

**Product name: TRADEMARK (imipenem/cilastatin)**

**Formulation: IV**

**ATC Code: J01D H51**

## **EUROPEAN UNION CORE SAFETY PROFILE**

### **TRADEMARK (imipenem/cilastatin) 500 mg/500 mg powder for solution for infusion**

#### **4.3 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).

#### **4.4 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 *Trademark*, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3). If an allergic reaction to *Trademark* 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 (see section 4.2).

##### Haematology

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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 (see section 4.1).

#### Interaction with valproic acid

The concomitant use of imipenem/cilastatin and valproic acid/sodium valproate is not recommended (see section 4.5).

#### Clostridium 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 (see section 4.8). 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.

#### Meningitis

*Trademark* 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, see section 4.2 and the subheading “Central nervous system” in this section.

#### 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 (see section 4.2). Anticonvulsant therapy should be continued in patients with a known seizure disorder.

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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 *Trademark* should be decreased or discontinued.

Patients with creatinine clearances of  $\leq 5$  ml/min/1.73 m<sup>2</sup> should not receive *Trademark* unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, *Trademark* is recommended only when the benefit outweighs the potential risk of seizures (see section 4.2).

#### Paediatric use

Clinical data are insufficient to recommend the use of *Trademark* 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.

*Trademark* 500 mg/500 mg contains 37.6 mg of sodium (1.6 mEq) which should be taken into consideration by patients on a controlled sodium diet.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Generalized seizures have been reported in patients who received ganciclovir and *Trademark*. 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 (see section 4.4).

#### 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 *Trademark* and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolized) imipenem decreased to approximately 60% of the dose when *Trademark* was

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administered with probenecid. Concomitant administration of *Trademark* and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.

#### **4.6 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 (see section 5.3). The potential risk for humans is unknown.

*Trademark* 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 *Trademark* 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.

#### **4.7 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 (see section 4.8).

#### **4.8 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%) (see section 4.4), 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.

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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 ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Event
Infections and infestations	Rare	pseudomembranous colitis, candidiasis
	Very rare	gastro-enteritis
Blood and lymphatic system disorders	Common	eosinophilia
	Uncommon	pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis
	Rare	agranulocytosis
	Very rare	haemolytic anaemia, bone marrow depression
Immune system disorders	Rare	anaphylactic reactions
Psychiatric disorders	Uncommon	psychic disturbances 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
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 mediastinal disorders	Very rare	dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Common	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 <i>Trademark</i>
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation

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System Organ Class	Frequency	Event
Hepatobiliary disorders	Rare	hepatic failure, 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, oligurial/anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of <i>Trademark</i> 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.
Reproductive system and breast disorders	Very rare	pruritus vulvae
General disorders and administration site conditions	Uncommon	fever, local pain and induration at the injection site, erythema at the injection site
	Very rare	chest discomfort, asthenia/weakness
Investigations	Common	increases in serum transaminases, increases in serum alkaline phosphatase
	Uncommon	A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

#### *Paediatric* ( $\geq 3$ months of age)

In studies of 178 paediatric patients  $\geq 3$  months of age, the reported adverse reactions were consistent with those reported for adults.

## **4.9 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 *Trademark*. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.