Drug Name	**Peramivir**
Brand Name(s)	Rapivab
Drug Class	Neuraminidase inhibitor
Restriction level	**Restricted to Infectious Diseases and Pulmonology/Critical Care**
Accepted Indications	Management of Influenza A or B in patients with the following: • Strict NPO (no NGT/OGT/G-tube/J-tube) • Concerns about poor gut absorption (i.e. ileus)
Unacceptable Uses	Management of Influenza A or B in a patient who can tolerate oral therapy whether by mouth, G-tube, or J-tube
Side Effects	Insomnia (3%), Diarrhea (8%), Hyperglycemia (serum glucose >160 mg/dL, 5%), Neutropenia (8%), Increased serum ALT/AST (3%), Increased CPK, 4%
Pregnancy Class	C
Dosing	**Adult**: 600 mg IV once* <u>Renal dosing:</u> - CrCl 30-50 mL/min: 200 mg dose IV once* - CrCl 15-29 mL/min: 100 mg dose IV once* - CrCl <10 mL/min or ESRD on HD: 100 mg dose once after HD‡ **Pediatrics**: - Children: 2-12 years: 12 mg/kg as a single dose; maximum 600mg - Adolescents ≥13 years: Refer to adult dosing <u>Renal dosing:</u> Infants, Children, and Adolescents <18 years: **Note:** Dosage adjustment based on renal function estimated using the Schwartz equation. CrCl ≥50 mL/minute/1.73 m^2: No adjustment necessary CrCl 31 to 49 mL/minute/1.73 m^2: 29 to 30 days of life: 1.5 mg/kg/dose once daily for 5 to 10 days 31 to 90 days of life: 2 mg/kg/dose once daily for 5 to 10 days 91 to 180 days of life: 2.5 mg/kg/dose once daily for 5 to 10 days 181 days of life through 5 years: 3 mg/kg/dose once daily for 5 to 10 days; maximum dose: 150 mg/dose 6 to 17 years: 2.5 mg/kg/dose once daily for 5 to 10 days; maximum dose: 150 mg/dose CrCl 10 to 30 mL/minute/1.73 m^2: 29 to 30 days of life: 1 mg/kg/dose once daily for 5 to 10 days 31 to 90 days of life: 1.3 mg/kg/dose once daily for 5 to 10 days 91 to 180 days of life: 1.6 mg/kg/dose once daily for 5 to 10 days 181 days of life through 5 years: 1.9 mg/kg/dose once daily for 5 to 10 days; maximum dose: 100 mg/dose 6 to 17 years: 1.6 mg/kg/dose once daily for 5 to 10 days; maximum dose: 100 mg/dose CrCl <10 mL/minute/1.73 m^2 (**not** on intermittent hemodialysis [HD] or continuous renal replacement therapy [CRRT]): 29 to 30 days of life: 1 mg/kg/dose on day 1, followed by 0.15 mg/kg/dose once daily for a total of 5 to 10 days 31 to 90 days of life: 1.3 mg/kg/dose on day 1, followed by 0.2 mg/kg/dose once daily for a total of 5 to 10 days 91 to 180 days of life: 1.6 mg/kg/dose on day 1, followed by 0.25 mg/kg/dose once daily for a total of 5 to 10 days 181 days of life through 5 years: 1.9 mg/kg/dose on day 1 (maximum dose day 1: 100 mg/dose), followed by 0.3 mg/kg/dose once daily for a total of 5 to 10 days; maximum dose: 15 mg/dose

	6 to 17 years: 1.6 mg/kg/dose on day 1 (maximum dose day 1: 100 mg/dose), followed by 0.25 mg/kg/dose once daily for a total of 5 to 10 days; maximum dose: 15 mg/dose CrCl <10 mL/minute/1.73 m^2 (**on** intermittent HD): 29 to 30 days of life: 1 mg/kg/dose on day 1, followed by 1 mg/kg/dose given 2 hours after each HD session **on dialysis days only** 31 to 90 days of life: 1.3 mg/kg/dose on day 1, followed by 1.3 mg/kg/dose given 2 hours after each HD session **on dialysis days only** 91 to 180 days of life: 1.6 mg/kg/dose on day 1, followed by 1.6 mg/kg/dose given 2 hours after each HD session **on dialysis days only** 181 days of life through 5 years: 1.9 mg/kg/dose on day 1, followed by 1.9 mg/kg/dose given 2 hours after each HD session **on dialysis days only**; maximum dose: 100 mg/dose 6 to 17 years: 1.6 mg/kg/dose on day 1, followed by 1.6 mg/kg/dose given 2 hours after each HD session **on dialysis days only**; maximum dose: 100 mg/dose CRRT: Limited data exist. Estimate total clearance by calculating CRRT clearance (CL_{CRRT}) depending on CRRT modality used (eg, CVVHD, Slow continuous ultrafiltration [SCUF]), plus any residual renal function, and adjust dosage according to CrCl recommendation. Adolescents ≥18 years: **Note:** Dosage adjustment based on renal function estimated using the Cockcroft-Gault formula. CrCl ≥50 mL/minute: No adjustment necessary CrCl 31 to 49 mL/minute: 150 mg once daily for 5 to 10 days CrCl 10 to 30 mL/minute: 100 mg once daily for 5 to 10 days CrCl <10 mL/minute (not on renal replacement therapy): 100 mg on day 1, followed by 15 mg once daily for 5 to 10 days Hemodialysis (HD): 100 mg on day 1, followed by 100 mg given 2 hours after each HD session on dialysis days only *Hospitalized/High risk patients: daily dosing recommended for 5-10 days ‡Hospitalized/High risk patients with CrCl <10 mL/min: - CrCl <10 mL/min: 100mg IV once, then 15mg IV daily - ESRD on HD: 100mg IV then 100mg IV given 2 hours after HD session

Questions to ask prior to approval:

1. Does the patient have laboratory evidence for Influenza A or B infection?
2. Can the patient tolerate any oral therapy (including via G-tube or J-tube)?

Answer of “no” to question #1 should prompt investigation for an alternative diagnosis.

Answer of “yes” to question #2 should prompt switch to oseltamivir.

Background:

Peramivir is one of several FDA approved treatments for Influenza A and B (others include oseltamivir, zanamivir, and baloxavir marboxil). It belongs to the neuraminidase inhibitor (NAI) class and prevents the release of new virions from infected cells. All NAI agents are FDA approved for the treatment of uncomplicated influenza in patients who have been ill for less than 48 hours.

Unlike oseltamivir, peramivir is available for intravenous administration. Most studies involving peramivir have demonstrated its efficacy in outpatient settings compared to placebo.[1] Similar to other NAI agents, when used within 48 hours of symptoms onset, peramivir has demonstrated a decrease in symptoms of influenza by an average of 21 hours compared to placebo. When compared to oseltamivir, peramivir was found to be noninferior.[2]

The use of antivirals for influenza is strongly recommended by both the CDC and the Infectious Diseases Society of America (IDSA) for outpatients at high-risk for developing complications of influenza. This includes the following:

- Children aged <5 years, especially aged <2 years
- Adults aged ≥65 years
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Persons with immunosuppression, including that caused by medications or by HIV infection (highest risk populations are those who are severely immunocompromised such as hematopoietic stem cell transplant recipients)
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection
- American Indian/Alaska Native people
- Persons with extreme obesity (i.e., body mass index ≥40 kg/m^2)
- Residents of nursing homes and other chronic care facilities

Both the CDC and IDSA recommend the use of a NAI in hospitalized patients with influenza *regardless* of whether symptoms have been present for more than 48 hours. While the benefit of NI therapy is best if administered within 48 hours of symptom onset, multiple studies (observational and meta-analyses) have reported clinical benefit even after 48 hours of illness onset. This includes an impact on the severity and incidence of complications influenza, hospital length of stay, and influenza-associated mortality.[1]

Oseltamivir remains the first line NAI for all hospitalized patients. Studies have demonstrated that oseltamivir administered via nasogastric tube in critically ill patients still results in adequate drug exposure. Similar findings have been noted for patients on extracorporeal membrane oxygenation (ECMO).

Use of peramivir should be restricted to those patients who need a NAI and are unable to take anything via the enteric route. There is no data to support peramivir being superior to other NAIs. One study looking at hospitalized patients receiving peramivir versus placebo plus standard of care showed no significant clinical benefit (though the majority of patients on standard of care therapy were receiving another NAI).[3] Combination therapy with other antivirals is not recommended; there is no data to demonstrate an additive or synergistic role with multiple antiviral agents.

While peramivir is FDA approved as a one-time intravenous infusion, clinical expert recommendation is to use daily therapy in high risk, hospitalized patients. Dose adjustments are needed for those with impaired renal function. The recommended duration of therapy is 5 to 10 days.

Note that the resistance mutations on influenza neuraminidase are thought to be shared between oseltamivir and peramivir. Hence, if there is a concern about an oseltamivir resistant influenza virus, it may not be susceptible to peramivir. If there is such a clinical concern, consultation with both Infectious Diseases and Infection Control is highly advised.

Reference:

1. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT, "Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza," *Clin Infect Dis* 2018; https://doi.org/10.1093/cid/ciy866
2. Kohno S, Yen MY, Cheong HJ, Hirotsu N, Ishida T, Kadota J, Mizuguchi M, Kida H, Shimada J, *Antimicrob Agents Chemother* 2011; 55(11): 5267-76.
3. de Jong MD, Ison MG, Monto MS, Metev H, Clark C, O'Neil B, Elder J, McCullough A, Collis P, Sheridan WP *Clin Infect Dis* 2014; 59(12): e172-e185