PREMAX®

Imipenem / Cilastatin
500 /500 mg, 20ml vial

containing powder for solution for IV infusion.

Presentation:
PREMAX®: Each 20 ml vial contains powder of 500 mg Imipenem (as 530 mg Imipenem Monohydrate) and 500 mg Cilastatin (as 530 mg Cilastatin Sodium salt) in packs of 1, 10 and 50 vials.
Excipients: Sodium Bicarbonate.
Pharmaceutical form:
Sterile powder for solution for IV infusion.
Therapeutic indications
PREMAX® is indicated for the treatment of the following infections in adults and children 1 year of age and above:
• complicated intra-abdominal infections.
• severe pneumonia including hospital and ventilator-associated pneumonia.
• intra- and post-partum infections.
• complicated urinary tract infections.
• complicated skin and soft-tissue infections.
PREMAX® may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Posology and method of administration
Posology:
The dose recommendations for **PREMAX®** represent the quantity of imipenem/cilastatin to be administered.
The daily dose of **PREMAX®** should be based on the type of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s) and the patient's renal function.
Adults and adolescents
For patients with normal renal function (creatinine clearance of ≥90 ml/min), the recommended dose regimens are:
500 mg/500 mg every 6 hours OR 1000 mg/1000 mg every 8 hours OR every 6 hours.
It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours.
A reduction in dose is necessary when creatinine clearance is < 90 ml/min (see Table 1).
The maximum total daily dose should not exceed 4000 mg/4000 mg per day.
Renal impairment
To determine the reduced dose for adults with impaired renal function:
1. The total daily dose (i.e. 3000/3000 ,2000/2000 or 4000/4000 mg) that would usually be applicable to patients with normal renal function should be selected.
2. From table 1 the appropriate reduced dose regimen is selected according to the patient's creatinine clearance. For infusion times see Method of administration.

Creatinine clearance (mL/min) is:	If TOTAL DAILY DOSE is: 2000 mg/day	If TOTAL DAILY DOSE is: 3000 mg/day	If TOTAL DAILY DOSE is: 4000 mg/day
≥90 (normal)	500 q6h	1000 q8h	1000 q6h

reduced dosage (mg) for patients with renal impairment:

<90 - ≥60	400 q6h	500 q6h	750 q8h
<60 - ≥30	300 q6h	500 q8h	500 q6h
<30 - ≥15	200 q6h	500 q12h	500 q12h

Patients with a creatinine clearance of <15 ml/min
These patients should not receive **PREMAX®** unless haemodialysis is instituted within 48 hours.
Patients on haemodialysis
When treating patients with creatinine clearances of <15 ml/min who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 15 to 29 ml/min (see table 1).
Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive **PREMAX®** after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, **PREMAX®** is recommended only when the benefit outweighs the potential risk of seizures.
Currently there are inadequate data to recommend use of **PREMAX®** for patients on peritoneal dialysis.
Hepatic impairment
No dose adjustment is recommended in patients with impaired hepatic function.
Elderly population
No dose adjustment is required for the elderly patients with normal renal function.
Paediatric population ≥1 year of age
For paediatric patients ≥1 year of age, the recommended dose is 15/15 or 25/25 mg/kg/dose administered every 6 hours.
It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25/25 mg/kg administered every 6 hours.
Paediatric population <1 year of age
Clinical data are insufficient to recommend dosing for children less than 1 year of age.
Paediatric population with renal impairment
Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine > 2 mg/dl).
Method of administration
PREMAX® is to be reconstituted and further diluted prior to administration. Each dose of ≤500 mg/500 mg should be given by intravenous infusion over 20 to 30 minutes. Each dose >500 mg/500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.
Contraindications
• Hypersensitivity to the active substances or to any of the excipients.
• Hypersensitivity to any other carbapenem antibacterial agent.
• Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).
Special warnings and precautions for use
General
The selection of imipenem/cilastatin to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with **PREMAX®**, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to **PREMAX®** occurs, discontinue the therapy immediately. Serious anaphylactic reactions require immediate emergency treatment.
Hepatic
Hepatic function should be closely monitored during treatment with imipenem/cilastatin due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure and fulminant hepatitis).
Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin. There is no dose adjustment necessary.
Haematology
A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin.
Antibacterial spectrum
The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. The use of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections are suspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when Pseudomonas aeruginosa infections are suspected or proven to be involved in the approved indications.
Interaction with valproic acid
The concomitant use of imipenem/cilastatin and valproic acid/sodium valproate is not recommended.
Clostridioides difficile
Antibiotic-associated colitis and pseudomembranous colitis have been reported with imipenem/cilastatin and with nearly all other anti-bacterial agents and may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of imipenem/cilastatin. Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for Clostridioides difficile should be considered. Medicinal products that inhibit peristalsis should not be given.
Meningitis
PREMAX® is not recommended for the therapy of meningitis.
Renal impairment
Imipenem-cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function.
Central nervous system
CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence close adherence to recommended dose schedules is urged especially in these patients . Anticonvulsant therapy should be continued in patients with a known seizure disorder.
Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.
If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dose of **PREMAX®** should be decreased or discontinued.
Patients with creatinine clearances of <15 ml/min should not receive **PREMAX®** unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, **PREMAX®** is recommended only when the benefit outweighs the potential risk of seizures .
Paediatric population
Clinical data are insufficient to recommend the use of **PREMAX®** in children under 1 year of age or paediatric patients with impaired renal function (serum creatinine >2 mg/dl). See also above under Central nervous system.
Sodium
This medicinal product contains 37.6 mg sodium (1.6 mmol) per vial, equivalent to %1.9 of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a controlled sodium diet.
Interaction with other medicinal products and other forms of interaction
Generalized seizures have been reported in patients who received ganciclovir and **PREMAX®** . These medicinal products should not be used concomitantly unless the potential benefit outweighs the risks.
Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of imipenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered.
Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects.
There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.
Concomitant administration of **PREMAX®** and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolised) imipenem decreased to approximately %60 of the dose when **PREMAX®** was administered with probenecid. Concomitant administration of **PREMAX®** and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.
Paediatric population
Interaction studies have only been performed in adults.

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Fold mm: **105x52,5**
Orig. punch size : **ACSI092F01**
Thickness: **0,076 mm**
g/sq.mt: **60 gr/m²**
PHARMACODE: **1017**

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Fertility, pregnancy and lactation
Pregnancy
There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women.
Studies in pregnant monkeys have shown reproductive toxicity. The potential risk for humans is unknown.
PREMAX® should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.**Breast-feeding**
Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore, it is unlikely that the suckling infant will be exposed to significant quantities. If the use of **PREMAX®** is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.
Fertility
There are no data available regarding potential effects of imipenem/cilastatin treatment on male or female fertility.
Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, there are some side effects (such as hallucination, dizziness, somnolence, and vertigo) associated with this product that may affect some patients' ability to drive or operate machinery.
Undesirable effects
In clinical trials including 1,723 patients treated with imipenem/cilastatin intravenous the most frequently reported systemic adverse reactions that were reported at least possibly related to therapy were nausea (%2.0), diarrhoea (%1.8), vomiting (%1.5), rash (%0.9), fever (%0.5), hypotension (%0.4), seizures (%0.4), dizziness (%0.3), pruritus (%0.3), urticaria (%0.2), somnolence (%0.2). Similarly, the most frequently reported local adverse reactions were phlebitis/thrombophlebitis (%3.1), pain at the injection site (%0.7), erythema at the injection site (%0.4) and vein induration (%0.2). Increases in serum transaminases and in alkaline phosphatase are also commonly reported.
The following adverse reactions have been reported in clinical studies or during post-marketing experience.
All adverse reactions are listed under system organ class and frequency: Very common (≥10/1), Common (≥100/1 to <10/1), Uncommon (≥1,000/1 to <100/1), Rare (≥10,000/1 to <1,000/1), Very rare (<10,000/1) and not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Common side effects: Blood and lymphatic system disorders: eosinophilia , Vascular disorders: thrombophlebitis, Gastrointestinal disorders: diarrhoea, vomiting, nausea , Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with **PREMAX®** Skin and subcutaneous tissue disorders: rash (e.g. exanthematous), Investigations: increases in serum transaminases, increases in serum alkaline phosphatase.
Uncommon: Blood and lymphatic system disorders: pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis, Psychiatric disorders: psychic disturbances including hallucinations and confusional states, Nervous system disorders: seizures, myoclonic activity, dizziness, somnolence, Vascular disorders: hypotension, Skin and subcutaneous tissue disorders: urticaria, pruritus, General disorders and administration site conditions: fever, local pain and induration at the injection site, erythema at the injection site, Investigations: A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen
Rare: Infections and infestations:pseudomembranous colitis, candidiasis, Blood and lymphatic system disorders: agranulocytosis, Immune system disorders: anaphylactic reactions, Nervous system disorders: encephalopathy, paraesthesia, focal tremor, taste perversion, Ear and labyrinth disorders: hearing loss, Gastrointestinal disorders: staining of teeth and/or tongue, Hepatobiliary disorders:hepatic failure, hepatitis, Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, Renal and urinary disorders: acute renal failure, oligurial/anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of PRIMAXIN in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present,
Very Rare: Infections and infestations:gastro-enteritis, Blood and lymphatic system disorders:haemolytic anaemia, bone marrow depression, Nervous system disorders: aggravation of myasthenia gravis, headache ,Ear and labyrinth disorders: vertigo, tinnitus, Cardiac disorders: cyanosis, tachycardia, palpitations, Vascular disorders: flushing, Respiratory, thoracic and mediastinal disorders:dyspnoea, hyperventilation, pharyngeal pain,Gastrointestinal disorders: haemorrhagic colitis, abdominal pain, heartburn,glossitis, tongue papilla hypertrophy, increased salivation , Hepatobiliary disorders:fulminant hepatitis, Skin and subcutaneous tissue disorders: hyperhidrosis, skin texture changes, Musculoskeletal and connective tissue disorders:polyarthralgia, thoracic spine pain, Reproductive system and breast disorders:pruritus vulvae, General disorders and administration site conditions: chest discomfort, asthenia/weakness.
Not known:Nervous system disorders: agitation, dyskinesia
Paediatric population (≥3 months of age)
In studies of 178 paediatric patients ≥3 months of age, the reported adverse reactions were consistent with those reported for adults.
Reporting of suspected adverse reactions
Website: jpc@jfda.jo
The link to the electronic reporting on JFDA website (WWW.jfda.com):
https://primaryreporting.who-umc.org/JO
Tel: +962-6-5632000
rapid response number QR Code:

Overdose
Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. No specific information is available on treatment of overdose with **PREMAX®**. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.
Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01D H51
Mechanism of action
PREMAX® consists of two components: imipenem and cilastatin sodium in a 1:1 ratio by weight.
Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium Streptomyces cattleya.
Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).
Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.
Pharmacokinetic properties
Imipenem
Absorption
In normal volunteers, intravenous infusion of **PREMAX®** over 20 minutes resulted in peak plasma levels of imipenem ranging from 12 to 20 µg/ml for the 250 mg/250 mg dose, from 21 to 58 µg/ml for the 500 mg/500 mg dose, and from 41 to 83 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg /1000 mg doses were 17, 39, and 66 µg/ml, respectively. At these doses, plasma levels of imipenem decline to below 1 µg/ml or less in four to six hours.
Distribution
The binding of imipenem to human serum proteins is approximately %20.
Biotransformation
When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I. Individual urinary recoveries ranged from 5 to %40, with an average recovery of %20-15 in several studies.
Cilastatin is a specific inhibitor of dehydropeptidase-I enzyme and effectively inhibits metabolism of imipenem so that concomitant administration of imipenem and cilastatin allows therapeutic antibacterial levels of imipenem to be attained in both urine and plasma.
Elimination
The plasma half-life of imipenem was one hour. Approximately 70% of the administered antibiotic was recovered intact in the urine within ten hours, and no further urinary excretion of imipenem was detectable. Urine concentrations of imipenem exceeded 10 µg/ml for up to eight hours after a 500 mg/500 mg dose of **PREMAX®**. The remainder of the administered dose was recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenem was essentially nil.
No accumulation of imipenem in plasma or urine has been observed with regimens of **PREMAX®**, administered as frequently as every six hours, in patients with normal renal function.
Cilastatin
Absorption
Peak plasma levels of cilastatin, following a 20 minute intravenous infusion of **PREMAX®**, ranged from 21 to 26 µg/ml for the 250 mg/250 mg dose, from 21 to 55 µg/ml for the 500 mg/500 mg dose and from 56 to 88 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg/1000 mg doses were 22, 42, and 72 µg/ml respectively.
Distribution
The binding of cilastatin to human serum proteins is approximately %40.
Biotransformation and elimination
The plasma half-life of cilastatin is approximately one hour. Approximately %80-70 of the dose of cilastatin was recovered unchanged in the urine as cilastatin within 10 hours of administration of **PREMAX®**. No further cilastatin appeared in the urine thereafter. Approximately %10 was found as the N-acetyl metabolite, which has inhibitory activity against dehydropeptidase comparable to that of cilastatin. Activity of dehydropeptidase-I in the kidney returned to normal levels shortly after the elimination of cilastatin from the blood stream.
Storage condition: store below 30 °C.
Incompatibilities:
This medicinal product is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate. However, it can be administered into an I.V. system through which a lactate solution is being infused.
This medicinal product must not be mixed with other medicinal products except those mentioned in Reconstitution section.
Special precautions for disposal and other handling
Each vial is for single use only.
Reconstitution:
Contents of each vial must be transferred to 100 ml of an appropriate infusion solution: 0.9 % sodium chloride. In exceptional circumstances where 0.9 % sodium chloride cannot be used for clinical reasons 5 % glucose may be used instead.
A suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the vial. Shake well and transfer the resulting mixture to the infusion solution container.
CAUTION: THE MIXTURE IS NOT FOR DIRECT INFUSION.
Repeat with an additional 10 ml of infusion solution to ensure complete transfer of vial contents to the infusion solution. The resulting mixture should be agitated until clear.
The concentration of the reconstituted solution is approximately 5 mg/ml for both imipenem and cilastatin.
Variations of colour, from colourless to yellow, do not affect the potency of the product.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
After reconstitution:
Diluted solutions should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two hours.

I-0060-LM0-R3/EE OCT. 2022

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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P.O. Box 1019 Amman 11947, Jordan

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