Ronim 250mg, 500mg
(Doripenem) For Intravenous Infusion
For Injection

رونم انجکشن
۲۵۰ ملی گرام، ۵۰۰ ملی گرام

QUALITATIVE AND QUANTITATIVE COMPOSITION
Ronim For Injection 250mg
Each vial contains:
Doripenem Monohydrate eq. to Doripenem…..250mg
(Innovator's specification)
Ronim For Injection 500mg
Each vial contains:
Doripenem Monohydrate eq. to Doripenem…..500mg
(Innovator's specification)

DESCRIPTION
Ronim (Doripenem monohydrate) is a synthetic broad spectrum carbapenem antibiotic structurally related to beta-lactam antibiotics.

CLINICAL PHARMACOLOGY
Mechanism of Action: Doripenem belongs to the carbapenem class of antimicrobials. Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential penicillin-binding proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death. **Pharmacodynamics:** Similar to other beta-lactam antimicrobial agents, the time that unbound plasma concentra-tion of doripenem exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamic relationship for doripenem has not been evaluated in patients. **Pharmacokinetics: Absorption:** There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in subjects with normal renal function. **Distribution:** The average binding of doripenem to plasma proteins is approximately 8.1% and is independent of plasma drug concentrations. The median (range) volume of distribution at steady state in healthy subjects is 16.8 L (8.09–55.5 L), similar to extracellular fluid volume (18.2 L). **Metabolism:** Metabolism of doripenem to a microbiologically inactive ring-opened metabolite (doripenem-M1) occurs primarily via dehydropeptidase-I. The mean (SD) plasma doripenem M1 to doripenem AUC ratio following single 500 mg and 1 g doses in healthy subjects is 18% (7.2%). **Elimination:** Doripenem is primarily eliminated unchanged by the kidneys. Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy adults, less than 1% of the total radioactivity was re-covered in feces after one week.

INDICATIONS AND USAGE
Ronim (Doripenem) for injection is indicated as a single agent for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. **Usage:** To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ronim and other antibacterial drugs, Ronim should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

CONTRAINDICATIONS
Ronim is contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

INTERACTIONS
- Co-administration of RONIM with valproic acid causes the serum concentrations of valproic acid to fall below the therapeutic range, increasing the risk for breakthrough seizures. If administration of RONIM is necessary, supplemental anti-convulsant therapy should be considered.
- Probenecid interferes with the active tubular secretion of doripenem, resulting in increased plasma concentrations of doripenem. Coadminis-tration of probenecid with RONIM is not recommended.

USE IN SPECIFIC POPULATION
Pregnancy: Category B: There are no adequate and well-controlled studies in pregnant women therefore this drug should be used during pregnancy only if clearly needed. **Nursing mothers:** It is not known whether this drug is excreted in human milk caution should be exercised when RONIM is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric use:** As elderly patients are more likely to have decreased renal function or prerenal azotemia, care should be taken in dose selection, and it may be useful to monitor renal function. **Renal patients:** Dosage adjustment is required in patients with moderately or severely impaired renal function.

PRECAUTIONS
Increased Mortality in Ventilator Associated Bacterial Pneumonia: Doripenem is not approved for the treatment of ventilator associated bacterial pneumonia. **Hypersensitivity Reactions:** Serious and occasionally fatal hypersensitivity (anaphylactic) and serious skin reactions have been reported in patients receiving beta-lactam antibiotics. If an allergic reaction to RONIM occurs, discontinue the drug. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment, as clinically indicated. **Seizures:** Seizures have been reported during treatment with doripenem. Doripenem-treated patients with pre-existing central nervous system (CNS) disorders (e.g. stroke or history of seizures), patients with compromised renal function and patients given doses greater than 500 mg every 8 hours appear to be at greater risk for developing seizures. **Interaction with Valproic Acid:** Due to a drug interaction, patients with seizure disorders controlled with valpro-ic acid or sodium valproate will be at an increased risk for breakthrough seizures when treated with RONIM concomitantly. **Clostridium difficile-Associated Diarrhea:** Clostridium difficile-associ-ated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. If CDAD is sus-pected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. **Development of Drug Resistant Bacteria:** Prescribing RONIM in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. Pneumonitis with Inhalational Use When RONIM has been used investigationally via inhalation, pneumonitis has occurred. RONIM should not be administered by this route

ADVERSE REACTIONS
Leukopenia, neutropenia, thrombocytopenia, anaphylaxis nervous system, seizure, renal impairment/failure, Interstitial pneumonia, toxic epidermal necrolysis, Stevens-Johnson Syndrome.

DOSAGE AND ADMINISTRATION
The recommended dosage of RONIM is 500 mg administered every 8 hours by intravenous infusion over one hour in patients ≥18 years of age. The recommended dosage and administration by infection is described in Table 1: Dosage of RONIM by Infection.

Infection	Dosage	Frequency	Infusion Time (hours)	Duration
Complicated intra-abdominal infection	500mg	every 8 hours	1	5–14 days*
Complicated UTI, including pyelonephritis	500mg	every 8 hours	1	10 days*†

* Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated. † Duration can be extended up to 14 days for patients with concurrent bacteremia.

Patients with Renal Impairment:
Dosage of RONIM in Patients with Renal Impairment

Estimated CrCl (mL/min)	Recommended Dosage Regimen of RONIM
>50	No dosage adjustment necessary
≥ 30 to ≤ 50	250 mg* administered intravenously (over 1 hour) every 8 hours
> 10 to < 30	250 mg* administered intravenously (over 1 hour) every 12 hours

Preparation of Solutions: RONIM does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparation of the infusion solution. RONIM infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product. **Preparation of 500 mg RONIM dose using the 500 mg vial:** Constitute the 500mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultant concentration is approximately 50 mg/mL. **CAUTION:** THE CONSTITUT-ED SUSPENSION IS NOT FOR DIRECT INJECTION. **Preparation of 250 mg RONIM dose using the 250 mg vial:** Constitute the 250 mg vial with 10 mL of sterile water for injection or 0.9% sodium chloride injection (normal saline) and gently shake to form a suspension. The resultantconcentration is approximately 25 mg/mL. **CAUTION:** THE CONSTITUTED SUSPENSION IS NOT FOR DIRECT INJECTION. **Compatibility:** The compatibility of RONIM with other drugs has not been established. RONIM should not be mixed with or physically added to solutions containing other drugs. **Storage of Constituted Solutions:** Following dilution of the suspension with normal saline or 5% dextrose, RONIM infusions stored at room temperature or under refrigeration should be completed according to the times in table below:
Table: Storage and Stability Times of Infusion Solutions Prepared in Normal Saline or 5% Dextrose

Infusion prepared in	Stability Time at Room Temp. (includes room temperature storage and infusion time)	Stability time at 2-8°C (Refrigeration) (includes refrigerator storage and infusion time)
Normal saline	12 hours	72 hours
5% Dextrose	4 hours	24 hours

Constituted RONIM suspension or RONIM infusion should not be frozen.

OVERDOSAGE: In the event of overdose, RONIM should be discontinued and general supportive treatment given. Doripenem can be removed by hemodialysis. In subjects with end-stage renal disease administered RONIM 500 mg, the mean total recovery of doripenem and doripenemM1 in the dialysate following a 4-hour hemodialysis session was 259 mg (52% of the dose). However, no information is available on the use of hemodialysis to treat overdosage.

INSTRUCTIONS
Dosage as directed by the physician. Store at 25°C, excursions permitted to 15°C-30°C. Protect from sunlight and moisture. See package insert for the preparation of intravenous solution, compatibility, stability and storage of reconstituted solution. Not for direct infusion. Discard unused portion.
Injection should not be used if container is leaking, solution is cloudy or it contains un-dissolved particles.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION
Ronim (Doripenem) for Injection 250mg is available in glass vial along with insert.
Ronim (Doripenem) for Injection 500mg is available in glass vial along with insert.

علامات / طریقہ استعمال: رونم پیٹ اور پیشاب کی نالی کے پیچیدہ امراض کے علاج کے لئے تجویز کردہ ہے۔

مضر اثرات: لیوکوپینیا، نیوٹروپینیا، گردوں کی خرابی، انٹرسٹیشیل نمونیہ، ایپیڈرمل نیکروسس۔

احتیاطی تدابیر: حاملہ خواتین اور دودھ پلانے والی مائیں ضرورت پڑنے کے پیش نظر

صرف ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
بچے، بزرگ اور گردوں کے امراض میں مبتلا مریض ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
گلوسٹریڈیم ڈیفیسل سے منسلک ڈائریا کا خدشہ ہوتے ہی رونم کا استعمال روک دیں۔

ہدایات: خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۵ ڈگری سینٹی گریڈ پر رکھیں محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
سورج کی روشنی اور نمی سے محفوظ رکھیں۔ انجکشن کے ایک مجلول کے دھندلا ہونے یا کسی بھی قسم کے غیر حل پذیر مادے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔ غیر استعمال شدہ محلول ضائع کردیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔
سسپنشن کو براہ راست استعمال نہ کریں۔

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