

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RAPIVAB safely and effectively. See full prescribing information for RAPIVAB.

RAPIVAB™ (peramivir injection), for intravenous use
Initial U.S. Approval: [2014]

INDICATIONS AND USAGE

RAPIVAB is an influenza virus neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. (1)

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. (1)
- Efficacy could not be established in patients with serious influenza requiring hospitalization. (1)

DOSAGE AND ADMINISTRATION

- Administer as a single dose within 2 days of onset of influenza symptoms (2.1)
- Recommended dose is 600 mg, administered by intravenous infusion for a minimum of 15 minutes (2.1)
- Renal Impairment: Recommended dose for patients with creatinine clearance 30-49 mL/min is 200 mg and the recommended dose for patients with creatinine clearance 10-29 mL/min is 100 mg (2.2)
- Hemodialysis: Administer after dialysis. (2.2)
- RAPIVAB must be diluted prior to administration (2.3)
- See the Full Prescribing Information for drug compatibility information (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 200 mg in 20 mL (10 mg/mL) in a single-use vial (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Serious skin/hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have occurred with RAPIVAB. (5.1)
- Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

ADVERSE REACTIONS

Most common adverse reaction (incidence >2%) is diarrhea (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-844-273-2327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Live attenuated influenza vaccine (LAIV), intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB, unless medically indicated (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use if benefit outweighs risk. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RAPIVAB is indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days.

Limitations of Use:

- Efficacy of RAPIVAB is based on clinical trials of naturally occurring influenza in which the predominant influenza infections were influenza A virus; a limited number of subjects infected with influenza B virus were enrolled.
- Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use RAPIVAB [see *Microbiology (12.4)*].
- The efficacy of RAPIVAB could not be established in patients with serious influenza requiring hospitalization [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Acute Uncomplicated Influenza

Administer RAPIVAB within 2 days of onset of symptoms of influenza.

The recommended dose of RAPIVAB in adult patients 18 years of age or older with acute uncomplicated influenza is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

2.2 Dosing in Patients with Renal Impairment

Significantly increased drug exposures were observed when RAPIVAB was administered to subjects with renal dysfunction [see *Clinical Pharmacology (12.3)*]. Therefore, the RAPIVAB dose should be reduced for patients with baseline creatinine clearance below 50 mL/min using the recommendations in Table 1. No dose adjustment is required for single administration of RAPIVAB in patients with creatinine clearance of 50 mL/min or higher [see *Clinical Pharmacology (12.3)*].

In patients with chronic renal impairment maintained on hemodialysis, RAPIVAB should be administered after dialysis at a dose adjusted based on renal function (Table 1) [see *Clinical Pharmacology (12.3)*].

Table 1. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance* (mL/min)		
	≥50	30-49	10-29
Recommended Dose (mg)	600	200	100

* Calculated using the Cockcroft and Gault equation.

2.3 Preparation of RAPIVAB for Intravenous Infusion

Use aseptic technique during the preparation of RAPIVAB to prevent inadvertent microbial contamination. There is no preservative or bacteriostatic agent present in the solution.

Follow the steps below to prepare a diluted solution of RAPIVAB:

- (a) Do not use if seal over bottle opening is broken or missing.
- (b) Visually inspect RAPIVAB for particulate matter and discoloration prior to administration.
- (c) Dilute an appropriate dose of RAPIVAB 10 mg/mL solution [see *Dosage and Administration (2)*] in 0.9% or 0.45% sodium chloride, 5% dextrose, or lactated Ringer's to a maximum volume of 100 mL.
- (d) Administer the diluted solution via intravenous infusion for 15 to 30 minutes.
- (e) Discard any unused diluted solution of RAPIVAB after 24 hours.

Once a diluted solution of RAPIVAB has been prepared, administer immediately or store under refrigerated conditions (2°C to 8°C or 36° to 46°F) for up to 24 hours. If refrigerated, allow the diluted solution of RAPIVAB to reach room temperature then administer immediately.

2.4 Drug Compatibility

RAPIVAB injection is compatible with 0.9% or 0.45% sodium chloride, 5% dextrose, or lactated Ringer's. Do not mix or co-infuse RAPIVAB with other intravenous medications.

RAPIVAB injection is compatible with materials commonly used for administration such as polyvinylchloride (PVC) bags and PVC-free bags, polypropylene syringes, and polyethylene tubing.

3 DOSAGE FORMS AND STRENGTHS

Each vial of RAPIVAB injection contains 200 mg per 20 mL (10 mg per mL) as a clear, colorless solution [see *How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin/Hypersensitivity Reactions

Rare cases of serious skin reactions, including erythema multiforme, have been reported with RAPIVAB in clinical studies and in postmarketing experience; Stevens-Johnson syndrome has been reported with RAPIVAB in postmarketing experience. Appropriate treatment should be instituted if a serious skin reaction occurs or is suspected.

5.2 Neuropsychiatric Events

Influenza can be associated with a variety of neurologic and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur in uncomplicated influenza as well.

There have been postmarketing reports (from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RAPIVAB. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of RAPIVAB to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior.

5.3 Risk of Bacterial Infections

There is no evidence for efficacy of RAPIVAB in any illness caused by agents other than influenza viruses. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RAPIVAB has not been shown to prevent such complications.

Prescribers should be alert to the potential for secondary bacterial infections and treat with antibiotics as appropriate.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious skin and hypersensitivity reactions [see *Warnings and Precautions* (5.1)]
- Neuropsychiatric Events [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five randomized, double-blind, controlled trials, 1,399 subjects with acute uncomplicated influenza received a single dose of RAPIVAB, administered intravenously or intramuscularly, at doses up to 600 mg. Among the 664 subjects receiving RAPIVAB 600 mg (intravenous or intramuscular), the most commonly observed adverse reaction was diarrhea, occurring at a rate of 8% versus 7% in subjects receiving placebo. No subject receiving RAPIVAB 600 mg experienced a serious adverse event and less than 1% discontinued study because of an adverse reaction.

Clinically significant laboratory abnormalities (DAIDS Grade 2-4) listed in Table 2 occurred more frequently in subjects treated with RAPIVAB 600 mg (intravenous or intramuscular) than placebo. Only events occurring at $\geq 2\%$ are included.

Table 2: Laboratory Abnormalities Occurring in $\geq 2\%$ of Subjects Treated with RAPIVAB 600 mg

Laboratory Parameter Abnormality ^a	RAPIVAB 600 mg	Placebo
Alanine Aminotransferase (> 2.5 x ULN)	(N=654) 3%	(N=430) 2%
Serum Glucose (> 160 mg/dL)	(N=660) 5%	(N=433) 3%
Creatine Phosphokinase (≥ 6.0 x ULN)	(N=654) 4%	(N=431) 2%

Neutrophils (< 1.000 x10⁹/L)	(N=654) 8%	(N=430) 6%
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a. Frequencies based on treatment-emergent laboratory abnormalities

In a subset of subjects with serious influenza requiring hospitalization treated with RAPIVAB 600 mg as monotherapy (N=101) the following adverse reactions were also reported more frequently with RAPIVAB as compared to placebo: constipation (4% versus 2%), insomnia (3% versus 0%), AST increased (3% versus 2%), and hypertension (2% versus 0%).

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of RAPIVAB in Japan. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic: Stevens-Johnson Syndrome, exfoliative dermatitis, rash [see *Warnings and Precautions (5.1)*]

Psychiatric: abnormal behavior, hallucination [see *Warnings and Precautions (5.2)*]

7 DRUG INTERACTIONS

This section describes clinically relevant drug interactions with RAPIVAB. Drug-drug interaction studies are described elsewhere in the labeling [see *Clinical Pharmacology (12.3)*].

7.1 Influenza Vaccines

Inactivated influenza vaccine can be administered at any time relative to use of RAPIVAB. For live attenuated influenza vaccine (LAIV), antiviral drugs may inhibit viral replication and thus may reduce vaccine efficacy. The concurrent use of RAPIVAB with LAIV intranasal has not been evaluated. Because of the potential for interference between these two products, avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB unless medically indicated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled trials of RAPIVAB in pregnant women. Because animal reproduction studies are not always predictive of human response, and peramivir has been shown to cross the placenta in animal studies, RAPIVAB should be used during pregnancy only if clearly needed.

Animal Data

Reproductive toxicity studies have been performed in rats and rabbits. In rats, no treatment-related maternal and fetal toxicities were observed when RAPIVAB was given by intravenous bolus at the maximum feasible dose of 600 mg/kg, representing exposures approximately 8-fold that in humans at the recommended dose. However, when RAPIVAB was administered by continuous intravenous infusion, fetal anomalies of reduced renal papilla and dilated ureters were observed. The exposure at the no-observed-adverse-effect level (NOAEL) was 0.8-fold the exposures in humans at the recommended dose. In rabbits, maternal toxicity (decreased food consumption and body weight,

nephrotoxicity) and developmental toxicity (abortion or premature delivery) were observed. The exposure in rabbits at the NOAEL was 8-fold the exposure in humans at the recommended dose.

8.3 Nursing Mothers

RAPIVAB has not been studied in nursing mothers. It is not known whether RAPIVAB is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RAPIVAB and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Studies in rats demonstrated that RAPIVAB is excreted in milk at levels below the mother's plasma drug concentration with levels (AUC) approximately 0.5-fold those in the maternal blood.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients less than 18 years of age have not been established.

In a single arm trial conducted in Japan, 117 pediatric subjects with uncomplicated influenza ages 28 days to 16 years were treated with a single dose of RAPIVAB 10 mg/kg. The most frequent clinical and laboratory adverse events included decreased neutrophil count, diarrhea, and vomiting.

8.5 Geriatric Use

Clinical trials of RAPIVAB did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in exposures between the elderly and younger subjects [see *Clinical Pharmacology (12.3)*].

8.6 Patients with Impaired Renal Function

A reduced dose of RAPIVAB is recommended for patients with creatinine clearance below 50 mL/min [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*]. Dose adjustment is not required for a single administration of RAPIVAB for patients with creatinine clearance 50 mL/min or higher [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*].

In patients with chronic renal impairment maintained on hemodialysis, RAPIVAB should be administered after dialysis at a dose adjusted based on renal function [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*].

8.7 Patients with Serious Influenza Requiring Hospitalization

The use of RAPIVAB was not shown to provide benefit in patients with serious influenza requiring hospitalization [see *Indications and Usage (1)* and *Clinical Studies (14.2)*].

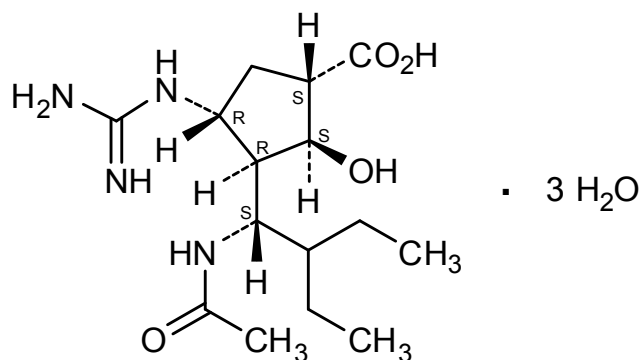
10 OVERDOSAGE

There is no human experience of acute overdosage with RAPIVAB. Treatment of overdosage with RAPIVAB should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with RAPIVAB.

RAPIVAB is cleared by renal excretion and can be cleared by hemodialysis.

11 DESCRIPTION

RAPIVAB (peramivir) is an inhibitor of influenza virus neuraminidase. The chemical name is (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamiimidoylamino)-2-hydroxycyclopentanecarboxylic acid, trihydrate. The chemical formula is $C_{15}H_{28}N_4O_4 \cdot 3H_2O$, representing a molecular weight of 382.45. The molecular structure is as follows:



RAPIVAB injection is a clear, colorless, sterile, isotonic solution (200 mg per 20 mL) in glass vials fitted with rubber stoppers and royal blue flip-off seals. Each mL contains 10 mg peramivir (on an anhydrous basis) in 0.9% sodium chloride solution. The pH may have been adjusted with sodium hydroxide, USP and/or hydrochloric acid, USP. The pH is 5.5 – 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Peramivir is an antiviral drug with activity against influenza virus [see *Microbiology (12.4)*].

12.2 Cardiac Electrophysiology

At twice the maximum recommended dose, RAPIVAB did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of RAPIVAB was evaluated in Phase 1 trials in adults. The pharmacokinetic parameters following intravenous administration of RAPIVAB (0.17 to 2 times the recommended dose) showed a linear relationship between dose and exposure parameters (C_{max} and AUC).

Following intravenous administration of a single dose of RAPIVAB 600 mg over 30 minutes, a maximum serum concentration (C_{max}) of 46,800 ng/mL (46.8 µg/mL) was reached at the end of infusion. $AUC_{0-\infty}$ values were 102,700 ng•hr/mL.

Distribution

In vitro binding of peramivir to human plasma proteins is less than 30%.

Based on a population pharmacokinetic analysis, the central volume of distribution was 12.56 L.

Metabolism and Elimination

Peramivir is not a substrate for CYP enzymes, does not affect glucuronidation, and is not a substrate or inhibitor of P-glycoprotein mediated transport.

Peramivir is not significantly metabolized in humans.

The elimination half-life of RAPIVAB following IV administration to healthy subjects of 600 mg as a single dose is approximately 20 hours. The major route of elimination of RAPIVAB is via the kidney. Renal clearance of unchanged peramivir accounts for approximately 90% of total clearance. Negligible accumulation was observed following multiple doses, either once or twice daily, for up to 10 days.

Specific Populations

Race: Pharmacokinetics of peramivir was evaluated primarily in Caucasians and Asians. Based on a population pharmacokinetic analysis including race as a covariate, volume of distribution was dependent on weight and Asian race. No dose adjustment is required based on weight or Asian race.

Gender: Peramivir pharmacokinetics was similar in male and female subjects.

Geriatric Patients: Peramivir pharmacokinetics in elderly subjects was similar to non-elderly subjects. Peak concentrations of peramivir after a single 4 mg/kg IV dose were approximately 10% higher in elderly subjects when compared to young adults (22,647 vs 20,490 ng/mL, respectively). Exposure (AUC_{0-12}) to peramivir at steady state was roughly 34% higher in elderly subjects compared to young adults (61,572 vs 46,000 ng•hr/mL, respectively). Dose adjustment is not required for elderly subjects.

Patients with Impaired Renal Function: A trial was conducted in subjects with various degrees of renal impairment. When compared to a concurrent cohort with normal renal function, no change in mean C_{max} was observed (6 subjects per cohort). However, mean $AUC_{0-\infty}$ after a single 2 mg/kg IV dose was increased by 28%, by 302%, and by 412% in subjects with creatinine clearance 50-79, 30-49, and 10-29 mL/min, respectively.

Hemodialysis was effective in reducing systemic exposure of peramivir by 73% to 81%.

A reduced dose of RAPIVAB is recommended for patients with creatinine clearance below 50 mL/min [see *Dosage and Administration (2.2)*].

Patients with Hepatic Impairment: The pharmacokinetics of peramivir in subjects with hepatic impairment has not been studied. No clinically relevant alterations to peramivir pharmacokinetics are expected in patients with hepatic impairment based on the route of peramivir elimination.

Assessment of Drug Interactions

The potential for CYP mediated interactions involving RAPIVAB with other drugs is low, based on the known elimination pathway of RAPIVAB, and data from in vitro studies indicating RAPIVAB does not induce or inhibit cytochrome P450.

There was no evidence of drug-drug interactions when RAPIVAB was administered with oral rimantadine, oseltamivir, or oral contraceptives containing ethinyl estradiol and levonorgestrel; or when peramivir IM was administered with oral probenecid.

RAPIVAB is primarily cleared in the urine by glomerular filtration.

12.4 Microbiology

Mechanism of Action

Peramivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells. The median neuraminidase inhibitory activity (IC_{50} values) of peramivir in biochemical assays against influenza A/H1N1 virus, influenza A/H3N2 virus, and influenza B virus clinical isolates were 0.16 nM (n=44; range 0.01- 1.77 nM), 0.13 nM (n=32; range 0.05-11 nM), and 0.99 nM (n=39; range 0.04-54.2 nM), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate.

Antiviral Activity

The antiviral activity of peramivir against laboratory strains and clinical isolates of influenza virus was determined in cell culture. The concentrations of peramivir required for inhibition of influenza virus in

cell culture varied depending on the assay method used and the virus tested. The median 50% effective concentrations (EC₅₀ values) of peramivir in cell culture assays were 2.6 nM (n=13; range 0.09-21 nM), 0.08 nM (n=17; range 0.01-1.9 nM) and 4.8 nM (n=11; range 0.06-120 nM) for influenza A/H1N1 virus, A/H3N2 virus, and B virus strains, respectively.

The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.

Resistance

Cell culture: Influenza A and B virus isolates with reduced susceptibility to peramivir were recovered by serial passage of virus in cell culture in the presence of increasing concentrations of peramivir. Reduced susceptibility of influenza virus to inhibition by peramivir may be conferred by amino acid substitutions in the viral neuraminidase or hemagglutinin proteins (Table 3).

Table 3: Amino Acid Substitutions Selected by Peramivir in Cell Culture Studies

Protein	Type/Subtype		
	A/H1N1	A/H3N2	B
HA	D129S, R208K	N63K, G78D, N145D, K189E	T139N, G141E, R162M, D195N, T197N, Y319H
NA	N58D, I211T, H275Y		H275Y

In vivo: Influenza A and B virus isolates with amino acid substitutions associated with reduced susceptibility to peramivir were observed in clinical isolates collected during clinical trials with peramivir (Table 4). Amino acid substitutions have also been observed in viral isolates sampled during community surveillance studies which may be associated with reduced susceptibility to peramivir (Table 4). The clinical impact of this reduced susceptibility is unknown.

Table 4: Neuraminidase Amino Acid Substitutions Associated with Reduced Susceptibility to Peramivir in Clinical Virus Isolates

Protein		Type / Subtype		
		Influenza A/H1N1 (N1 numbering)	Influenza A/H3N2	Influenza B (B numbering in brackets)
NA	Clinical Trial	H275Y	R292K, N294S	-
	Community Surveillance Studies	I223R/V, S246N, H275Y	E119V, Q136K D151A/E/G/N/V	P141S (P139S), D198E/N/Y (D197E/N/Y), I222T/V (I221T/V), R371K (R374K)

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received RAPIVAB. Prescribers should consider available information from the CDC on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use RAPIVAB.

Cross Resistance

Cross-resistance between peramivir, oseltamivir and zanamivir was observed in neuraminidase biochemical assays and cell culture assays. The amino acid substitutions that resulted in reduced

susceptibility to peramivir and either oseltamivir or zanamivir are summarized in Table 5. The clinical impact of this reduced susceptibility is unknown.

Table 5: Summary of Amino Acid Substitutions with Cross-Resistance between Peramivir and Oseltamivir or Zanamivir in Susceptibility Assays

	Protein	Type/ Subtype		
		A/H1N1 (N1 Numbering)	A/H3N2	B
Oseltamivir	HA	-	N63K, N145D	-
	NA	E119V, D151G/N, Y155H, D198G, I223/R/V, S246N, H275Y, N294S	E119I/V, R292K, N294S	P139S, G140R, D197E/N/Y, I221T/V, H275Y, R371K
Zanamivir	HA	-	N63K, N145D	-
	NA	Q136K, Y155H, D198G, S246N, N294S	E119G/V, T148I, D151A/G/N/V, R292K, N294S	E116A/D/G, P139S, R149K, D198E/N, R292K, R371K

No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase inhibitor class (peramivir, oseltamivir, zanamivir) and the M2 ion channel inhibitor class (amantadine, rimantadine). However, a virus may carry a neuraminidase inhibitor resistance-associated substitution in neuraminidase and an M2 ion channel inhibitor resistance-associated substitution in M2 and may therefore be resistant to both classes of inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

Immune Response

No influenza vaccine/peramivir interaction study has been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies by intravenous injection of peramivir were not performed. However, in an oral carcinogenicity study in Sprague-Dawley rats no drug-related neoplasms were observed at drug exposures 0.2- to 0.5-fold that of humans at the clinically recommended dose of 600 mg/day.

Mutagenesis

Peramivir was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including the Ames bacterial reverse mutation assay, the Chinese hamster ovary chromosomal aberration test, and the in vivo mouse micronucleus test with intravenous administration.

Impairment of Fertility

Peramivir had no effects on mating or fertility in rats up to 600 mg/kg/day, at which exposures were approximately 8-fold of those in humans at the clinically recommended dose.

13.2 Animal Toxicology and/or Pharmacology

Peramivir caused renal tubular necrosis and abnormal renal function in rabbits. Toxicities included tubular dilatation and necrosis with protein casts in cortical areas, dilated tubules with mineralization

in corticomedullary junction areas, and multifocal tubular regeneration. The rabbit appeared to be the sensitive species for peramivir renal toxicity, which was noted at exposures approximately 2- to 4-fold those in humans at the clinically recommended dose.

14 CLINICAL STUDIES

14.1 Acute Uncomplicated Influenza in Adults

Study 621 was a randomized, multicenter, blinded trial conducted in Japan that evaluated a single intravenous administration of RAPIVAB 300 mg, RAPIVAB 600 mg, or placebo administered over 30 minutes in subjects 18 to 65 years of age with acute uncomplicated influenza. Subjects were eligible if they had fever greater than 38°C (axillary) and a positive rapid antigen test for influenza virus, accompanied by at least two symptoms (cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue, or headache). In addition, all subjects enrolled were allowed to take fever-reducing medications.

Study treatment was started within 48 hours of onset of symptoms. Subjects participating in the trial were required to self-assess their influenza symptoms as “none”, ‘mild’, ‘moderate’, or ‘severe’ twice daily. The primary endpoint, time to alleviation of symptoms, was defined as the number of hours from initiation of study drug until the start of the 24 hour period in which all seven symptoms of influenza (cough, sore throat, nasal congestion, headache, feverishness, myalgia and fatigue) were either absent or present at a level no greater than mild for at least 21.5 hours.

The overall efficacy population, consisting of subjects with confirmed influenza and administered study drug, totaled 297 subjects. Among the 98 subjects enrolled in the RAPIVAB 600 mg dose group, the mean age was 34 years; 55% were male; 34% were smokers; 99% were infected with influenza A virus and 1% were infected with influenza B virus. The majority of subjects (53%) had influenza illness lasting less than 24 hours at the time of presentation.

Overall, subjects receiving RAPIVAB 600 mg experienced alleviation of their combined influenza symptoms a median of 21 hours sooner than those receiving placebo. The median time to recovery to normal temperature (less than 37°C) in the 600 mg group was approximately 12 hours sooner compared to placebo.

Insufficient numbers of subjects infected with influenza B virus were enrolled to determine efficacy of RAPIVAB in this influenza type.

14.2 Serious Influenza Requiring Hospitalization

The efficacy of RAPIVAB could not be established in patients with serious influenza requiring hospitalization [see *Indications and Usage (1)*].

A randomized, double-blind, multicenter, placebo-controlled trial (Study 301) was conducted in 398 subjects with serious influenza requiring hospitalization. In this trial, subjects were randomized to receive RAPIVAB 600 mg daily for 5 days plus standard of care versus standard of care plus placebo within 72 hours of start of symptoms. The primary endpoint was time to clinical resolution defined as the time in hours from initiation of study treatment until resolution of at least 4 of 5 signs (temperature, oxygen saturation, respiration rate, heart rate, or systolic blood pressure), maintained for at least 24 hours. RAPIVAB plus standard of care did not improve median time to clinical resolution compared with standard of care alone.

16 HOW SUPPLIED/STORAGE AND HANDLING

RAPIVAB injection is a clear, colorless sterile, isotonic solution. Each single-use vial contains 200 mg per 20 mL (10 mg/mL) of peramivir in a clear glass vial (NDC # 61364-181-01). RAPIVAB injection is supplied in cartons containing three single-use vials (NDC # 61364-181-03).

Store vials of RAPIVAB injection in original cartons at 20° to 25°C (68° to 77°F). Excursions are permitted to 15° to 30°C (59° to 86°F).

Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION

Advise patients of the following:

- There is a risk of serious skin reactions with RAPIVAB use. Patients should seek immediate medical attention if a skin reaction occurs [see *Warnings and Precautions (5.1)*].
- There is a risk of neuropsychiatric events in patients with influenza. Patients should contact their physician if they experience signs of abnormal behavior after receiving RAPIVAB [see *Warnings and Precautions (5.2)*].

RAPIVAB is a registered trademark of BioCryst Pharmaceuticals, Inc. All other trademarks herein are the property of their respective owners.

Manufactured for and distributed by:
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