Peramivir (Rapivab®)

National Drug Monograph

March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Peramivir is a neuraminidase inhibitor with activity against influenza A and B viruses.
Indication(s) Under Review in this document (may include off label)	Peramivir is indicated for the treatment of acute, uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. Please note the prescribing information states the following limitations of use: • Efficacy based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled. • Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. • Efficacy could not be established in patients with serious influenza requiring hospitalization.
Dosage Form(s) Under Review	200mg single-use 20 mL vial (10mg/mL) for injection
REMS	☐ REMS ☒ No REMS ☒ Postmarketing Requirements
Pregnancy Rating	Pregnancy Category C

Executive Summary

Efficacy	• Approval of peramivir was based upon a single pivotal Phase 2 trial, two supporting Phase 2 trials, and one supporting Phase 3 trial (refer to Table 1) evaluating adult patients with acute, uncomplicated influenza who presented within 48 hours of symptom onset; all trials were randomized, multicentered, double-blind, and placebo-controlled. The primary efficacy endpoint used in these trials was the time-to-alleviation of symptoms, as self-monitored by patients, and was assessed in the intent-to-treat-infected population (i.e., all patients who received the study drug and had laboratory confirmed influenza). Analysis of pooled data from these trials showed that peramivir reduced the duration of influenza symptoms by ~20 hours compared to placebo. • Peramivir has also been studied in patients (both adult and pediatric) hospitalized with severe influenza, though additional benefit beyond standard of care therapy has not been demonstrated.
Safety	• Data are available for five well-controlled Phase 2/3 clinical trials in acute, uncomplicated influenza. In patients with uncomplicated influenza, the most common adverse event was diarrhea (8% with peramivir vs. 7% for placebo); laboratory abnormalities included increases in ALT, serum glucose, and creatine phosphokinase and decrease in neutrophil count. • The prescribing information for peramivir warns of possible neuropsychiatric events (e.g., delirium, hallucinations, or abnormal behavior) and severe skin reactions/hypersensitivities (e.g., erythema multiforme and Stevens–Johnson syndrome) associated with its use. Both oseltamivir and zanamivir carry a similar warning/precaution regarding neuropsychiatric events, while oseltamivir also carries a warning/precaution regarding possible severe skin reactions.
Potential Impact	• CDC recommends that neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) be considered for the treatment of patients

	with acute, uncomplicated influenza who present within 48 hours of symptom onset. For patients with more severe disease requiring hospitalization, CDC recommends the use of oral oseltamivir for those patients capable of tolerating or absorbing oral or enteric administration; intravenous peramivir or investigational intravenous zanamivir should be considered for those patients unable to tolerate oral or enteric administration.

Background

Purpose for review

Peramivir received FDA approval in December 2014.

Issues to be determined:

- ✔ Evidence of need
- ✔ Does peramivir offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations
Oseltamivir	-Oral formulations only. -Approved for treatment and prophylaxis of influenza in adult and pediatric patients. -Demonstrated efficacy for both influenza A and B.
Zanamivir	-Inhaled formulations only; serious, fatal bronchospasm have been reported; prescribing information does not recommend use in patients with underlying airway disease. -Approved for treatment and prophylaxis of influenza in adult and pediatric patients. -Demonstrated efficacy for both influenza A and B. -Maintains activity against oseltamivir-resistant A/H1N1 viruses carrying H275Y mutation.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2015) using the search terms "RWJ 270201", "BCX-1812", "peramivir", and "Rapivab". The search was limited to studies performed in humans and published in the English language. Additionally, the reference sections of identified papers were reviewed for other possibly relevant publications. This search strategy returned a number of phase 2 and phase 3 clinical trials, as well as a review of the use of peramivir during the 2009 influenza A (H1N1) pandemic. The discussion of efficacy below includes information from the trials of peramivir in adult patients with acute, uncomplicated influenza reviewed by FDA[2,3,4,5]. Additional information from trials in adult patients hospitalized with severe influenza is also briefly reviewed. Lastly, a discussion of the use of peramivir as part of the emergency investigational new drug (eIND) during the 2009 influenza A/H1N1 pandemic is provided.

Review of Efficacy

The FDA review of peramivir for the treatment of acute, uncomplicated influenza was based upon one pivotal Phase 2 trial and three supporting trials (two Phase 2 and one Phase 3)[2]. All of these trials assessed the effect of peramivir as a single dose administered IV or IM on "the time-to-alleviation-of-symptoms (TTAS)" compared to placebo. Patients were required to self-monitor seven target influenza symptoms (headache, aches/pains in muscles/joints, feverishness, fatigue, cough, sore throat, and nasal congestion) and grade them on a scale of 0–3 (absent, mild, moderate, and severe). The primary endpoint, TTAS, was defined as the number of hours from the initiation of treatment until all seven target symptoms were rated either 0 (absent) or 1 (mild) and remained so for 21.5 hours. See Table 1 below for an overview of these trials as well as two other Phase 3 informative trials reviewed by FDA. Of note, two of these trials (BCX1812-212 and 0815T0631) were conducted at

a time when the predominant strain of seasonal influenza A (H1N1) carried the H275Y neuraminidase mutation known to confer resistance to oseltamivir and peramivir. This prevented trial 0815T0631 from being considered as a pivotal trial[2].

FDA also reviewed three trials involving hospitalized patients with confirmed or suspected influenza (Refer to Table 2)[2,6,7,8]. Two of these trials used the "time-to-clinical-resolution (TTCR)" as their primary efficacy endpoint, while the third used the change in influenza virus titer as the primary efficacy endpoint, though TTCR was included as a secondary endpoint. Please note that FDA approval was not granted for the use of peramivir in hospitalized patients with severe or complicated influenza virus infection.

In response to the 2009 influenza A (H1N1) pandemic, FDA approved peramivir for compassionate use under an emergency investigational new drug (eIND) program[9]. During this time, peramivir IV was provided to 31 patients hospitalized for severe influenza virus infection. These patients were generally young (26/31 ≤ 49 years of age) and relatively healthy (17/35 had no underlying medical conditions), with the most common comorbidities being obesity (11/31), COPD/asthma (7/31), and diabetes (3/31). All patients had pneumonia with respiratory failure (30/31 requiring mechanical ventilation, 17/31 requiring vasopressor support, and 13/31 suffering acute renal failure); 19/31 patients had an APACHE II score ≥ 20; and 28/31 had prior or continuing treatment with either oseltamivir (27/31) or zanamivir (1/31). The median duration of illness prior to the request for peramivir was 12 days, with a median hospitalization time of 4 days. The median duration of treatment with peramivir was 10 days (range 1 to 14 days). Survival following initiation of peramivir was 76.7% at 14 days, 66.7% at 28 days, and 59.0% at 56 days.

Table 1: Clinical Trials of Peramivir in Adults with Acute, Uncomplicated Influenza Virus Infection

Trial	Design	Location	Interventions in Primary Efficacy Population	Primary Efficacy Endpoint: Median TTAS (95% CI)
0722T0621 *Pivotal* *Phase 2*	Randomized, double-blind, placebo-controlled	75 sites in Japan	PRV 300mg IV x 1 (n = 99)[1] PRV 600mg IV x 1 (n = 97)[1] Placebo IV x 1 (n = 100)[1]	59.1h (50.9–72.4) [p = 0.0092] 59.9h (54.4–68.1) [p = 0.0092] 81.1h (68.0–101.5)
BCX1812-211 *Supportive* *Phase 2*	Randomized, double-blind, placebo-controlled	151 sites in 7 countries including US	PRV 150mg IM x 1 (n = 104)[1] PRV 300mg IM x 1 (n = 106)[1] Placebo IM x 1 (n = 109)[1]	*Pooled analysis* 150mg: 114.1h (95.2–145.5) 300mg: 113.2h (88.4–130.4) Placebo: 134.8h (113.5–163.8)
BCX1812-311 *Supportive* *Phase 3*	Randomized, double-blind, placebo-controlled	37 sites in US	PRV 300mg IM x 1 (n = 57)[1] Placebo IM x 1 (n = 25)[1]	
BCX1812-212 *Supportive* *Phase 2*	Randomized, double-blind, placebo-controlled	66 sites in 4 countries, including US	PRV 600mg IM x 1 (n = 132)[2] Placebo IM x 1 (n = 147)[2]	91.1h (77.7–109.7) 106.9h (90.4–127.4)
0815T0631 *Informative* *Phase 3*	Randomized, double-blind, active control	146 sites in Japan, Taiwan, and South Korea	PRV 300mg IV x 1 (n = 364)[1,3] PRV 600mg IV x 1 (n = 362)[1,3] Oseltamivir 75mg PO BID for 5 days (n = 365)[1,3]	78.0h (68.4–88.6)[4] 81.0h (72.7–91.5)[4] 81.8h (73.2–91.1)
0816T0632 *Informative* *Phase 3*	Randomized, double-blind, non-controlled; patients with high-risk factors	37 sites in Japan	PRV 300mg IV QD for 1 to 5 days (n = 18)[5] PRV 600mg IV QD for 1 to 5 days (n = 19)[5]	114.4h (40.2–235.3)[6] 42.3h (30.0–82.7)[6]

Overall quality of evidence: Moderate (Refer to Appendix A); please note that all trials were funded by Shionogi or its partner BioCryst Pharmaceuticals
Abbreviations—PRV: peramivir

1. Primary efficacy endpoint was assessed in the intent-to-treat-infected (ITTI) population (i.e., all patients who received study drug and who had confirmed influenza virus infection)
2. Primary efficacy endpoint was assessed in ITTI-A population (i.e., all patients who received study drug and who had confirmed infection with influenza A virus infection); 230/281 patients enrolled with influenza A had A(H1N1) carrying H275Y mutation for resistance to oseltamivir and peramivir
3. 427/428 A(H1N1) viruses sequenced carried the H275Y mutation, and median IC_{50} values for A(H1N1) viruses to oseltamivir (100.00nM, the upper limit of the assay) and peramivir (21.59nM) were elevated as a result
4. Non-inferiority criteria for comparison to oseltamivir satisfied
5. Primary efficacy endpoint was assessed in per-protocol-set
6. Confidence intervals presented are 90% confidence intervals rather than 95%

Table 2: Clinical Trials of Peramivir in Patients Hospitalized with Confirmed or Suspected Influenza

Trial	Design	Location	Interventions in Primary Efficacy Population	Primary Efficacy Endpoint: Median TTCR (95% CI)[1]
BCX1812-201 *Informative* *Phase 2*	Randomized, double-blind, double-dummy, active control; hospitalized adults with severe influenza	43 sites in 7 countries	PRV 200mg IV QD for 5 days (n = 40) PRV 400mg IV QD for 5 days (n = 41) Oseltamivir 75mg PO BID for 5 days (n = 41)	37.0h (22.0–48.7) 23.7h (16.0–38.9) 28.1h (22.0–37.0)
BCX1812-301 *Informative*	Randomized, double-blind, placebo-controlled; hospitalized adults and	86 sites in 20 countries	PRV 600mg IV QD + SOC for 5 days (n = 78) Placebo + SOC for 5 days (n = 43)	42.5h (34.0–57.9) 49.5h (40.0–61.9)

Phase 3	children with influenza	including US[2]		
BCX1812-302 *Informative* *Phase 3*	Randomized, open-label; hospitalized adults and children with confirmed or suspected influenza	59 sites in 5 countries including US	PRV 600mg IV QD for 5 or 10 days (n = 70) PRV 300mg IV BID for 5 or 10 days (n = 57)	166.0h (84.0–273.0)[3] 45.0 h (41.0–118.0)[3]

Abbreviation—PRV: peramivir; SOC: standard of care (did not include neuraminidase inhibitors in primary efficacy population)

1. TTCR outpoint **has not been validated in patients with influenza**, but was agreed upon in conjunction with FDA reviewers; there have been no well-controlled trials of neuraminidase inhibitors in hospitalized patients using this endpoint
2. 89.2% of patients (108/121) in primary efficacy population were from India and Eastern Europe
3. TTCR was assessed as a secondary efficacy endpoint; primary endpoint was the change in influenza virus titer from baseline

Trial 0722T0621: Efficacy and Safety of Intravenous Peramivir for Treatment of Seasonal Influenza Virus Infection[3]

Table 3: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Aged 20–64 years	Respiratory dysfunction requiring pharmacotherapy
Onset of influenza-like illness within previous 48hrs	Convulsions or other neurologic symptoms
Positive influenza rapid antigen test at enrollment	Active clinically important chronic illness
Temperature ≥38°C	Known HIV infection
2 of 7 influenza symptoms rated moderate or severe:	Renal impairment requiring hemodialysis
Headache, aches/pains in muscles/joints, feverishness, fatigue, cough, sore throat, nasal congestion	Suspected bacterial infection
	Treatment with steroids or immunosuppressants
	Use of anti-influenza drugs in past 7 days
	History of allergy/hypersensitivity to anti-influenza drugs or acetaminophen
	Pregnant, breast feeding, or likely to become pregnant

Table 4: Baseline characteristics in intent-to-treat-infected population

Characteristic	Peramivir 300mg (n = 99)	Peramivir 600mg (n = 97)	Placebo (n = 100)
Gender	46.5% male	54.6% male	51.0% male
Age, years (mean ± SD)	34.2 ± 9.8	33.9 ± 10.4	34.4 ± 9.6
Weight, kg (mean ± SD)	61.15 ± 12.69	63.12 ± 15.18	61.85 ± 13.11
Current smokers	34.3%	33.0%	34.0%
Influenza subtype			
A/H1	74 (74.7%)	69 (71.1%)	72 (72.0%)
A/H3	21 (21.2%)	25 (25.8%)	24 (24.0%)
B	2 (2.0%)	1 (1.0%)	0 (0.0%)
Baseline temperature, °C (mean ± SD)	38.44 ± 0.43	38.64 ± 0.53	38.50 ± 0.46

Table 5: Time to alleviation of symptoms in intent-to-treat infected population

Outcome	Peramivir 300mg	Peramivir 600mg	Placebo
Overall	*n = 99*	*n = 97*	*n = 100*
Median hours (95% CI)	59.1 (50.9–72.4)	59.9 (54.5–68.1)	81.8 (68.0–101.5)
Hazard ratio (95% CI)	0.681 (0.511–0.909)	0.666 (0.499–0.890)	
Adjusted *p* value	0.0092	0.0092	
Influenza A/H1	*n = 74*	*n = 69*	*n = 72*
Median hours	52.5	62.6	81.4
Hazard ratio	0.779	0.899	
Adjusted *p* value	0.1458	0.5384	
Influenza A/H3	*n = 21*	*n = 25*	*n = 24*
Median hours	76.1	50.5	81.0
Hazard ratio	0.542	0.326	
Adjusted *p* value	0.0556	0.0008	

Summary: In a Japanese population of **relatively young, previously-healthy subjects** with **uncomplicated** cases of **predominantly influenza A**, administration of a single IV dose of peramivir, 300mg or 600mg, significantly **reduced the**

duration of self-monitored influenza symptoms by **slightly more than 20 hours** compared to placebo. Number of patients (3 total) was insufficient to demonstrate efficacy for use in influenza B virus infection.

Trial BCX1812-301 Evaluation of Intravenous Peramivir for Treatment of Influenza in Hospitalized Patients[7]

Table 9: Inclusion and exclusion criteria

Inclusion Criteria	*Exclusion Criteria*
Age ≥ 6 years of age	Hospitalized for > 24 hours at time of screening
Positive influenza rapid antigen test	Prior treatment with neuraminidase inhibitors or adamantane
Temperature ≥ 38.0°C oral or ≥ 38.6°C tympanic/rectal	Confirmed bacterial infection
≥ 2 of 3 vital signs abnormal	
Respiration rate	
Heart rate	
Systolic blood pressure	
≥ 1 respiratory symptom for < 72 hours	
≥ 1 constitutional symptom for < 72 hours	
≥ 1 risk factor[1]	

1. Risk factors: illness severity that justified hospitalization; age ≥ 60 years; presence of chronic lung disease requiring pharmacotherapy; history of unstable CHF or angina; presence of diabetes mellitus; oxygen saturation < 94%; history of chronic renal impairment not requiring peritoneal dialysis; serum creatinine > 2.0mg/dL

- Patients randomized 2:1 to receive IV peramivir 600mg (10mg/kg, max 600mg, in children and adolescents) or placebo for 5 days
  - Study drug was given in addition to the study site's standard of care (SOC) for influenza
  - Some study sites included a neuraminidase inhibitor (NAI), such as oseltamivir or zanamivir, in their SOC
- Primary outcome was **time to clinical resolution (TTCR)**
  - Defined as resolution of at least 4 of 5 vital signs for 24 with normalization of temperature and oxygen saturation
  - Assessment parameters
    - Temperature
    - Oxygen saturation
    - Heart rate
    - Systolic blood pressure
    - Chest radiograph
    - Subject-rated influenza symptoms (4-point ISSS)
    - Ability to perform daily activities
  - Outcome assessed using multiple regression analysis in the non-NAI SOC group
    - Assuming reduction of TTCR by ≥18 hours in peramivir group, calculated 160 patients needed to achieve 90% power to detect a hazard ratio of 0.57
    - Interim analysis planned at 70% enrollment to assess adequacy of sample size

Table 10: Baseline characteristics in non-NAI SOC population at interim analysis

Characteristic	*Peramivir + SOC (n = 78)*	*Placebo + SOC (n = 43)*
Geographic location		
North America	7.4%	
Western Europe	0.0%	
Eastern Europe	41.3%	
India	47.9%	
Gender	53% male	53% male
Age, years (mean (range))	44 (19–86)	40 (13–72)
BMI (mean (range))	24.3 (15.9–45.2)	25.3 (15.2–41.9)
Current smokers	10%	19%
Influenza subtype		
A/H3N2	54.1%	55.2%
A/H1N1 (2009)	30.8%	29.8%
Baseline temperature, °C (mean ± SD)	38.53 ± 0.49	38.48 ± 0.49
Duration of illness ≤ 48 hours	64%	74%
ICU admission at baseline	19%	19%

Table 11: Results of interim analysis of time to clinical resolution in non-NAI SOC population

Outcome	Peramivir + SOC	Placebo + SOC
Overall	*n = 78*	*n = 43*
Median hours (95% CI)	42.5 (37.0–71.1)	49.5 (40.0–61.9)
P value	0.97	
Initiation within 48 hours	*n = 50*	*n = 32*
Median hours (95% CI)	42.9 (35.4–63.0)	58.2 (37.0–71.1)
ICU admission at baseline	*n = 15*	*n = 8*
Median hours (95% CI)	31.5 (22.8–47.5)	50.2 (7.8–61.9)

- Based on interim analysis, it was determined that >320 patients would be needed in primary analysis group to demonstrate statistical significance, and the study was terminated due to futility

Summary: In a population of patients **primarily from India and Eastern Europe** hospitalized with influenza, treatment with **peramivir 600mg daily for 5 days** in addition to standard of care **was not shown to significantly improve the time to clinical resolution**. A small reduction in time to resolution was found for patients receiving therapy within the first 48 hours of symptoms or directly admitted to the ICU, but it was not significant in either case.

Potential Off-Label Use

Peramivir is currently FDA approved for use as a single IV dose in the treatment of acute, uncomplicated influenza for adults aged 18 years or older. Possible off-label uses include administration of multiple daily doses for the treatment of severe influenza in hospitalized patients or any use in patients under 18 years of age.

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Serious skin reactions, including erythema multiforme and Stevens–Johnson syndrome, have been reported in rare cases[1]. • Neuropsychiatric events, primarily abnormal behavior and delirium, have been reported with the use of neuraminidase inhibitors, including peramivir, in patients with influenza. Such events appear to be uncommon and have been reported primarily in pediatric patients[1,2].

Safety Considerations

This safety assessment is based upon data from five randomized, double-blind, controlled trials who each received a single dose of peramivir either intravenously or intramuscularly for the treatment of acute, uncomplicated influenza. Data, when available, are also reported from the trials of hospitalized patients who received peramivir intravenously for the treatment of severe influenza. Additionally, safety information from postmarketing use of peramivir in Japan, including both formal surveillance studies and spontaneous reporting of adverse events by patients or providers, is also discussed.

Adverse Reactions Noted in Clinical Trials of Adults with Acute, Uncomplicated Influenza

Common adverse reactions	• Diarrhea: 51/664 (7.6%) with peramivir vs. 31/436 (7.1%) with placebo[1,2]
Death/Serious adverse reactions	• 1 death reported during clinical trials of peramivir which was not deemed related to the study drug[2] • No serious AEs considered related to the study drug[2]
Discontinuations due to adverse reactions	• Prescribing information states <1% patients receiving peramivir 600mg[1]
Laboratory abnormalities	• Elevations in serum ALT (> 2.5x ULN): 20/654 (3.0%) • Elevations in serum glucose (> 160mg/dL): 30/660 (4.5%) • Elevations in creatine phosphokinase (≥ 6x ULN): 29/654 (4.4%)

	• Reduction in neutrophils (< 1.000x10^3/µL): 54/654 (8.2%)

Adverse Reactions Noted in Clinical Trials of Hospitalized Patients with Severe Influenza	
Common adverse reactions	• Constipation: 4% with peramivir vs. 2% with placebo; insomnia: 3% vs. 0%; and hypertension: 2% vs. 0% in a set of 101 patients treated with peramivir 600mg IV monotherapy[1]
Death/Serious adverse reactions	• 27 deaths reported in the three trials of hospitalized patients with severe influenza (24/585 [4%] in peramivir arm vs. 3/134 [2%] in placebo arm), but none were deemed related to the study drug; most deaths were related to progression of influenza or associated complications[2] • No serious AEs considered related to the study drug[2]
Discontinuations due to adverse reactions	• Not available in PI or FDA review

Postmarketing Surveillance Studies in Japan (October 2010 through February 2012)[2]	
Total adverse events	• 78 events reported in 51/1174 adult patients
Common adverse reactions	• Diarrhea (22 events), vomiting (10 events), and nausea (8 events)
Death/Serious adverse reactions	• No deaths or serious AEs reported

Spontaneous Reporting of AEs during Postmarketing Use in Japan (January 2010 to September 30, 2013)[2]	
Total adverse events	• Spontaneous AEs reported in 220 adult patients and 20 patients of unreported age
Common adverse reactions	• AEs reported in 126 adult patients and 20 patients of unreported age • Diarrhea, vomiting, and nausea most common • Rash, urticaria, dizziness, and hallucinations also commonly reported • 14 events total of abnormal behavior, delirium, or hallucinations in 13 adult patients
Death/Serious adverse reactions	• SAEs reported for 94 adult patients • 2 cases of sudden death reported • Most common: 10 reports of hepatic abnormalities; 6 reports each of shock and anaphylaxis; 5 reports of hemorrhagic enterocolitis; 4 reports of acute renal failure • 1 case of Stevens–Johnson syndrome and 2 cases of exfoliative dermatitis reported; all patients has possible confounding factors (other medications or history of drug hypersensitivity)

Drug Interactions

Drug-Drug Interactions: The use of neuraminidase inhibitors, including peramivir, may decrease the efficacy of the live attenuated influenza vaccine (LAIV), due to inhibition of viral replication. The concurrent use of peramivir and LAIV has not been studied but it is recommended to avoid administering LAIV within two weeks prior to or 48 hours following use of peramivir if possible. This does not apply to inactivated influenza vaccine[1].

Risk Evaluation

As of January, 2015

Sentinel event advisories
- None

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Peramivir 200mg/20mL IV soln	None	None	None	Penciclovir Perampanel

Rapivab	None	None	None	Rapamune Ramucirumab Ranibizumab

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Centers for Disease Control and Prevention recommendations[11]:

- For outpatients with acute, uncomplicated influenza presenting within 48 hours of symptom onset, the CDC recommends the use of oral oseltamivir for 5 days, inhaled zanamivir for 5 days, or intravenous peramivir as a single dose.
- For hospitalized patients with severe influenza, CDC recommends oral or enterically-administered oseltamivir in those patients able to tolerate it. Some experts have recommended the use of higher doses of oseltamivir (e.g., 150mg twice-daily) in immunocompromised or severely ill patients; however, data suggest that there may be no additional benefit to higher dosing. For patients unable to tolerate oral or enteric administration (eg, patients with gastric stasis, malabsorption, or gastrointestinal bleeding), CDC recommends consideration of the use of IV peramivir 600mg daily while also noting that high-quality evidence of benefit is lacking. Additionally IV zanamivir is currently under investigation for use in this setting and may be available through an ongoing Phase 3 clinical trial or through emergency investigational new drug request. Inhaled zanamivir is not recommended in this setting due to a lack of sufficient evidence. The optimal duration of treatment for treatment with neuraminidase inhibitors for severe or complicated influenza is unknown, and CDC recommends clinical judgment be used to guide the determination of duration in patients with prolonged illness.

Microbiology/virology:

- Biochemical and cell culture assays show that peramivir possesses *in vitro* activity against influenza A and B viruses[2,10].
- Influenza viruses may develop decreased susceptibility, as tested by various *in vitro* assays, to one or more of the neuraminidase inhibitors via mutations to the genes coding for the hemagglutinin or neuraminidase proteins. Moreover, a mutation which confers greatly decreased susceptibility to one neuraminidase inhibitor may only slightly decrease the activity of another or may not affect it at all. As an example, in the period from 2007 to 2009, isolates of the predominant A(H1N1) strain, A/Brisbane/59/2007, carrying the H275Y mutation to the neuraminidase enzyme showed highly-reduced susceptibility (>100-fold increase in IC_{50}) to oseltamivir and peramivir with little change in the susceptibility to zanamivir. However, a single mutation alone is not sufficient for determining or predicting the overall resistance profile, as isolates of the A(H1N1)pdm09 virus, which replaced A/Brisbane/59/2007 as the predominant strain in 2009, carrying the H275Y mutation showed highly-reduced susceptibility to oseltamivir, while only showing moderately-reduced (10–100-fold increase in IC_{50}) susceptibility to peramivir; please note that the majority of influenza A(H1N1)pdm09 viruses do not carry the H275Y mutation and are susceptible to oseltamivir[10].
- Influenza virus isolates with reduced *in vitro* susceptibility to peramivir have been recovered from patients, both in pre-approval clinical trials and those with no known exposure to neuraminidase inhibitors[1,2,10].
- The relationship between *in vitro* susceptibility to the various neuraminidase inhibitors and clinical outcomes is currently unclear[1,2].

Postmarketing requirements:

- In its approval of peramivir, FDA imposed a number of postmarketing requirements on the manufacturer with respect to pharmacokinetics, safety, and efficacy in pediatric, geriatric, and high-risk populations[2].
- FDA is also requiring the analysis and submission of clinical resistance data from previous trials as well as conduction of new trials to determine the effects of cross-resistance between the different neuraminidase inhibitors[2].
- Lastly, FDA has committed the manufacturer to submitting data related to the safety and efficacy of peramivir for the treatment of acute, uncomplicated influenza caused by influenza B virus infection[2].
- For detailed information on postmarketing requirements and commitments refer to FDA review documents[2].

Dosing and Administration

The recommended dose of peramivir is 600mg as a one-time IV infusion given over at least 15 minutes for patients 18 years or older with acute, uncomplicated influenza. Please note that peramivir should be administered within 2 days (48 hours) of onset of influenza symptoms[1].

Dose Adjustment in Renal Impairment

Estimated creatinine clearance	Dose
≥ 60 mL/min	600mg
30–49 mL/min	200mg
10–29 mL/min	100mg
Chronic renal impairment maintained on hemodialysis	Dose after dialysis based on renal function

Special Populations (Adults)

	Comments
Patients with Influenza B Virus Infection	• Use of peramivir has not been shown to be beneficial in patients with influenza B virus infection[1,2].
Patients with Serious Influenza Requiring Hospitalization	• Use of peramivir has not been shown to provide benefit in patients with severe influenza requiring hospitalization[1,2].
Elderly	• Clinical trials included an insufficient number of patients over 65 yrs old to determine any-related differences in responses. Clinical experiences have thus far not identified any differences in exposures in the elderly as compared to younger patients[1].
Pregnancy	• Pregnancy Category C[1]
Lactation	• Peramivir has not been studied in nursing mothers, and it is not known if it is excreted in human breast milk. Use in nursing mothers should weigh the potential benefits/clinical need against risk of harm or possible adverse events to the infant[1].
Renal Impairment	• Dose adjustment required for creatinine clearance <50mL/min[1].
Hepatic Impairment	• The pharmacokinetics have not been studied in patients with hepatic impairment; however, no clinically significant alterations are expected based on the known route of elimination[1].
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- The Centers for Disease Control and Prevention report that an estimated 200,000 people in the US are hospitalized with complications related to influenza virus infection each year. Additionally, CDC reports that deaths related to influenza have typically ranged from approximately 3,000 to 49,000 deaths per year. Patients over 65 years of age are at particularly high risk for influenza-related complications, accounting for ~90% of deaths and between 50-60% of hospitalizations[12].
- Peramivir is approved for use in the treatment of acute, uncomplicated influenza in adults 18 years of age and older. It is administered as a single 600mg dose given by IV infusion over at least 15 minutes. Given that controlled trials have failed to show benefit in the treatment of hospitalized patients with severe influenza, peramivir has not been approved by FDA for use in these patients[12].
- CDC recommends that neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) be considered for the treatment of patients with acute, uncomplicated influenza who present within 48 hours of symptom onset. For patients with more severe disease requiring hospitalization, CDC recommends the use of oral oseltamivir for those patients capable of tolerating or absorbing oral or enteric administration; intravenous peramivir or investigational intravenous zanamivir may be considered for those patients unable to tolerate oral or enteric administration[12].

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Prepared Jan 2015: Marcus Kouma, PharmD Contact person: Melinda Neuhauser, PharmD, MPH; VA PBM Services

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.