Hospital Authority
Information on the Use of Intravenous Zanamivir and Peramivir in Human Swine Influenza

1. Background

Intravenous neuraminidase inhibitor, namely Zanamivir and Peramivir, are used in clinical trials or as alternatives for the treatment of severe influenza illness in pandemic on a compassionate-use basis such as Human Swine Influenza (HSI)[1]. Peramivir is an unapproved drug which has been granted Emergency Use Authorization (EUA) on 19 November 2009 by the US FDA for treatment of pandemic influenza in the US only[2-4]. Currently, Zanamivir and Peramivir are unregistered drugs in Hong Kong. Department of Health (DH) has approved Peramivir as "Emergency Stock" which requires retrospective report to DH about the names who have been given the drug according to legal requirement. The Task Force on Human Swine Influenza has reviewed the clinical evidence as well as drug insert and came to a consensus on the suggested use of these two drugs in HA hospitals. When prescribing these drugs, clinicians have to follow current policy on the use of unregistered drugs in HA hospitals, to seek approval from the COS of the department and to inform hospital pharmacy of the administration.

2. Clinical information of Zanamivir and Peramivir

2.1 Evidence showed that Zanamavir might be effective in isolates of influenza A/H1N1 with oseltamivir resistance due to H275Y/H274Y mutation[5-6]. However, there is lack of clinical data on its efficacy in young children particular those aged below 6 months.

2.2 Clinical trials showed that Peramivir has non-inferiority to oseltamivir in treatment effectiveness. There is no clinical data for those aged below 18 years old. Peramavir should not be used in patients with documented or highly suspected oseltamivir resistance due to H275Y/H274Y mutation

3. Recommended Indications

As salvage therapy for hospitalized patients with severe or critical conditions due to HSI (e.g. viral pneumonia with respiratory failure), the followings are suggested indications on the use of intravenous Zanamivir and Peramivir for HSI patients:

3.1 Patient not responding to either oral oseltamivir or inhaled zanamivir, or

3.2 Drug delivery by a route other than IV (e.g. enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or

3.3 The clinician judges IV therapy is appropriate due to other circumstances.

4. Informed Consent

The Task Force recommended obtaining informed consent from patients prior to prescription of these drugs. In case the patient was in altered mental status, signatures of two registered medical practitioners are required. Clinicians are suggested to inform patients or their next-of-kin these are unregistered drugs authorized for use in emergency situations.

5. Regimens

The standard regimen of intravenous Zanamivir for adults with normal renal function is 600mg twice daily; for Peramivir, the recommended regimen is 600mg daily. Dosage adjustment is needed for patients with renal impairment and for paediatric patients.

Initial Dose Amounts [1] and Twice Daily Maintenance Dose Regimens of IV Zanamivir for Adults, Adolescents, Children and Individuals with Renal Impairment

Adults and Adolescents	**Initial Dose [1]**	**Maintenance Dose**				
		CrCl (mL/min)				
		≥ 80	**50 to <80**	**30 to <50**	**15 to <30 [3]**	**<15 [4]**
	600 mg	600 mg	400 mg	250 mg	150 mg	60 mg
Paediatrics (≥6 months) Weight Range	**Initial Dose [1]**	**Maintenance Dose**				
		CrCl (mL/min/1.73m^2)				
		≥ 80	**50 to <80**	**30 to <50**	**15 to <30 [3]**	**<15 [4]**
19 to 37 kg [2]	16 mg/kg	16 mg/kg	11 mg/kg	6.5 mg/kg	4 mg/kg	1.5 mg/kg
11 to <19 kg	20 mg/kg	20 mg/kg	13 mg/kg	8 mg/kg	5 mg/kg	2 mg/kg
<11 kg	24 mg/kg	24 mg/kg	16 mg/kg	10 mg/kg	6 mg/kg	2.5 mg/kg

1. The initial dose for each subject is the dose specified for CrCl ≥ 80, i.e. 600mg for adults and adolescents and either 16, 20 or 24 mg/kg for paediatrics ≤37 kg body weight.
2. Children who are <13 years of age but who weigh >37kg should receive the recommended dose for adults and adolescents.
3. The time interval between initial dose and start of maintenance doses for subjects with CrCl of 15 to <30 is 24h.

The time interval between initial dose and start of maintenance doses for subjects with CrCl of <15 is 48h.

Once-Daily Dose Regimens of IV Peramivir for Adults, Children and Individuals with Renal Impairment

Adults	**CrCl (mL/min)**			
	50 to 80	**31 to 49**	**10 to 30**	**<10 or haemodialysis**
	600 mg	150 mg	100 mg	100 mg on Day 1, then 100 mg given 2 hrs after each HD session **on dialysis days only**

Paediatrics[2] Age	**CrCl (mL/min/1.73m^2)**				
	50 to 80	**31 to 49**	**10 to 30**	**<10, not on intermittent HD or CRRT**	**<10, on intermittent HD**
Birth to 30 days	6 mg/kg	1.5 mg/kg	1 mg/kg	1 mg/kg on Day 1, then 0.15 mg/kg QD	1 mg/kg on Day 1, then 1 mg/kg given 2 hrs after each HD session **on dialysis days only**
31 days to 90 days	8 mg/kg	2 mg/kg	1.3 mg/kg	1.3 mg/kg on Day 1, then 0.2 mg/kg QD	1.3 mg/kg on Day 1, then 1.3 mg/kg given 2 hrs after each HD session **on dialysis days only**
91 days to 180 days	10 mg/kg	2.5 mg/kg	1.6 mg/kg	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**
181 days to 5 years	12 mg/kg	3 mg/kg	1.9 mg/kg	1.9 mg/kg on Day 1, then 0.3 mg/kg QD	1.9 mg/kg on Day 1, then 1.9 mg/kg given 2 hrs after each HD session **on dialysis days only**
6 years to 17 years	10 mg/kg	2.5 mg/kg	1.6 mg/kg	1.6 mg/kg on Day 1, then 0.25 mg/kg QD	1.6 mg/kg on Day 1, then 1.6 mg/kg given 2 hrs after each HD session **on dialysis days only**

[2] Dosing in pediatric patients is based upon modeling. No paediatric patients have received Peramivir in clinical trials.

6. Monitoring

Monitor patients clinically for occurrence of adverse events (e.g. allergic reaction) and the laboratory parameters as shown in the following table. Any adverse events should be recorded in detail in medical records.

Laboratory Parameter	Timing
Complete blood picture with differential counts	On initiation, Day 3 of therapy and end of therapy, and during therapy if clinically indicated
Glucose, calcium, serum bicarbonate, renal function tests	On initiation, Day 3 of therapy and end of therapy, and during therapy if clinically indicated
Liver function tests	On initiation and conclusion of therapy, and during therapy if clinically indicated
Urinalysis	On initiation and conclusion of therapy, and during therapy if clinically indicated.
Creatinine clearance (serum creatinine at a minimum)	Completed prior to initiation of dosing and followed carefully throughout dosing as clinically appropriate

7. Reference

1. Calfee DP, Peng AW, Cass LM, Lobo M, Hayden FG. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999;43(7):1616-20.
2. http://www.cdc.gov/h1n1flu/eua/EUA%20Peramivir%20Letter%20-%20Frieden.pdf, Accessed on 29 December 2009.
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4. Birnkrant D, Cox E. The Emergency Use Authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med* 2009;361(23):2204-7.
5. Kidd IM, Down J, Nastouli E, Shulman R, Grant PR, Howell DC, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 2009;374(9694):1036.
6. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients - Seattle, Washington, 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(32):893-6.