▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – RAPIVAB™ (PERAMIVIR)

1 NAME OF THE MEDICINE

Peramivir.

200mg/20mL per vial concentrate solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial of concentrate contains 200 mg peramivir.
1 mL concentrate solution for infusion contains 10 mg peramivir (anhydrous basis).

Excipients with known effect

Each mL of concentrate contains 0.154 mmol sodium, which is 3.54 mg of sodium.
For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Concentrate solution for infusion. Rapivab is a clear, colourless, sterile, isotonic solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rapivab is indicated for the treatment of acute influenza infection in adults and children 2 years and older who have been symptomatic for no more than two days.

Clinical trials have not established the efficacy of repeated doses of Rapivab in patients with serious influenza requiring hospitalisation.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Adults and Adolescents (13 years of age and older)
The recommended dose of Rapivab in adult and adolescent patients 13 years of age or older is a single 600 mg dose, administered via intravenous infusion for 15 to 30 minutes.

Paediatric Patients (2 to 12 years of age)
The recommended dose of Rapivab in paediatric patients 2 to 12 years of age is 12 mg/kg (up to a maximum dose of 600 mg), administered via intravenous infusion for 15 to 30 minutes.

Dosing in Patients with Renal Impairment
Significantly increased drug exposures were observed when Rapivab was administered to adult subjects with renal dysfunction (see Section 5.2 Pharmacokinetic properties). 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 Section 5.2 Pharmacokinetic properties).

In patients with chronic renal impairment maintained on haemodialysis, Rapivab should be administered after dialysis at a dose adjusted based on renal function (Table 1) (see Section 5.2 Pharmacokinetic properties).

Table 1: Dosage Adjustment for Adults and Adolescents (13 years and older) and Paediatric Patients (2 to 12 years of age) with Altered Creatinine Clearance

Recommended Dose	Creatinine Clearance* (mL/min)		
	≥50	30-49	10-29
Adults and Adolescents (13 years and older)	600 mg	200 mg	100 mg
Paediatric Patients (2 to 12 years of age)**	12 mg/kg	4 mg/kg	2 mg/kg

* Calculated using the Cockcroft and Gault equation

** Up to maximum dose of 600 mg

Method of Administration

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

- Do not use if seal over bottle opening is broken or missing.
- Visually inspect Rapivab for particulate matter and discolouration prior to administration.
- Dilute the required dose of Rapivab in sodium chloride 9 mg/mL (0.9 %) or 4.5 mg/mL (0.45 %) solution for infusion, 5 % dextrose or Ringer lactate solution to a volume of 100 mL.
- Administer the diluted solution via intravenous infusion for 15 to 30 minutes.
- Discard any unused diluted solution of Rapivab after 24 hours.
- Product is for single use in one patient only.
- Discard any residue.

Once a diluted Rapivab solution has been prepared, administer immediately or store in a refrigerator (2 °C – 8 °C) for up to 24 hours. If refrigerated, allow the diluted Rapivab solution to reach room temperature, and then administer immediately.

4.3 CONTRAINDICATIONS

Rapivab is contraindicated in patients with known serious hypersensitivity or anaphylaxis to peramivir or any component of the product. Severe allergic reactions have included anaphylaxis, erythema multiforme and Stevens-Johnson Syndrome (see Section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical trials have not established the efficacy of repeated doses of Rapivab over placebo or other treatments for influenza in hospitalised patients. Efficacy of Rapivab is based on clinical trials of naturally occurring influenza in which the predominant influenza infection was influenza A virus. Data on treatment of influenza B are limited.

Influenza viruses change over time. Emergence of resistant 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.

Efficacy of Rapivab in patients who begin treatment after 2 days of symptoms has not been established.

Serious Skin/Hypersensitivity Reactions

Rare cases of serious skin reactions, including erythema multiforme, have been reported with Rapivab in clinical studies and in post-marketing experience. Cases of anaphylaxis and Stevens-Johnson Syndrome have been reported in post-marketing experience with Rapivab. Discontinue Rapivab and institute appropriate treatment if anaphylaxis or a serious skin reaction occurs or is suspected. The use of Rapivab is contraindicated in patients with known serious hypersensitivity or anaphylaxis to peramivir (see Section 4.3 Contraindications and Section 4.8 Adverse effects (Undesirable effects)).

Neuropsychiatric Events

Influenza can be associated with a variety of neurological and behavioural symptoms that can include events such as hallucinations, delirium, and abnormal behaviour, 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 post-marketing reports of delirium and abnormal behaviour 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 paediatric 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 behaviour.

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.

Use in renal impairment

A reduced dose is recommended for patients with creatinine clearance below 50 mL/min (see Section 4.2 Dose and method of administration).

Not a substitute for vaccination

Rapivab is not a substitute for influenza vaccination and the use of Rapivab must not affect the evaluation of individuals for annual vaccination. Rapivab should be used for the treatment of influenza only when epidemiological data indicate that influenza is circulating in the community.

Viral Types

Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. The influenza A/H1N1 virus subtype containing the H275Y mutation is associated with reduced susceptibility to Rapivab. 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.

Use in the elderly

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.

Paediatric use

The safety and efficacy of Rapivab for the treatment of influenza has been established in paediatric patients 2 to 17 years of age. Use of Rapivab for this indication is supported by evidence from adequate and well-controlled trials in adults and data from a randomised, active-controlled study of 110 adolescent and paediatric subjects with acute influenza who received open-label treatment with a single dose of Rapivab or 5 days of treatment with oseltamivir administered within 48 hours of onset of symptoms of influenza (see Section 4.2 Dose and method of administration and Section 5 Pharmacological properties). The paediatric study included:

- 13 to 17 years of age: 21 subjects treated with Rapivab 600 mg
- 2 to 12 years of age: 67 subjects treated with Rapivab 12 mg/kg (up to a maximum dose of 600 mg).

Safety and efficacy of Rapivab in paediatric patients less than 2 years of age have not been established.

Effects on laboratory tests

Elevated liver enzymes have been reported in healthy persons and patients with influenza-like illness receiving Rapivab.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The potential for CYP interactions of Rapivab with other medicines is low, based on the known elimination pathway of Rapivab. Data from *in vitro* studies indicate that Rapivab does not induce or inhibit cytochrome P450.

Inactivated influenza vaccine can be administered at any time relative to use of Rapivab.

For live attenuated influenza vaccine, antiviral medicines may inhibit viral replication and thus reduce vaccine efficacy. Concurrent use of Rapivab and intranasal live attenuated influenza vaccine has not been evaluated. Live attenuated influenza vaccines are not recommended to be used until 48 hours following Rapivab administration.

There was no evidence of interactions with oral rimantadine, oseltamivir or oral contraceptives (containing ethinyloestradiol and levonorgestrel), or when Rapivab was administered with oral probenecid.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Rapivab had no effects on mating or fertility in rats up to 600 mg/kg/day, at which exposures were approximately 6-fold (BSA comparison) of those in humans at the clinically recommended dose.

Use in pregnancy – Pregnancy Category B3

Risk Summary

Limited available data with Rapivab use in pregnant women are insufficient to determine a drug-associated risk of adverse developmental outcomes. There are risks to the mother and foetus associated with influenza in pregnancy.

Data

Animal Data

Reproductive toxicity studies have been performed in rats and rabbits. In rats, Rapivab was administered once daily by intravenous bolus injection at doses of 200, 400, and 600 mg/kg/day on gestational days 6-17. No treatment-related fetal toxicities were observed when Rapivab was administered by intravenous bolus injection at the maximum feasible dose of 600 mg/kg, resulting in exposures approximately 6 times those in humans at the recommended dose. Rapivab was also administered by continuous intravenous infusion to rats at daily doses of 50, 400, and 1000 mg/kg/day on gestational days 6-17. Dose related increases in the incidence of foetal abnormalities of reduced renal papilla and dilated ureters were observed at 400 and 1000 mg/kg/day. The systemic drug exposure in rats at a dose without foetal effects was less than the exposures in humans at the recommended dose.

In rabbits, Rapivab was administered once daily by intravenous bolus injection at doses of 25, 50, 100, and 200 mg/kg/day on gestational days 7-19. Developmental toxicity (abortion or premature delivery) was observed at maternally toxic dose levels (100 and 200 mg/kg/day) resulting in exposures approximately 5 times those in humans at the recommended dose. The exposure in rabbits at doses without developmental toxicity was less than the exposure in humans at the recommended dose.

A pre/post-natal developmental toxicity study was performed in pregnant rats administered Rapivab once daily by intravenous infusion at doses of 50, 200, 400 and 600 mg/kg/day on gestational day 6 through lactation day 20. No significant effects of Rapivab on developmental outcomes were observed in nursing pups at up to the highest dose tested.

Influenza is more likely to cause severe illness in pregnant women than in non-pregnant women. Changes in the immune system, heart, and lungs during pregnancy, and up to post-partum, increase the risk of severe illness, hospitalisations and death. Pregnant women infected with influenza are at increased risk for significant complications with the pregnancy and the foetus, including premature labour and delivery.

Use in lactation

There are no data on the presence of Rapivab in human milk, the effects on the breastfed infant, or the effects on milk production. Rapivab is present in rat milk. Limited clinical data during lactation preclude a clear determination of the risk of Rapivab to an infant during lactation; therefore, 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.

A pharmacokinetic study was performed in lactating rats administered a single intravenous dose of Rapivab (10 mg/kg) on lactation/post-partum days 11-13. The maximum concentration of Rapivab in milk was reached at 0.75 hours post-dose. The milk to plasma AUC ratio of Rapivab was approximately 0.5.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rapivab has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Adverse Reactions in Adults (18 years of age and older)

In five randomised, double-blind, controlled trials, 1,399 subjects with acute 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 diarrhoea, 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 (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 ≥ 2% are included.

Table 2: Laboratory Abnormalities Occurring in ≥ 2% of Subjects Treated with Rapivab 600 mg

Laboratory Parameter Abnormality*	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%

* Frequencies based on treatment-emergent laboratory abnormalities

In a subset of subjects with serious influenza requiring hospitalisation 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%).

Adverse Reactions in Adolescent and Paediatric Subjects (2 to 17 years of age)

Assessment of adverse reactions is based on a randomised, active-controlled study in which 110 adolescent and paediatric subjects ages 2 to 17 years of age with acute influenza received open-label treatment with a single dose of Rapivab (N=88), or 5 days of treatment with oseltamivir (N=22). The safety profile of Rapivab in subjects 2 to 17 years of age was generally similar to that observed in adults. Specific adverse reactions reported in paediatric subjects treated with Rapivab (occurring in ≥2% of subjects) and not reported in adults included vomiting (3% versus 9% for oseltamivir), fever (3% versus 0%) and tympanic membrane erythema (2% versus 0%, respectively, for each of these

events). The only clinically significant laboratory abnormality (Grade 2) occurring in ≥2% of paediatric subjects treated with Rapivab was proteinuria by dipstick analysis (3% versus 0% for oseltamivir).

Post-marketing surveillance

The following additional adverse reactions have been identified during post-approval use of Rapivab. Because post-marketing 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, however, based on exposure and reporting rates, these events are estimated to be rare or very rare.

Dermatologic: Stevens-Johnson Syndrome, erythema multiforme, exfoliative dermatitis, rash

General disorders and administration site conditions: anaphylactic/anaphylactoid reactions

Psychiatric: abnormal behaviour, hallucinations, delirium

Psychiatric events (including abnormal behaviour) were more commonly reported in children, especially of younger ages, than adults.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience of acute overdose with Rapivab in humans. Treatment of an overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.
Rapivab is cleared by renal excretion and can be cleared by haemodialysis. There is no specific antidote to treat an overdose of this medicine.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Rapivab is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells. The median neuraminidase inhibitory activities (IC_{50} values) of Rapivab in biochemical assays against influenza A/H1N1 virus, influenza A/H3N2 virus and influenza B virus clinical isolates were 0.16 nM, 0.13 nM and 0.99 nM, respectively, in a neuraminidase assay with a fluorescently labelled MUNANA substrate.

Resistance

No changes in the median post-treatment IC_{50} values from subjects treated with Rapivab were detected in multiple studies in the clinical development program. Changes in individual post-treatment Rapivab IC_{50} values were detected for some subjects. The only mutation in neuraminidase detected in more than one post-treatment clinical virus isolate associated with increased Rapivab

IC_{50} was an H275Y mutation which was detected in 9 of 481 (1.9 %) of subjects infected with an influenza A/H1N1 virus. Influenza A/H1N1 and B strain viruses with reduced susceptibility to peramivir have been found among clinical isolates from patients not exposed to Rapivab. The clinical impact of this reduced susceptibility is unknown and may be strain dependent.

Cross Resistance

Cross-resistance has been observed between some oseltamivir-resistant and some zanamivir-resistant influenza virus mutations generated *in vitro*. The most notable cross-resistance mutation is the H275Y substitution, which is associated with reduced susceptibility to Rapivab and oseltamivir. No studies have been performed to assess the risk of the emergence of cross-resistance from clinical isolates.

Immune Response

No influenza vaccine/Rapivab interaction study has been conducted.

Clinical Trials

Acute Influenza in Adults

A randomised, multicentre, blinded trial conducted in Japan evaluated a single intravenous administration of Rapivab 300 mg or 600 mg, or placebo administered over 30 minutes in subjects 20 to 65 years of age with acute influenza. Subjects were eligible if they had fever greater than 38°C 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).

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 efficacy population included 297 subjects. Among the 99 subjects enrolled in the Rapivab 600 mg dose group, 97% were infected with influenza A virus and 1% with influenza B virus.

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 of fever to less than 37°C in the 600 mg group was approximately 12 hours sooner compared to placebo.

Acute Influenza in Children

A randomised, multicentre, open-label, active-controlled trial to evaluate the safety, pharmacokinetics and efficacy of a single intravenous dose of Rapivab administered for a minimum of 15 minutes in subjects 2 to 17 years of age with acute influenza who had fever greater than or equal to 37.8°C (oral) with at least one respiratory symptom (cough or rhinitis) or a positive influenza rapid antigen test.

Study treatment was started within 48 hours of onset of symptoms. Subjects were randomised to receive Rapivab 600 mg (13 to 17 years of age), Rapivab 12 mg/kg up to a maximum dose of 600 mg (2 to 12 years of age), or oral oseltamivir BID for 5 days. In addition, all enrolled subjects were allowed to take fever-reducing medications.

The overall efficacy population, consisting of subjects with confirmed influenza who were administered study drug, totalled 84 subjects. Among the 69 subjects treated with Rapivab, the median age was 7.9 years; 55% were male; 58% were infected with influenza A virus, 36% were infected with influenza B virus, and 6% were co-infected with influenza A and B viruses.

The primary endpoint was the safety of Rapivab compared to oseltamivir as measured by adverse events, laboratory analysis, vital signs and physical exams. Secondary endpoints included efficacy outcomes such as time to resolution of influenza symptoms and time to resolution of fever; however, the trial was not powered to detect statistically significant differences in these secondary endpoints.

Subjects receiving Rapivab experienced a median time to alleviation of their combined influenza symptoms of 79 hours (interquartile range: 34-122 hours) compared to 107 hours (interquartile range: 57-145 hours) in subjects receiving oseltamivir. The median time to recovery to normal temperature (less than 37°C) was 40 hours (interquartile range: 19-68 hours) and 28 hours (interquartile range: 15-41 hours) in subjects receiving Rapivab and oseltamivir, respectively.

Serious Influenza in Adults Requiring Hospitalisation

A randomised, double-blind, multicentre, placebo-controlled trial was conducted in 398 subjects with serious influenza requiring hospitalisation. In this trial, subjects were randomised to receive Rapivab 600 mg daily for 5 days plus standard of care versus placebo plus standard of care within 72 hours of start of symptoms. Standard of care could include neuraminidase inhibitors (oseltamivir and zanamivir).

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.

Rapivab has also been administered during emergency use in severe influenza in hospitalised patients. During the 2009-2010 H1N1 pandemic, patients were dosed once daily for a period of up to 10 days. Similar patient outcomes were observed with Rapivab as have been previously observed with oseltamivir.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In clinical studies in adults following intravenous administration, the rate of entry of Rapivab into the systemic circulation is dependent on the duration of infusion; in most studies, the duration of infusion was 15 to 30 minutes.

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 46.8 micrograms/mL was reached at the end of infusion. $AUC_{0-\infty}$ values were 102.7 micrograms•hr/mL.

Distribution

In vitro binding of Rapivab to human plasma proteins is less than 30 %. Based on a population pharmacokinetic analysis, the central volume of distribution was 12.56 L.

Metabolism

Rapivab is not a substrate for CYP enzymes, does not affect glucuronidation, and is not a substrate or inhibitor of P-glycoprotein mediated transport. Rapivab is not significantly metabolised in humans.

Excretion

The elimination half-life of Rapivab following intravenous 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 Rapivab accounts for approximately 90% of total clearance. Negligible accumulation was observed following multiple doses, either once or twice daily, for up to 10 days.

Pharmacokinetics in Special Populations

Race

Pharmacokinetics of Rapivab was evaluated primarily in Caucasians and Asians. From the population pharmacokinetic analysis, it was concluded that no dose adjustment is required based on race.

Gender

Rapivab pharmacokinetics was similar in male and female subjects.

Paediatric Patients

The pharmacokinetics of Rapivab has been evaluated in a study in paediatric subjects 2 to 17 years of age with acute influenza. Pharmacokinetic sampling in this study was limited to approximately 3 hours after administration of Rapivab. Pharmacokinetics of Rapivab in subjects 13 to 17 years of age was similar to those in adult subjects, with a C_{max} of 54,300 ng/mL and $AUC_{0\text{-last}}$ of 72,400 ng•h/mL after administration of a single 600 mg dose. Pharmacokinetics of Rapivab in subjects 2 to 12 years of age (C_{max} of 64,800 ng/mL and $AUC_{0\text{-last}}$ of 85,300 ng•h/mL) administered a single 12 mg/kg dose was also similar to that in adult subjects administered a single 600 mg dose.

Elderly

Rapivab pharmacokinetics in elderly subjects was similar to non-elderly subjects. No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Renal impairment

A trial was conducted in adult 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 $AUC_{0\text{-}\infty}$ after a single 2 mg/kg intravenous dose was increased in subjects with reduced creatinine clearance values.

Haemodialysis was effective in reducing systemic exposure of Rapivab by 73 to 81 % in subjects with renal impairment.

A reduced dose of Rapivab is recommended for patients with creatinine clearance below 50 mL/min (see Section 4.2 Dose and method of administration).

The pharmacokinetics of Rapivab has not been studied in paediatric subjects with renal impairment. Given that the pharmacokinetics in paediatric subjects is comparable to that observed in adults, the same proportional dose reduction in paediatric patients is recommended (see Section 4.2 Dose and method of administration).

Hepatic impairment

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Rapivab was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation assays, the Chinese hamster ovary chromosomal aberration test, and the *in vivo* mouse micronucleus test with intravenous administration. All assays were validated by the appropriate use of positive and negative controls.

Carcinogenicity

Carcinogenicity studies by intravenous injection of Rapivab were not performed. However, in an oral carcinogenicity study in rats no drug-related neoplasms were observed at drug exposures 0.3-fold that of humans (AUC comparisons) at the clinically recommended dose of 600 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride 9 mg/mL (0.9 %) solution for injection
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other products except those mentioned in Section 4.2 Dose and method of administration.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials of Rapivab injection in original cartons below 25°C. Temperature excursions of 15° to 30°C are permitted.

6.5 NATURE AND CONTENTS OF CONTAINER

Rapivab injection is a clear, colourless sterile, isotonic concentrate solution for infusion. Each single-use vial contains 200 mg per 20 mL (10 mg/mL) of peramivir in a clear glass vial fitted with a rubber stopper and royal blue flip-off plastic seal. Rapivab injection is supplied in cartons containing three single-use vials.

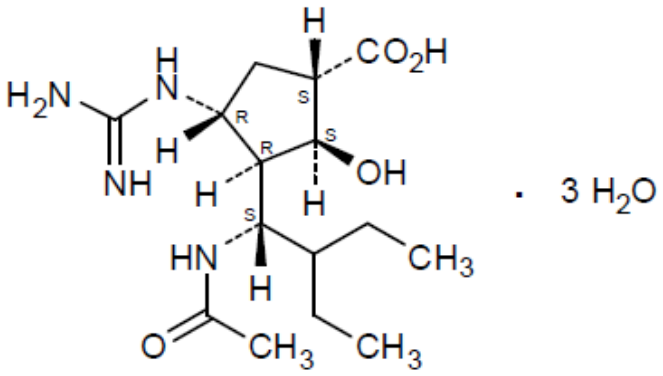
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name is (1S,2S,3R,4R)-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-(carbamimidoylamino)-2hydroxycyclopentanecarboxylic acid, trihydrate. The chemical formula is $C_{15}H_{28}N_4O_4 \cdot 3H_2O$, representing a molecular weight of 382.45.

Chemical structure



CAS number

1041434-82-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Biocelect Pty Ltd ABN: 88 168 092 171
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Telephone: 1300 907 411
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9 DATE OF FIRST APPROVAL

21 March 2018

10 DATE OF REVISION

10 September 2021

RAPIVAB™ is a trademark of BioCryst Pharmaceutical, Inc.

Summary table of changes

Section changed	Summary of new information
Heading, 1, 4.8	Minor editorial changes as per TGA requirement
8,10	Updates to reflect change of sponsor