

**GUIDANCE DOCUMENT**

**ZANAMIVIR AQUEOUS SOLUTION FOR COMPASSIONATE USE IN  
SERIOUS INFLUENZA ILLNESS**

**BACKGROUND**

Limited supplies of zanamivir aqueous solution are available on a compassionate use basis for the treatment of serious influenza illness in the setting of a pandemic threat. 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. In clinical studies, zanamivir solution has been administered to 120 patients by the IV route, at doses up to 600mg twice daily for 5 days. In addition, a total of 126 patients enrolled in several clinical trials received zanamivir solution administered via nebulization at doses of up to 16mg four times daily for 5 days. Furthermore, an additional 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 all studies, zanamivir was generally well tolerated and no clinically significant safety issues were identified.

**OBJECTIVES**

1. To provide a mechanism to supply zanamivir aqueous solution on a compassionate use basis for treatment of serious influenza illness in the setting of a pandemic threat.
2. To obtain limited pharmacokinetic, safety and efficacy information on zanamivir aqueous solution when administered by inhaled nebulized or IV route.

**PATIENTS**

**Inclusion Criteria**

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

- Male or female patients hospitalized with serious influenza illness in the setting of a pandemic threat.
- Laboratory confirmation of influenza (e.g. by PCR, rapid assay or culture)
- Patients unable to use the other approved influenza antiviral drugs, or in whom treatment with nebulized or IV zanamivir is considered more appropriate.
- For IV administration of zanamivir, patients must be  $\geq 6$  months of age.

**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 fetus.  
Note: The safety of zanamivir when used during pregnancy has not been established. Reproductive studies performed in rats and rabbits indicated that placental transfer of

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zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer in humans.

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

## DOSAGE AND ADMINISTRATION

### 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 (infants  $\leq 6$  months should receive nebulized zanamivir)
- 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 exposure)
  - underlying airways disease (IV administration is recommended)

### Dosage Regimen

#### IV Administration:

The standard dosage for IV administration is 600mg twice daily for individuals  $\geq 13$  years of age with normal renal function. The appropriate dosage for younger children and infants should be determined by body weight (Table 1). In addition, subjects with renal impairment should receive an adjusted dose of IV zanamivir based on calculated creatinine clearance (Table 1).

**Table 1. Twice-Daily Dose Regimens of IV Zanamivir for Adults, Children and Individuals with Renal Impairment (see IV Preparation below for details)**

Adults and Adolescents	CLcr (mL/min)				
	$\geq 80$	50 to $<80$	30 to $<50$	15 to $<30$	$<15$
	600 mg	400 mg	250 mg	150 mg	60 mg
Pediatrics ( $\geq 6$ months)	CLcr (mL/min/1.73m <sup>2</sup> )				
	$\geq 80$	50 to $<80$	30 to $<50$	15 to $<30$	$<15$
Weight Range					
19 to 37 kg <sup>1</sup>	16 mg/kg	11 mg/kg	6.5 mg/kg	4 mg/kg	1.5 mg/kg
11 to $<19$ kg	20 mg/kg	13 mg/kg	8 mg/kg	5 mg/kg	2 mg/kg
$<11$ kg	24 mg/kg	16 mg/kg	10 mg/kg	6 mg/kg	2.5 mg/kg

<sup>1</sup> Children who are less than 13 years of age but who weigh  $>37$ kg should receive the recommended dose for adults and adolescents.

*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.

**Duration**

The duration of treatment for both IV and nebulized zanamivir is 5 days. Physicians should consider extending the initial 5-day treatment course for an additional 5 days if ongoing viral shedding is detected. Requests for additional treatment should be directed to GlaxoSmithKline.

**PHARMACEUTICAL INFORMATION**

**Presentation**

Zanamivir aqueous solution 10mg/mL is supplied as a sterile clear, colorless 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 at up to 30°C.

**Nebulized Zanamivir Preparation**

A 5 day treatment course for 1 patient requires 5 vials.

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.

Any solution remaining in the vial 24 hours after the sterile seal is first breached should be discarded; the product is non-preserved. During that 24 hour period the vial should be refrigerated.

**IV Zanamivir Preparation**

A standard 5 day treatment course (600 mg twice daily) for an adolescent or adult with normal renal function requires 30 vials. However, weight-based (mg/kg) doses for children are less than 600mg BID. Additionally, zanamivir is renally eliminated as unchanged drug, and dosage should be adjusted for subjects with renal impairment. Accordingly, the actual number of vials required for IV administration will differ based on patient age/weight and renal function.

*IV Zanamivir Dosage Determination for Adolescents and Adults:*

- Assess renal function by determination of creatinine clearance (CL<sub>Cr</sub>, in mL/min), which may be calculated from age, body weight, serum creatinine and gender, as follows:

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For serum creatinine in units of mg/dL:

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

where AGE = age in years, WT = body weight in kg, and Scr = serum creatinine in mg/dL. For pregnant women, pre-pregnancy body weight should be used in the calculation.

For serum creatinine in units of micromoles/liter:

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

where AGE = age in years, WT = body weight in kg, and Scr = serum creatinine in  $\mu$ M. For pregnant women, pre-pregnancy body weight should be used in the calculation.

- Based on the CLcr determination, adults and adolescents should receive IV zanamivir doses ranging from 60 to 600 mg twice daily, as shown:

Adults and Adolescents	CLcr (mL/min)				
	$\geq 80$	50 to <80	30 to <50	15 to <30	<15
	600 mg	400 mg	250 mg	150 mg	60 mg

- The total volume of zanamivir solution required per dose (“mL ZAN”) = Dose (mg) \* 1 mL/10 mg, where “Dose (mg)” is taken from table above. This volume (“mL ZAN”) is referenced in the text below describing preparation of the IV solution.
- Based on renal function, the number of vials of zanamivir solution required for a 5-day treatment course for adolescents or adults is:

CLcr (mL/min)	# Vials for 5-day Treatment Course <sup>a</sup>
<15	5
15 to <30	10
30 to <50	15
50 to <80	20
$\geq 80$	30

<sup>a</sup> Number of vials specified allows for at least one new vial per day and is, therefore, a potential overage of that actually needed.

*IV Zanamivir Dosage Determination for Children ( $\geq 6$  months of age):*

- Assess renal function by determination of creatinine clearance (CLcr, in mL/min/1.73m<sup>2</sup>), which may be calculated from height and serum creatinine, as follows:

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For serum creatinine in units of mg/dL:

$$CLcr(mL/min/1.73m^2) = \frac{0.55 \cdot HT}{Scr}$$

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

For serum creatinine in units of micromoles/liter:

$$CLcr(mL/min/1.73m^2) = \frac{48.6 \cdot HT}{Scr}$$

where HT = height in cm and Scr = serum creatinine in  $\mu$ M.

- Based on the CLcr determination and body weight, children should receive IV zanamivir doses (mg/kg) ranging from 1.5 to 24 mg/kg twice daily, as shown:

Pediatrics ( $\geq 6$ months)	CLcr (mL/min/1.73m <sup>2</sup> )				
	$\geq 80$	50 to <80	30 to <50	15 to <30	<15
Weight Range					
19 to 37 kg <sup>1</sup>	16 mg/kg	11 mg/kg	6.5 mg/kg	4 mg/kg	1.5 mg/kg
11 to <19 kg	20 mg/kg	13 mg/kg	8 mg/kg	5 mg/kg	2 mg/kg
<11 kg	24 mg/kg	16 mg/kg	10 mg/kg	6 mg/kg	2.5 mg/kg

<sup>1</sup> Children who are less than 13 years of age but who weigh >37kg should receive the recommended dose for adults and adolescents.

- The total volume of zanamivir solution required per dose (“mL ZAN”) = Dose (mg/kg) \* WT (kg) \* 1 mL/10 mg, where “Dose (mg/kg)” is taken from the table above. This volume (“mL ZAN”) is referenced in the text below describing preparation of the IV solution.

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- Based on renal function and body weight, the number of vials of zanamivir solution required for a 5-day treatment course for children is:

CLcr (mL/min/1.73m <sup>2</sup> )	Weight Range (kg)	# Vials for 5-day Treatment Course <sup>a</sup>
<15	All ≤ 37	5
15 to <30	≤ 25	5
	>25 to 37	10
30 to <50	≤ 12	5
	>12 to 30	10
	>30 to 37	15
50 to <80	≤ 6	5
	>6 to 15	10
	>15 to 27	15
	>27 to 37	20
≥ 80	≤ 8	10
	>8 to 15	15
	>15 to 25	20
	>25 to 31	25
	>31 to 37	30

<sup>a</sup> Number of vials specified allows for at least one new vial per day and is, therefore, a potential overage of that actually needed..

Use of aseptic techniques is required throughout preparation of the dose. To avoid volume dilution, withdraw and discard “mL ZAN” (see description above) saline from a 250mL IV Infusion bag containing 0.9% sodium chloride prior to addition of zanamivir solution (bags may have a further overage of saline included, which can also be removed if considered necessary). Use a sterile syringe to withdraw “mL ZAN” from the required number of 20mL vials of zanamivir solution and inject volume into the saline bag. (Note: the 250mL infusion volume referenced here is appropriate for standard dosing of adults and adolescents with normal renal function. Volume adjustments for pediatric patients and individuals with renal impairment may be appropriate based on the total dose and volume of zanamivir administered. *It is important that the final concentration of zanamivir administered should NOT be lower than 0.2mg/mL.*)

After the zanamivir solution is added to the saline bag, the contents should be gently manipulated by hand, in order to mix thoroughly. The dose should then be administered to the patient within 24 hours of the preparation of the bag. If the bag is not administered immediately after preparation, it should be refrigerated to minimize the opportunity for microbial proliferation.

Zanamivir infusion should be administered at a constant rate over approximately 30 minutes (e.g., at an infusion rate of 500mL/hr for a 250mL infusion volume). Infusions should be given approximately 12 hours apart. For patients on intermittent hemodialysis, the schedule should be arranged so that the recommended dose of zanamivir is given after completion of hemodialysis.

**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, centers 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.**

**DATA COLLECTION**

In order to maintain a register of all patients who receive zanamivir solution on a compassionate use basis, and to obtain consistent baseline and follow-up data on these patients, the following brief information is requested on the Data Collection form provided.

**Baseline data and relevant medical history:** to include Emergency IND number (US only), investigator name and institution, patient number (a chronological number assigned by your institution is sufficient), date of birth (age), sex, ethnic origin, a brief medical history including co-morbidities, pregnancy status, relevant concurrent medications, nature of influenza symptoms and date/time of onset of influenza symptoms. Comments regarding the following assessments/evaluations would also be helpful to include: temperature, vital signs, oxygen saturation, and chest X-ray.

**Diagnosis of influenza infection:** the dates, methods and results of influenza virus diagnosis.

**Relevant medications/interventions:** details and dates of other relevant medications/interventions, such as mechanical ventilation and supplemental oxygen.

**Zanamivir treatment:** a record of the zanamivir treatment administration including date, dose and dosing frequency.

**Collection of virology samples:** if samples were collected, a record is required of the date, timing of the sample (e.g. pre-, during, or post-treatment), source of sample, and method of isolation.

**Collection of pharmacokinetic samples:** if samples were collected for pharmacokinetic analysis, record the actual date and time of each PK blood sample, along with the date, start time and end time of the associated zanamivir dose.

**Clinical progression of influenza and outcome for the patient:** a brief narrative of the progression of disease, and clinical outcome for the patient. Comments regarding the following assessments/evaluations would be helpful to include: influenza symptoms, temperature, vital signs, oxygen saturation, chest X-rays, and length of hospitalization.

### **Return of information to GlaxoSmithkline**

Once the outcome for the patient is known, the Data Collection form should be returned to GlaxoSmithKline.

### **SAFETY EVALUATIONS**

**Recording of adverse events.** The requesting physician is responsible for reporting all events meeting the criteria and definition of a serious adverse event (SAE). All patients that receive at least one dose of zanamivir should be monitored. Serious adverse events should be reported in the Serious Adverse Event forms provided, from the time of first dose of study drug until up to 14 days after completing treatment.

#### **Definition of a 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 subject 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 subject 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 judgement 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 subject 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.

## VIROLOGY SAMPLES

Virology samples can provide highly valuable information. If taken, samples should be sent to Phil Yates in Clinical Virology, UK (see Appendix 1 for contact details; please call or email for appropriate packaging and shipping information). Depending on the number and quality of the samples, GlaxoSmithKline will conduct a number of laboratory assays to assess susceptibility monitoring, viral load measurement and sequence analysis.

### Sample types

Nasopharyngeal aspirates or throat swabs should be taken immediately prior to treatment, and then ideally, at daily intervals during the course of treatment. If daily sampling is not possible, then samples should be taken as frequently as possible. Swabs should be collected in viral transport medium with antibiotics [0.5% BSA, penicillin (100 – 500 U/mL), streptomycin (100 – 500 µg/mL), gentamicin (100 µg/mL) and amphotericin B (2 µg/mL in MEM)].

### Storage of virology samples

Samples should be stored at -70°C. Freezing and thawing significantly reduces the chances of recovering live virus and viral RNA, so this should be avoided if at all possible. If -70°C storage is not available, please store samples at 4°C for up to 48 hours and contact GlaxoSmithKline to arrange shipment. Do not place any samples at -20°C as this temperature does not allow virus recovery on thawing.

## PHARMACOKINETIC SAMPLES

Physicians are encouraged to collect samples for pharmacokinetic (PK) analysis when feasible. For each patient, 3 blood samples (3mL each) should ideally be collected, as follows:

### IV administration:

- Sample 1 to be taken at 30 minutes (just prior to end of infusion) after the first dose on Day 1
- Sample 2 to be taken pre-dose (prior to start of infusion), and
- Sample 3 to be taken at 30 minutes (just prior to end of infusion) after a dose on Day 4 or Day 5 of treatment (Samples 2 and 3 should bracket the same dose).

### Nebulized administration:

- Sample 1 to be collected within 0.5 – 1.5 hours after the first dose on Day 1
- Sample 2 to be collected pre-dose (just prior to start of nebulization), and
- Sample 3 to be collected 0.5 – 1.5 hours post-dose after a dose on Day 4 or 5 of treatment (Samples 2 and 3 should bracket the same dose)

Blood for pharmacokinetic assessments may be obtained by individual needle stick or via IV cannula, and should be collected into a labeled 3mL red top (plain tube, no anticoagulant) collection tube. If a cannula is used for collection of the whole blood samples, the cannula should be inserted into an arm vein within sufficient time before sample collection and may be kept patent using a dilute heparin solution as a flush. An

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initial volume of approximately 1.0 mL of blood will be collected and discarded prior to collection of each 3 mL whole blood sample to ensure that the saline or heparin solution does not artificially dilute the samples. If PK samples are collected via individual needle sticks rather than through a cannula, then no extra blood needs to be collected and discarded prior to the collection of the sample.

Upon collection, blood samples should be allowed to coagulate at room temperature for 30 minutes and then centrifuged for 15 minutes at 1000 g (preferably at 4°C). After centrifugation, the serum fraction of each sample should be transferred via pipette to a 1.8mL NUNC tube and immediately stored in an upright position in a non-self-defrosting freezer at -30°C or colder (-70°C preferred) until shipped to GlaxoSmithKline for analysis. The storage tube should be labelled with physician name and/or institution, patient number, and date/time of the blood sample collection. The label should be affixed so that all information remains legible. The actual date and time of each PK blood sample collection should be recorded on the data collection form, along with the date, start time and end time of the associated zanamivir dose.

If obtained, serum PK samples should be sent to:

Chad Woodard  
GlaxoSmithKline  
2512 South Tricenter Blvd  
Docks 16-18  
Durham, NC 27713 USA

Please call one of the pharmacokinetics contacts noted in Appendix 1 prior to shipment for appropriate packaging and shipping details.

## APPENDIX 1. GlaxoSmithKline Contact Information

### Clinical Virology Contact

Questions relating to virology samples should be directed to Phil Yates (UK):  
Telephone: +44 1438 763887  
Fax: +44 1438 768232  
Email: phil.j.yates@gsk.com

### Pharmacokinetics Contacts

Questions related to pharmacokinetic samples should be directed to one of the following:

Chad Woodard	+1 919-483-8363
Johanna Morrill	+1 919-483-1175
John A Dunn	+1 919-483-1235

### Clinical Contacts

Questions regarding clinical (non-medical) matters can be directed to:

Choy Man (US)  
Telephone: +1 919 483 8039  
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**Medical Advisors**

Questions about medical/clinical matters should be addressed to:

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