, No. 11, November 2010.

Wolfe C, Turner D, Rudd C, Pham J, Cheifetz I. Intravenous Zanamivir for Critical Illness due to Pandemic H1N1 Influenza. Society of Critical Care Medicine 40th Critical Care Congress. Jan 2011. Posters #777.

APPENDIX 7: SUMMARY OF CLINICAL SAFETY FOR ZANAMIVIR

An overview of the available safety data for IV zanamivir from Phase I studies, Phase II and Phase III studies and the Compassionate Use Program

1.0. Overall Risk-Benefit Assessment

IV zanamivir has been made available under the Compassionate Use Program for seriously ill, hospitalised patients with proven or suspected influenza infection and for whom suitable approved alternative anti-viral treatment is unavailable, inappropriate or ineffective. A large recent retrospective study of hospitalised patients with influenza A H1N1pdm2009 found that antiviral treatment was often delayed, especially in the presence of concurrent pneumonia, leaving them at risk for severe outcomes including ARDS, sepsis and death (Jain 2012). The severity of the influenza-related disease or of the underlying medical conditions and concomitant medications in patients receiving intravenous zanamivir in this compassionate use program confounds the analysis of a potential association between intravenous zanamivir and the adverse events reported.

No new important safety information which would impact negatively on the risk to benefit balance of IV zanamivir has been identified from the compassionate use program to date or from the concluded clinical studies outlined as follows and the risk/benefit profile of IV zanamivir for the treatment of influenza infection under the compassionate use program continues to be favourable. The compassionate use program is ongoing and all data collected will continue to be monitored and assessed on a regular basis.

2.0. Relenza for Inhalation Safety Summary

Data from both treatment and prophylaxis studies supporting the registration of inhaled zanamivir (RELENZA) indicated a safety profile comparable to placebo. No differences were observed between treatment groups in studies involving pediatric, elderly or high-risk subjects. Relenza has been marketed since 1999; post-marketing safety monitoring has included reports of severe skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Reactions such as rash, vasovagal-like reactions, bronchospasm, dyspnoea, convulsions and psychiatric events such as depressed level of consciousness, abnormal behaviour, hallucinations and delirium have also been reported during Relenza administration in patients with influenza.

3.0. Intravenous Zanamivir Exposure

As part of the early clinical pharmacology program for inhaled zanamivir, subjects were exposed to IV zanamivir in a number of studies to test effects of systemic exposure. In these studies, 193 healthy adult subjects received single doses of zanamivir (ranging from 1 to 600mg) and 85 healthy adult subjects received multiple doses of zanamivir (two doses of 100, 200 or 600mg IV; 600mg IV twice daily for

five days; or continuous infusion for 12 hours after a loading dose). Exposure from the Phase II and Phase III studies as well as the CU program are discussed below.

3.1. Phase I Clinical Pharmacology Safety Summary

In an integrated safety analysis of clinical studies of IV zanamivir performed prior to 2006, the most commonly reported drug-related AE was headache (14% in Study NAIB1008 and 17% in Study NAIB1009). Across clinical studies in which the IV formulation was evaluated, there were no clinically significant trends in laboratory values, ECG findings, or vital signs.

Studies NAI106784, NAI108127 and NAI114346 discussed below were conducted after the pre-2006 integrated safety analysis was performed.

3.2. Study NAI106784 (BAL Study)

In this study to evaluate serum and pulmonary PK following administration of inhaled (n=6) and IV zanamivir (n=36) to healthy adult subjects, the overall safety profile for inhaled zanamivir (two 10mg doses 12 hours apart) and zanamivir administered IV (two doses of 100mg, 200mg or 600mg 12 hours apart) or as a 12-hour continuous infusion (6mg loading dose plus 3mg/h) was similar to the previously reported safety profile for zanamivir. Zanamivir administered as a continuous infusion had a similar safety profile as that observed with the intermittent infusion. No SAEs or deaths were reported in this study.

The most commonly reported AEs were leukocytosis (6 reports), neutrophilia (5 reports), post-procedural complications (5 reports), pharyngolaryngeal pain (4 reports), dizziness (4 reports) and cough (3 reports). Three subjects reported 4 AEs which were considered by the investigator to be drug-related. The drug-related AEs were abnormal T-wave on ECG, back pain, pain in extremity, and headache. No severe AEs were reported.

One subject was withdrawn from the study due to an AE: a subject in the zanamivir 600mg IV q12h group had a mild abnormal T wave on ECG that was considered by the investigator to be possibly related to study drug. The subject remained asymptomatic with stable vital signs. Creatine kinase-MB and troponin tests were normal. Medical follow-up excluded cardiac ischemia. The ECG returned to baseline in 7 days. This report was the only clinically significant ECG value documented during the study.

3.3. Study NAI108127 (Renal Impairment Study)

In this study evaluating safety and PK after administration of single doses of 100mg IV zanamivir to 16 subjects with normal or impaired renal function, 1 subject with a prior history of coronary artery disease was withdrawn due to an SAE of myocardial infarction, which was not related to investigational product. Few AEs were reported during the study. Only two AEs were reported in more than one subject: diarrhea (3 subjects) and headache (3 subjects).

3.4 Study NAI114346 (Thorough QTc Study)

In this study, 40 healthy adults were enrolled and received single doses of IV zanamivir (600 mg and 1200 mg), IV placebo, and oral moxifloxacin 400 mg as a

positive control in a randomized crossover. A total of 10 subjects (25%) reported 18 AEs during the study, however only 3 subjects reported 4 AEs during treatment with IV zanamivir 600 mg or 1200 mg. All AEs were Grade 1, with the exception of two AEs of Grade 2 vomiting (1 during placebo and 1 during moxifloxacin treatments). The most frequently reported AE was headache, which was experienced by 1 subject (3%) receiving zanamivir 600 mg, 3 subjects (8%) receiving placebo, and 2 subjects (5%) receiving moxifloxacin. No drug-related AEs occurred during treatment with IV zanamivir 1200 mg and only 1 drug-related AE occurred during treatment with IV zanamivir 600 mg (Grade 1 headache). There were no deaths, serious or severe AEs, or AEs leading to withdrawal. No clinically significant trends in laboratory values, vital signs, or safety ECGs were observed. Neither the single therapeutic (600 mg) dose nor the single supratherapeutic (1200 mg) dose of IV zanamivir had any effect on cardiac repolarization as measured by QTc interval duration.

3.5. Phase II Study NAI113678 (Open label Study in Hospitalized Subjects)

A total of 201 subjects were treated with IV zanamivir in the open-label Phase II study NAI113678, including 14 adolescents (age 13 to <18 years), 57 pediatric subjects (6 months to <13 years), 3 pregnant and one immediate post-partum subjects. Subjects received 600 mg IV zanamivir adjusted for age and renal function for a duration of 5 to 10 days.

Data for the adult cohort are final, but as statistical analysis for the adolescent and pediatric cohorts is still ongoing, the data for these younger subjects are preliminary and may be subject to change.

No safety signals or clinically significant trends in laboratory values, vital signs or ECGs that were considered attributable to the administration of IV zanamivir were identified in the adult cohort or, based on preliminary analysis, in the adolescent/pediatric cohort. Eighty-five percent of adults and 72% of adolescents/pediatrics reported AEs during the study while SAEs were reported for 34% of adults and 21% of adolescents/pediatrics. The all cause mortality rate was 20% for adults and 7% for adolescent/pediatric subjects, which is comparable to or better than that reported for other similar populations with severe influenza described in this time period. No fatal SAEs were attributable to study drug. Protocol defined liver events meeting stopping criteria were identified in 13% of adult subjects and 3% of adolescent/pediatric subjects; however, causality was confounded by ICU status, multi-system organ failure, influenza strain (elevated liver enzymes have been noted in hospitalized patients infected with influenza A/H1N1pdm2009 [**Error! Reference source not found.**, 2012]), underlying medical conditions and numerous concomitant medications. There was no overall change in median ALT, AST or bilirubin.

3.6. Phase III Study NAI114373 (Randomized, Double-blind Study in Hospitalized Subjects)

The study enrolled a total of 626 subjects of which 615 received at least one dose of investigational product and comprised the Safety Population. Subjects were randomized to either 600mg IV zanamivir, 300mg IV zanamivir or 75mg oral oseltamivir, twice daily for 5 to10 days.

Statistical analysis of NAI114373 is ongoing, therefore the data provided are preliminary and may be subject to change.

Adverse events were reported in 61% of subjects, reflecting a hospitalized patient population. The nature and frequency of adverse events were similar across treatment groups. The most commonly reported AEs were diarrhea, constipation and increased ALT.

Adverse events considered by the investigator to have a possible causal relationship to the study drug were reported in 13% of subjects, with slightly more considered attributable to study drug in the oseltamivir arms (17%) compared with the 300mg and 600mg IV zanamivir arms (12% and 11%, respectively).

One hundred and nine subjects (18%) reported SAEs during the study, there were no notable differences in SAEs across treatment groups (Table 1) and reported SAEs were consistent with the population of hospitalized patients with complicated/severe influenza illness.

Table 1 Serious Adverse Events (Including Fatal Events) occurring in at least 2% of Subjects in any Treatment Group (Safety Population)

Preferred Term	IV zanamivir 300mg (N=201) n (%)	IV zanamivir 600mg (N=209) n (%)	Oseltamivir 75mg (N=205) n (%)
Any Event	**38 (19)**	**33 (16)**	**38 (19)**
Respiratory failure	5 (2)	4 (2)	5 (2)
Pneumonia	7 (3)	1 (<1)	4 (2)
Acute respiratory distress syndrome	4 (2)	3 (1)	0
Septic shock	4 (2)	1 (<1)	2 (<1)
Acute kidney injury	4 (2)	0	0

Forty one subjects (7%) died during the study, 15 subjects (7%) in each of the IV zanamivir groups and 11 subjects (5%) in the oseltamivir group. The most common causes of death were respiratory failure, acute respiratory distress syndrome and septic shock.

The number of protocol defined liver events reported was low (2%) and was similar across treatment groups. There were no notable differences in clinical laboratory results or pattern of laboratory AEs across treatment groups.

3.7. Global Compassionate Use Program

All patients in the global IV zanamivir CU program were critically ill, with comorbidities and concurrent treatments, and lacked a comparison group. The severity of the influenza-related disease or of the underlying concurrent medical conditions in patients receiving IV zanamivir in this program confounds the analysis of a potential association with IV zanamivir.

3.7.1. Overview of Safety Data

As of the data-lock of 30 April 2015, SAEs had been reported in 350 of approximately 2393 patients treated in the CUP. A total of 630 SAEs were reported in these 350 patients. Figure 1 presents the distribution, by percentage of MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class, of the primary SAE reported for each patient.

Table 2 presents zanamivir exposure, SAEs and deaths data, grouped by age decade.

Of 280 patients with a fatal outcome, 5 were in pregnant or post-partum women, and 27 were in paediatric patients (<18 years of age). Sixty-four fatal cases were considered to be related or possibly related to zanamivir (including unknown causality reports). Where sufficient information was available, the large majority of these 64 fatal cases were confounded by severe concurrent medical conditions.

A total of 70 of the 350 patients with SAEs did not have a fatal outcome; 2 patients were pregnant and 7 were in paediatric patients. Of these 70 patients, the SAEs were considered related to zanamivir in 44 patients; the majority of these were confounded by severe concurrent medical conditions.

Figure 1 Distribution of Serious Adverse Events by System Organ Class (n=350 patients)

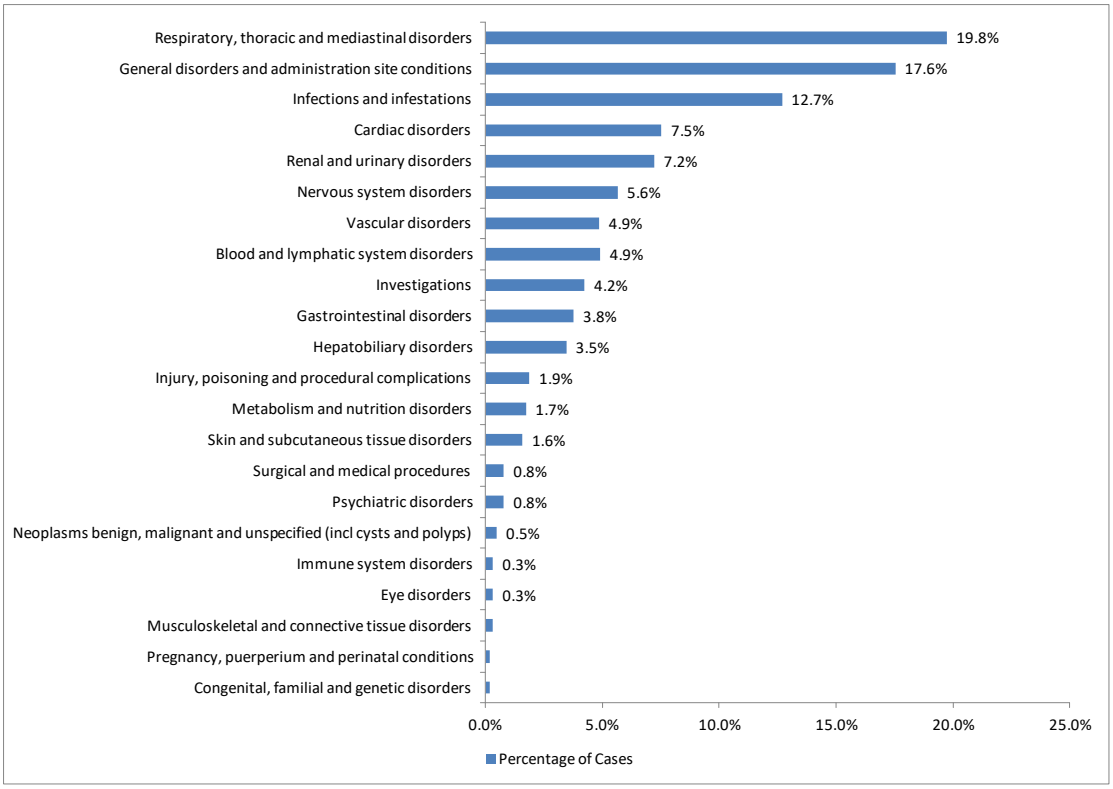


Table 2 Cumulative Summary by Age Decade of Number of SAEs and Deaths to 30 April 2015

Age (years)	No. of Patients treated	No. of patients with an SAE	No. of Deaths reported
<10	184	17	12
10 – 19	117	21	17
20 – 29	217	31	20
30 – 39	374	44	37
40 – 49	432	62	49
50 – 59	565	80	60
60 – 69	345	47	41
70 – 79	118	16	15
80 – 89	27	1	1
≥90	5	0	0
Unconfirmed age adults >18 yrs	0	3	0
Age unknown[1]	9	28	28
TOTAL	**2393**	**350**	**280**

[1]'No. of patients treated' (column 2) was obtained from the CRO handling drug provision to site and 'No. of patients with an SAE/Death' (columns 3 and 4) was obtained from the treating physician via an SAE form. The variable 'Age' was not available in the SAE form for 28 patients and was not fully reconciled between the two data sources

Appendix 7 References

Jain S, Benoit SR, Skarbinski J, Bramley AM, Finelli L. Influenza-associated pneumonia among hospitalised patients with 2009 pandemic influenza A (H1N1) virus – United States, 2009. *Clin Infect Dis* 2012;54(9):1221-9.

Papic N, Pangercic A, Vargovic M, et al. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. Influenza and Other Respiratory Viruses. 2012. 6(3), e2–e5.