MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Medicinal Product

IMICINEM-TF
powder for solution for infusion
500 mg/500 mg

Stamp: [APPROVED
by the MINISTRY OF HEALTH
OF THE REPUBLIC OF BELARUS
Order of the Ministry of Health
of the Republic of Belarus
No. 577 dd. 27.05.2020
MC No. 4 dd. 20.05.2020]

Trade name: Imicinem-TF.
International non-proprietary name: Imipenem/Cilastatin.
Pharmaceutical form: Powder for solution for infusion 500 mg/500 mg.
Description: White to pale yellow powder.
One vial contains: 500 mg Imipenem/500 mg Cilastatin and sodium bicarbonate.
Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Carbapenems.
ATC code: J01DH51.

Pharmacological properties

Pharmacodynamics

Imicinem-TF consists of two components: imipenem and cilastatin in a 1:1 ratio by weight.
Imipenem (N-formimidoyl-thienamycin) is a semi-synthetic derivative of thienamycin, a parent compound produced by the filamentous bacterium *Streptomyces cattleya*. Imipenem has a bactericidal effect by inhibiting the synthesis of the cell wall of gram-positive and gram-negative bacteria due to binding to penicillin-binding proteins (PBPs).
Cilastatin is a competitive, reversible and specific inhibitor of renal enzyme dehydropeptidase-I that metabolizes and inactivates imipenem. It has no antibacterial activity and does not affect the antibacterial activity of imipenem.

The relationship of pharmacokinetic/pharmacodynamic parameters

Imipenem refers to antibacterial agents with a time-dependent effect. The efficacy of imipenem is determined by the time (T) during which the concentration of the antibacterial agent exceeds the minimum inhibitory concentration (MIC) for a given pathogen (T>MIC).

Resistance mechanism

Bacterial resistance to imipenem can develop due to a decrease in the membrane permeability of gram-negative bacteria (by reducing the production of porins), a weakening of the PBPs affinity for imipenem, an increase in the excretion of imipenem from the cell by an efflux pump, and the production of beta-lactamases that hydrolyze carbapenems.
There is no cross-resistance between imipenem and drugs of the quinolone, aminoglycoside, macrolide and tetracyclines classes.

Breakpoints

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) established minimal inhibiting concentrations (MICs) breakpoints of imipenem to identify susceptible and resistant pathogens.

Minimum inhibitory concentrations (MICs) breakpoints[#]

Microorganisms	Susceptibility, mg/l	Resistance, mg/l
Enterobacteriaceae[1]	≤2	>8
Pseudomonas[2] spp.	≤4	>8
Acinetobacter spp.	≤2	>8

Microorganisms	Susceptibility, mg/l	Resistance, mg/l
Staphylococcus[3] spp.	Inferred from cefoxitin susceptibility	
Enterococcus spp.	≤4	>8
Streptococcus A, B, C, G	The beta-lactam susceptibility of beta-haemolytic *streptococcus* groups A, B, C and G is inferred from the penicillin susceptibility	
Streptococcus pneumoniae[4]	≤2	>2
Other streptococcii[4]	≤2	>2
Haemophilus influenzae[4]	≤2	>2
Moraxella catarrhalis[4]	≤2	>2
Neisseria gonorrhoeae	There is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with imipenem	
Gram-positive anaerobes	≤2	>8
Gram-negative anaerobes	≤2	>8
Non-species related breakpoint[5]	≤2	>8

[#] EUCAST, Version 1.1 dated 27.04.2010.
[1] *Proteus* and *Morganella* species are considered poor targets for imipenem.
[2] The breakpoints for *Pseudomonas* relate to high dose frequent therapy (1g every 6 hours).
[3] Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
[4] Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
[5] Non-species related breakpoint have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the overview of species-related breakpoints or footnotes.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Imipenem is active against the following microorganisms:

Gram-positive aerobes: *Enterococcus faecalis, Staphylococcus aureus* (methicillin-susceptible)[*], *Staphylococcus* coagulase-negative (methicillin-susceptible), *Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans* group.

Gram-negative aerobes: *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Serratia marcescens*.

Gram-positive anaerobes: *Clostridium perfringens*[**], *Peptostreptococcus* spp.[**]

Gram-negative anaerobes: *Bacteroides fragilis, Bacteroides fragilis* group, *Fusobacterium* spp., *Porphyromonas asaccharolytica, Prevotella* spp., *Veillonella* spp.

Species with acquired resistance

Gram-negative aerobes: *Pseudomonas aeruginosa, Acinetobacter baumannii.*

Inherently resistant species

Gram-positive aerobes: *Enterococcus faecium.*

Gram-negative aerobes: some strains of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*), *Legionella* spp., *Stenotrophomonas maltophilia* spp. (formerly *Xanthomonas maltophilia*, formerly *Pseudomonas maltophilia*).

Others: *Chlamydia* spp., *Chlamydophila* spp., *Mycoplasma* spp., *Ureaplasma urealyticum.*

[*] all methicillin-resistant staphylococci are resistant to imipenem/cilastatin.
[**] Non-species related breakpoint have been used (according to EUCAST).

Pharmacokinetics

Imipenem

Absorption

In normal volunteers, intravenous infusion of imipenem/cilastatin 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 and elimination

When used as a monotherapy, imipenem is metabolized in kidneys through dehydropeptidase-I. Individual elimination in urine varies from 5 to 40% with average elimination of 15-20% shown in several studies.

Cilastatin is a specific inhibitor of dehydropeptidase-I that effectively inhibits imipenem metabolism, therefore, when used concomitantly with imipenem and cilastatin, therapeutic antibacterial concentrations of imipenem are reached in urine and blood plasma.

The plasma half-life of imipenem was about 1 hour. About 70% of antimicrobial agent used was eliminated unchanged in the urine during 10 hours. Imipenem urine concentrations exceeded 10 μg/ml during 8 hours after imipenem/cilastatin given at a dose of 500 mg/500 mg. The remainder of the administered dose was recovered in the urine as antibacterial inactive metabolites, and faecal elimination of imipenem was essentially nil.

No accumulation of imipenem in plasma or urine has been observed with regimens of imipenem/cilastatin, 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 imipenem/cilastatin, 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. About 70-80% of cilastatin dose is excreted unchanged in the urine during 10 hours after imipenem/cilastatin administration. About 10% is excreted as N-acetyl-metabolite which has an inhibitory activity against dehydropeptidase consistent to that of cilastatin. Renal dehydropeptidase-I activity is back to normal immediately after cilastatin elimination from the circulation.

Pharmacokinetics in special populations

Following a single 250 mg/250 mg intravenous dose of imipenem/cilastatin, the area under the curve (AUCs) for imipenem increased 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine clearance (CrCL) 50-80 ml/min/1.73 m^2), moderate (CrCL 30 - <50 ml/min/1.73 m^2), and severe (CrCL <30 ml/min/1.73 m^2) *renal impairment*, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m^2), and AUCs for cilastatin increased 1.6-fold, 2.0-fold, and 6.2-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Following a single 250 mg/250 mg intravenous dose of imipenem/cilastatin given 24 hours after haemodialysis, AUCs for imipenem and cilastatin were 3.7-fold and 16.4-fold higher, respectively, as compared to subjects with normal renal function. Urinary recovery, renal clearance and plasma clearance of imipenem and cilastatin decrease with decreasing renal function following intravenous administration of imipenem/cilastatin. Dose adjustment is necessary for patients with impaired renal function.

Imipenem pharmacokinetics *in patients with hepatic dysfunction* has not been established. Due to

the limited extent of hepatic metabolism of imipenem, its pharmacokinetics is not expected to be affected by hepatic impairment. Therefore, no dose adjustment is recommended in patients with hepatic impairment.

Elderly

In healthy elderly volunteers (aged between 65 and 75 years with normal renal function for their age), imipenem/cilastatin pharmacokinetics at a single dose of 500 mg/500 mg (administered intravenously over 20 minutes) was consistent with that observed for patients with mild renal dysfunction, when there is no need to adjust the dose. The mean plasma half-lives of imipenem and cilastatin were 91±7.0 minutes and 69±15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin was observed.

Paediatric patients

Mean clearance and imipenem distribution volume was about 45% higher in paediatric patients (aged between 3 months and 14 years) as compared to adults. The AUC for imipenem following administration of 15/15 mg/kg per body weight of imipenem/cilastatin to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500 mg/500 mg dose. At the higher dose, the exposure following administration of 25/25 mg/kg imipenem/cilastatin to children was 9% higher as compared to the exposure in adults receiving a 1000 mg/1000 mg dose.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity and genotoxicity studies.

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys. Available evidence suggests that cilastatin prevents the nephrotoxicity by preventing entry of imipenem into the tubular cells.

A teratology study in pregnant cynomolgus monkeys given imipenem/cilastatin at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some cases. When doses of imipenem/cilastatin (approximately 100/100 mg/kg/day or approximately 3 times the usual recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem/cilastatin.

Therapeutic indications

Imicinem-TF is indicated for the treatment of the following infections in adults and children 1 year old and above:

- complicated intra-abdominal infections;
- severe pneumonia, including nosocomial and ventilator-associated pneumonia;
- intra- and post-partum infections;
- complicated urinary tract infections;
- complicated infections of the skin and soft tissues;
- bacteremia associated or presumably associated with any of the above-mentioned infections.

Imicinem-TF can be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications

Hypersensitivity to any of the components of medicinal product.

Hypersensitivity to any carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin relation) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

Special warnings and precautions for use

When imipenem/cilastatin is selected for the treatment, feasibility of the use of the carbapenem antimicrobial agent should be considered for every patient individually based on severity of infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
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 Imicinem-TF, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to Imicinem-TF occurs, discontinue the therapy immediately. *Serious anaphylactic reactions require immediate emergency treatment!*
During treatment with Imicinem-TF, control of *hepatic function* is required due to the risk of *hepatic toxicity* (e.g. increased levels of 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.
During treatment with Imicinem-TF, a positive *direct or indirect Coombs test* may develop.
The antibacterial spectrum of imipenem/cilastatin (especially in life-threatening conditions) should be considered before embarking on any empiric therapy. Moreover, 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 methicillin-resistant Staphylococcus aureus 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.
The concomitant use of Imicinem-TF and valporic acid/sodium valproate is not recommended.
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 diarrhea during or after the use of imipenem/cilastatin. Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Imicinem-TF is not recommended for the treatment of *meningitis*.
Imipenem/cilastatin accumulates in patients with *decreased renal function*. Adverse reactions from the central nervous system (CNS) may occur if the dose is not adjusted to the renal function.
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 which 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 Imicinem-TF should be decreased or discontinued.
Patients with creatinine clearances of $\leq$15 ml/min should not receive Imicinem-TF unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, Imicinem-TF is recommended only when the benefit outweighs the potential risk of seizures.
Pediatric population

Clinical data are insufficient to recommend the use of imipenem/cilastatin in children under 1 year of age or children with impaired renal function (serum creatinine >2 mg/dl).
Each vial of the Imicinem-TF 500 mg/500 mg contains 37.6 mg *sodium* (1.6 mEq) which should be considered when using in patients on a controlled sodium diet.

Fertility, pregnancy and lactation

There are no adequate and well-controlled studies for the use of imipenem/cilastatin *in pregnant women*. Reproductive toxicity has been observed in studies in pregnant monkeys. The potential risk for human has not been established. Imicinem-TF should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus.
Imipenem and cilastatin at minor doses are excreted in human *breast milk*. Little absorption of either compound occurs following oral administration. Therefore, it is unlikely that suckling will be exposed to significant quantities. If the use of Imicinem-TF is deemed necessary, the benefit of breastfeeding for the child should be weighed against the possible risk for the child.
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. Consideration should be given to the possibility of the influence of some adverse reactions associated with the use of the medicinal product (for example, hallucinations, dizziness, somnolence and vertigo) on the ability to drive and use machines.

Posology and method of administration

The dose recommendations for Imicinem-TF represent the quantity of imipenem/cilastatin to be administered.
The daily dose of Imicinem-TF should be based on the type and severity of the infection, excreted pathogen microorganism(s), patient's renal function and patient's weight.
Adults and adolescents (12 years of age and above)
For patients with normal renal function (creatinine clearance ≥90 mL/min) the recommended dose regimes are: 500 mg/500 mg every 6 hours or 1000 mg/1000 mg every 8 hours or every 6 hours.
If the infection is caused or presumably caused by less susceptible species of bacteria (e.g., *Pseudomonas aeruginosa),* and in very severe infection (e.g., patients with neutropenic fever), the administered dose is 1000 mg/1000 mg every 6 hours.
Reduced dose may be required if creatinine clearance <90 mL/min (see Table 1). The maximum total daily dose should not exceed 4000 mg/4000 mg per day.
Patients with renal impairment
To determine the reduced dose for adults with impaired renal function:
1. The total daily dose (i.e. 2000/2000, 3000/3000 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 subsection "Method of administration".

Table 1. Daily doses of imipenem/cilastatin in adults patients depending on the state of renal function based on creatinine clearance.

Total daily dose in patients with normal renal function (mg/day)	Creatinine clearance (mL/min)*			
	≥90	<90 - ≥60	<60 - ≥30	<30 - ≥15
	Dose, mg (interval, hours)			
2000/2000	500/500 (6)	400/400 (6)	300/300 (6)	200/200 (6)
3000/3000	1000/1000 (8)	500/500 (6)	500/500 (8)	500/500 (12)
4000/4000	1000/1000 (6)	750/750 (8)	500/500 (6)	500/500 (12)

*Patients with creatinine clearance <15 ml/min should not receive Imicinem-TF unless haemodialysis is instituted within 48 hours.

Patients on hemodialysis

Patients with creatinine clearance <15 mL/min, who are undergoing hemodialysis, should receive doses recommended for patients with creatinine clearance 15-29 mL/min (see Table 1).
Imipenem and cilastatin are cleared from circulatory duration hemodialysis. Patients should receive Imicinem-TF after hemodialysis at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be thoroughly monitored. For patients on hemodialysis, Imicinem-TF is recommended only when the benefit outweighs the potential risk of seizures.
There is a lack of data to recommend the use of Imicinem-TF to patients on peritoneal dialysis.
Hepatic impairment
No dose adjustment is recommended in patients with hepatic impairment.
Elderly
No dose adjustment is required for the elderly patients with normal renal function.
Children aged ≥1 year old
For paediatric patients ≥1 year of age, the recommended dose is 15/15 mg/kg or 25/25 mg/kg every 6 hours.
If the infection is caused or presumably caused by a less susceptible bacteria (e.g., *Pseudomonas aeruginosa*), and in very severe infection (e.g., neutropenic patients with a fever), the recommended dose is 25/25 mg/kg every 6 hours.
Children aged <1 year old
Clinical data are insufficient to recommend dosing for children less than 1 year of age.
Children with renal impairment
Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine >2 mg/dl).
Method of administration
Imicinem-TF 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 of >500 mg/500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion should be slowed.
Preparation and administration of solution
Reconstitution:
Contents of each vial must be transferred into 150 ml of the corresponding infusion solution – 0.9% sodium chloride solution. In exceptional cases when 0.9 % sodium chloride solution cannot be used for clinical reasons, 5% glucose solution can be used.
The suggested procedure is to add approximately 10 ml of the appropriate infusion solution to the medicinal product vial.
Shake the resulting mixture and transfer to a container with an infusion solution.
RESULTANT SUSPENSION MUST NOT BE USED FOR IMMEDIATE INFUSION!
Repeat the procedure with an additional 10 ml from the same infusion container to ensure complete transfer of the contents of the vial into the infusion solution. The mixture obtained in the infusion container should be shaken until a clear solution is formed.
Prepared solutions should be used immediately!
The time interval between the start of reconstitution and the end of the intravenous infusion should not exceed two hours.
Color variation of the solution from colorless to yellow produces no impact on the efficacy of the medicinal product.
Unused medicinal product and materials should be discarded according to local requirements.
Undesirable effects
In clinical trials including 1723 subjects 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.
All adverse reactions are listed under system organ class and frequency: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (from ≥1/10000 to <1/1000), very rare (<1/10000) and unknown (cannot be estimated from the information available).
Within each grouping, adverse reactions are presented in order of descending seriousness.
Infections and infestations: rare - pseudomembranous colitis, candidiasis; very rare - gastroenteritis.
Blood and lymphatic system disorders: common - eosinophilia; uncommon - pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis; rare - agranulocytosis; very rare - hemolytic anemia, bone marrow suppression.
Immune system disorders: rare - anaphylactic reactions.
Psychiatric disorders: uncommon - psychiatric disorders, including hallucinations and confusional states.
Nervous system disorders: uncommon - seizures, myoclonic activity, dizziness, somnolence; rare - encephalopathy, paraesthesia, focal tremor, taste perversion; very rare - aggravation of myasthenia gravis, headache; unknown - agitation, dyskinesia.
Ear and labyrinth disorders: rare - hearing loss; very rare - vertigo, tinnitus.
Cardiac disorders: very rare - cyanosis, tachycardia, palpitations.
Vascular disorders: common - thrombophlebitis; uncommon - hypotension; very rare - flushing.
Respiratory, thoracic and mediastinum-related disorders: very rare - dyspnoea, hyperventilation, pharyngeal pain.
Gastrointestinal disorders: common - diarrhea, vomiting, nausea (nausea and vomiting associated with imipenem/cilastatin, appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with imipenem/cilastatin); rare - teeth/tongue staining, very rare - hemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation.
Hepatobiliary disorders: rare - hepatic insufficiency, hepatitis; very rare - fulminant hepatitis.
Skin and subcutaneous tissue disorders: common - rash (e.g., exanthematous); uncommon - urticaria, pruritus; rare - toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis; very rare - hyperhidrosis, skin texture changes.
Musculoskeletal and connective tissue disorders: very rare - polyarthralgia, thoracic spine pain.
Renal and urinary disorders: rare - acute renal failure, oliguria/anuria, polyuria, urine discoloration (safe, not to be has no respect to hematuria). The influence of Imicinem-TF is difficult to assess in relation to renal function, as predisposing factors for prerenal azotemia or renal impairment should be present.
Reproductive system and breast disorders: very rare - itching vulva.
General disorders and administration site conditions: uncommon - fever, local pain and injection site induration, injection site erythema; very rare - chest discomfort, asthenia/weakness.
Investigations: common - increased serum transaminases, increased serum alkaline phosphatase; uncommon - positive direct Coombs test, increased prothrombin time, decreased haemoglobin, increased serum bilirubin, increased serum creatinine, increased blood urea nitrogen.
Paediatric population
Investigations including 178 children aged ≥3 months showed that the adverse reactions were consistent with those reported in adults.
Reporting of adverse reactions
It is important to report suspected adverse reactions after medicinal product registration in order to ensure continuous monitoring of the benefit-to-risk ratio. Healthcare professionals are encouraged to report any suspected adverse drug reactions through national ADR systems.
If any adverse reactions occur, patients are advised to consult a doctor or report adverse reactions to the Adverse Drug Reactions Information Database.

This recommendation applies to any possible adverse reactions, including those not listed in the instructions for medical use, including reports of ineffectiveness of the medicinal product. Adverse reaction reports provide more information on the safety of a medicinal product.

Overdose

Symptoms of the overdose that can occur are consistent with the profile of adverse reactions and may include seizures, confusion, tremor, nausea, vomiting, hypotension, bradycardia.

No specific information is available on treatment of overdose with Imicinem-TF. Imipenem and cilastatin are excreted by hemodialysis. However, usefulness of this procedure in the overdose setting is unknown.

Interaction with other medicinal products

Pharmaceutical interactions

Imicinem-TF solution should not be mixed or introduced simultaneously with other antimicrobial agents.

Imicinem-TF is chemically incompatible with lactate; therefore, *lactate-containing diluents should not be used* when preparing a solution of this medicinal product.

Generalized seizures have been reported in patients who received *ganciclovir* and imipenem/cilastatin. 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. Decreased valproic acid levels may result in inadequate seizure control. Simultaneous use of imipenem with valporic acid or sodium valproate is not recommended. An alternative antibiotics or anticonvulsants use should be taken into consideration.

Simultaneous administration of antimicrobials and *warfarin* may increase its anti-coagulant effects. There have been many reports of increases in the anticoagulant effects of *oral anticoagulants* (including warfarin) in patients concomitantly receiving antibiotics. This risk may vary on the underlying infection, age and general status of the patient, so it is difficult to assess the role of an antibacterial drug in increasing the International Normalized Ratio (INR). Frequent INR value assessment during and immediately after the concurrent use of antimicrobial agents and oral coagulants is recommended.

Concomitant administration of imipenem/cilastatin and *probenecid* resulted in minimal increases in plasma levels and half-life of imipenem. The urinary excretion of active (non-metabolized) imipenem decreased to approximately 60% of the dose administered concurrently with probenecid. Concomitant administration of imipenem/cilastatin and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.

Children

Interaction studies have only been performed in adults.

Storage and shelf life

Keep protected from moisture and light at a temperature not exceeding 25 °C.

Keep out of the reach of the children.

Shelf life is 2 years. Do not use beyond the labeled expiration date.

<u>After dilution:</u>

Use immediately freshly prepared solutions. The time interval between the start of recovery and the end of the intravenous infusion should not exceed two hours.

Prescription status

Prescription only medicinal product.

Packaging

500 mg/500 mg in 10 ml vials for injection. Vials are corked up by rubber stoppers and plugged up by aluminum caps with plastic covers. The plastic cover can have an inscription "FLIP OFF" or have no inscription.

5 vials with an instruction for medical use in a pack or 36 vials with instructions for medical use in a box (hospital packing).

Manufacturer
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