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MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Patient Information Leaflet

IMINICEM-TF (ИМИНИЦЕМ-ТФ)
Powder for solution for intravenous injection/ infusion
250 mg/250 mg, 500 mg/ 500 mg.

Invented trade name: Iminicem-TF

International Non-proprietary Name: Imipenem/ cilastatin

Pharmaceutical form: powder for solution for intravenous injection/ infusion 250 mg/250 mg, 500 mg/ 500 mg

Description: White to pale yellow powder.

Qualitative and quantitative composition:
1 vial contains:
250 mg/250 mg strength
250 mg imipenem / 250 mg cilastatin and sodium hydrogen carbonate
500 mg/ 500 mg strength
500 mg imipenem / 500 mg cilastatin and sodium hydrogen carbonate

Pharmacotherapeuticgroup: Antibiotic of carbapenems group.

ATC-code: J01DH51.

PHARMACOLOGICALPROPERTIES
Pharmacodynamics
Imicinem-TF is a broad spectrum antibiotic consisting of the two components. Imipenem exerts a bactericidal action by inhibiting cell wall synthesis in aerobic and anaerobic gram-positive and gram-negative pathogenic microorganisms. Cilastatin sodium inhibits dehydropeptidase – the enzyme that metabolizes imipenem in the kidneys, – which significantly increases the concentration of unchanged imipenem in the urinary tract.
Cilastatin sodium is devoid of antimicrobial activity *per se*, and has no effect on the beta-lactamase of the bacteria. The antimicrobial spectrum of Imicinem-TF includes virtually all clinically significant pathogenic microorganisms.
The antibiotic is *in vitro* active *against the following aerobic Gram-negative bacteria.* Achromobacter spp., Acinetobacter spp. (previously known as Mima - Herellea), Aeromonas hydrophila, Alcaligenes spp., Bordetella bronchicanis, Bordetella bronchiseptica, Bordetella pertussis, Brucella melitensis, Campylobacter spp., Capnocytophaga spp., Citrobacter spp. (including Citrobacter diversus, Citrobacter freundii), Eikenella corrodens, Enterobacter spp. (including Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae), Escherichia coli, Gardnerella vaginalis, Haemophilus influenzae (including beta-lactamase-producing strains), Haemophilus ducreyi, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella spp. (в т.ч. Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella ozaenae), Moraxella spp., Morganella morganii (previously known as Proteus morganii), Neisseria gonorrhoeae (including penicillinase-producing strains), Neisseria meningitidis, Pasteurelia multocida, Proteus spp. (including Proteus mirabilis, Proteus vulgaris), Plesiomonas shigelloides, Providencia spp. (including Providencia rettgeri / previously known as Proteus rettgeri, Providencia stuartii), Pseudomonas spp. (including Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas pseudomallei, Pseudomonas putida, Pseudomonas stutzeri), Salmonella spp. (including Salmonella typhi), Serratia spp. (including Serratia proteamaculans / previously known as Serratia liquefaciens, Serratia marcescens), Shigella spp., Yersinia spp. (including Yersinia enterocolitica, Yersinia pseudotuberculosis); *aerobic Gram-positive bacteria:* Bacillus spp., Enterococcus faecalis, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Nocardia spp., Pediococcus spp., Staphylococcus aureus (including penicillinase-producing strains), Staphylococcus epidermidis (including penicillinase-producing strains), Staphylococcus saprophyticus, Group B Streptococcus spp. (including Streptococcus agalactiae), Streptococcus spp. of Groups C and G, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans (including hemolytic alpha and gamma strains);

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anaerobic Gram-negative bacteria: Bacteroides spp., Bacteroides distasonis, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaomicron, Bacteroides unifortnis, Bacteroides vulgatus, Bilophila wadsworthia, Fusobacterium spp., Fusobacterium necrophorum, Fusobacterium nucleatum, Porphyromonas asaccharolytica (previously known as Bacteroides asaccharolytica), Prevotella bivia (previously known as Bacteroides bivius) Prevotella disiens (previously known as Bacteroides disiens), Prevotella intermedia (previously known as Bacteroides intermedius), Prevotella melanmogenica (previously known as Bacteroides melaninogenicus), Veillonella spp.; *anaerobic Gram-positive bacteria:* Actinomyces spp., Bifidobacterium spp., Clostridium spp. (including Clostridium perfringens), Eubacterium spp., Lactobaccilus spp., Mobilincus spp., Microaerophilic streptococcus, Peptococcus spp., Peptostreptococcus spp., Propionibacterium spp. (including Propionibacterium acnes); *other microorganisms:* Mycobacterium fortuitum, Mycobacterium smegmatis.
The following microorganisms *are resistant* to imipenem: Xanthomonas maltophilia (previously known as Pseudomonas maltophilia) and some Pseudomonas cepacia strains, as well as Streptococcus faecium and methicillin-resistant staphylococci.
In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.
Imicinem-TF was shown to be effective as a monotherapy, or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

Pharmacokinetics
Distribution
Following the intravenous administration, the bioavailability of imipenem is 98%. The antibiotic is well distributed, producing high concentrations in various tissues and body fluids. Plasma protein binding is 20%.

Metabolism and elimination
The major pathway of metabolism of imipenem is by hydrolysis of the beta-lactam ring by the renal dehydropeptidase-I. the elimination half-life of imipenem is 1 hour.

Pharmacokinetics in special populations
In patients with impaired renal function, as well as in the elderly patients (aged over 65 years), a decrease in total and renal clearance is observed, as well as the increased elimination half-life of imipenem.

Therapeutic indications
Polymicrobial and mixed aerobic-anaerobic infections, empiric therapy prior to identification of microbial pathogens. The drug product is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:
- *Lower respiratory tract infections.* Staphylococcus aureus (penicillinase-producing strains), Acmetobacter spp., Enterobacter spp., Escherichia coli, Haemophilus influenzae, Haemophilus paraintluenzae, Klebsiella spp., Serratia marcescens.
- *Urinary tract infections (complicated and uncomplicated).*Enterococcus faecalis Staphylococcus aureus (penicillinase-producing strains), Enterobacter spp., Escherichia coli Klebsiella spp., Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa
- *Intra-abdominal infections.* Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), Staphylococcus epidermidis, Citrobacter spp., Enterobacter spp., Escherichia coh, Klebsiella spp., Morganella morganii, Proteus spp., Pseudomonas aeruginosa, Bifidobacterium spp. Clostridium spp., Eubacterium spp., Peptococcus spp., Peptostreptococcus spp., Propionibacterium spp.' Bacteroides spp. (including Bacteroides fragilis), Fusobacterium spp.
- *Gynecological infections.* Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains**),** Staphylococcus epidermidis**,** Streptococcus agalactiae (group B streptococci) Enterobacter spp., Escherichia coli, Gardnerelia vaginalis**,** Klebsiella spp., Proteus spp., Bifidobacterium spp., Peptostreptococcus spp., Peptostreptococcus spp., Propionibacterium spp., Bacteroides spp. (including Bacteroides fragilis).
- *Bacterial sepsis.* Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), Enterobacter spp., Escherichia coli, Klebsiella spp., Pseudomonas aeruginosa, Serratia spp., Bacteroides spp. (including Bacteroides fragilis).
- *Bone and joint infections.* Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), Staphylococcus epidermidis, Enterobacter spp., Pseudomonas aeruginosa.

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- *Infections of skin and skin structures*. Enterococcus faecalis, Staphylococcus aureus (penicillinase-producing strains), Staphylococcus epidermidis, Acinetobacter spp., Citrobacter spp., Enterobacter spp., Escherichia coli, Klebsiella spp., Morganella morganii, Proteus vulgaris, Providencia rettgeri, Pseudomonas aeruginosa, Serratia spp., Peptococcus spp., Peptostreptococcus spp., Bacteroides spp. (including Bacteroides fragilis), Fusobacterium spp.
- *Endocarditis.* Staphylococcus aureus (penicillinase-producing strains).
- -*Polymicrobial infections.*

Imicinem-TF is indicated for polymicrobic infections including those in which S. pneumoniae (pneumonia, septicemia), S. pyogenes (skin and skin structure), or non penicillinase -producing S. aureus is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics. For pediatric use information, see "Special warnings and precautions for use" and "Posology and method of administration" sections.

Contraindications

The drug product is contraindicated in patients who have had previous hypersensitivity reactions to any component of the formulation, carbapenems, penicillins or other beta-lactam antibiotics. The drug product is contraindicated in children under 3 months of age.

Caution should be taken, when using Imicinem-TF in combination with potentially nephrotoxic drugs, as well as in patients with dyspepsia symptoms, especially those associated with colitis, and in elderly patients.

Special warnings and precautions for use

Use in pregnancy and lactation

Clinical safety of Imicinem-TF during pregnancy has not been established. Imicinem-TF should not be used during pregnancy except when the potential benefit justifies the potential risk. In each case, the drug must be used under the direct supervision of a physician.

If Imicinem-TF is to be administered to a nursing woman, the breastfeeding discontinuation should be considered.

Special warnings

Imicinem-TF is not indicated in patients with meningitis because safety and efficacy have not been established. If meningitis is suspected, an appropriate antibiotic should be used. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, Imicinem-TF is recommended only when the benefit outweighs the potential risk of the renal impairment aggravation.

During therapy of Pseudomonas aeruginosa infections, periodic susceptibility testing should be done when clinically appropriate.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Imicinem-TF, the drug product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are not available, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Pediatric use

Imicinem-TF may be used in children with sepsis. Efficacy and tolerability in infants under the age of 3 months and in children with impaired renal function have not yet been established.

Posology and method of administration

The total daily dosage for Imicinem-TF should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function, and body weight.

For *adults*, the average therapeutic dose for intravenous infusion is 1-2 g / day (calculated as imipenem) divided into 3-4 infusions. The maximum daily dose is 4 grams.

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Table 1 shows the recommended Imicinem-TF doses administered as intravenous infusion, depending on the severity of the infection.

Table 1

Severity of infection	Dose of Imicinem-TF	Interval between the infusions	Total daily dose
Mild	250 mg	6 hours	1 g
Moderate	500 mg	8 hours	1.5 g
	1 g	12 hours	2 g
Severe (fully susceptible organisms)	500 mg	6 hours	2 g
Severe and/ or life-threatening (organisms with moderate susceptibility to imipenem, primarily some strains of Pseudomonas aeruginosa)	1 g	8 hours	3 g
	1 g	6 hours	4 g

Doses less than or equal to 500 mg should be given by intravenous infusion over 20 to 30 minutes. Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.
To prevent *postoperative infections*, the drug product should be given in the dose of 1 g intravenously at induction of anesthesia, followed by subsequent dose of 1g after 3 hours. In the case of high risk surgical intervention, additional doses of 500 mg should be administered 8 hours and 16 hours after anesthesia. Imicinem-TF doses administered as an intravenous infusion to *the patients with the impaired renal function and body mass of ≥ 70 kg* are given in table 2.
Imicinem-TF should not be used in patients with creatinine clearance of less than 5 ml/min/1.73 m^2, unless hemodialysis is instituted within 48 hours.
Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive Imicinem-TF after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session.

Table 2

Daily dose based on the severity of infection *	Adjusted daily dose depending on the creatinine clearance (ml/min/1.73 m^2)		
	41-70	21-40	6-20
1 g	250 mg every 8 hours	250 mg every 12 hours	250 mg every 12 hours
1.5 g	250 mg every 6 hours	250 mg every 8 hours	250 mg every 12 hours
2 g	500 mg every 8 hours	250 mg every 6 hours	250 mg every 12 hours
3 g	500 mg every 6 hours	500 mg every 8 hours	500 mg every 12 hours
4 g	750 mg every 8 hours	500 mg every 6 hours	500 mg every 12 hours

* see table 1.

For pediatric patients over 3 months of age weighing less than 40 kg, the recommended dose of the drug product is 15-25 mg/kg/dose administered every six hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of P. aeruginosa) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) may be used in patients with cystic fibrosis.
The drug product *is not recommended in pediatric patients with CNS infections* because of the risk of seizures and *is not recommended in pediatric patients < 30 kg with impaired renal function*, as no safety data are available.

Instructions for preparation and administration of solution
Imicinem-TF should be administered as an intravenous infusion.
A suggested procedure to prepare the *intravenous solution* is to add to the vial contents approximately 10 ml of the appropriate infusion solution: 0.9% sodium chloride solution, 5 %, 10 % aqueous dextrose solution, 5 % and 10 % mannitol solution.
CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION!
Shake well and transfer the resulting suspension to the container or vial with the remaining infusion solution (140 ml). Total volume of solution is 150 ml. Repeat using additional 10 ml of the diluted suspension, to ensure complete transfer of the contents of the vial to the infusion solution. Shake well and transfer the resulting suspension to the container or vial with the remaining infusion solution. The resulting mixture (150 ml) should be agitated until clear. *The product is chemically incompatible with lactate and must not be reconstituted in solutions that contain it.*

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Undesirable effects
Local reactions: intravenous administration may cause erythema, pain and infiltrates at the injection site, thrombophlebitis.
Allergic reactions: rash, pruritus, urticarial fever, fever, anaphylactic reactions, erythema multiforme, angioedema; rarely - exfoliative dermatitis, toxic epidermal necrolysis.
Gastrointestinal disorders: nausea, vomiting, diarrhea; a moderate increase in transaminases, bilirubin and / or serum alkaline phosphatase; discoloration of the teeth; rarely – pseudomembranous colitis, hepatitis.
Investigatiobs: eosinophilia, leukopenia, neutropenia (including agranulocytosis), thrombocytopenia, thrombocytosis, decreased hemoglobin levels. In some cases, a positive direct Coombs test was reported.
Renal and urinary disorders: Elevated serum creatinine and urea nitrogen levels were reported; rarely – oliguria / anuria, polyuria, acute renal failure. Cases of urine discoloration were also reported (this condition is safe and should not be confused with hematuria).
Nervous system disorders: as with other beta-lactam antibiotics, intravenous infusions of Imicinem-TF were reported to cause myoclonus, psychic disorders, including hallucinations and confusional states, epileptic seizures, paresthesia, taste disturbances.
Undesirable effects rarely require discontinuation of therapy and are generally moderate and transient; severe undesirable effects are rare.

Overdose
Symptoms: aggravation of the adverse events.
Treatment: In the case of overdose, discontinue the drug product or reduce the dose thereof, treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdose setting is questionable.

Interaction with other medicinal products and other forms of interaction
Pharmaceutical interaction.
The product must not be mixed or physically added to other antimicrobials.
The product is chemically incompatible with lactate and must not be reconstituted in solutions that contain it.
При одновременном применении с пенициллинами, цефалоспоринами и другими бета-лактамными антибиотиками возможна перекрестная аллергия.
Concomitant use of penicillins, cephalosporins and other beta-lactam antibiotics may cause cross allergenicity.

Storage conditions and shelf-life
Store in a dry and dark place at the temperature not above 25°C.
Keep out of reach of the children.
2 years. Do not use beyond the labeled expiration date.

Prescription status
Prescription only medicine.

Presentation
20 mg/ 250 mg or 500 mg/ 500 mg in a 10 ml vial.
5 vials in a pack or 36 vials in a box (for inpatient facilities).

Manufacturing company
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