SUMMARY OF PRODUCT CHARACTEISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

LASTPEN-1GM (Imipenem & Cilastatin for Injection USP**)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial Contains:

Sterile Imipenem USP

Eq. to Anhydrous Imipenem… .....500 mg

Sterile Cilastatin Sodium USP

Eq. to Anhydrous Cilastatin… .....500 mg

Sodium Bicarbonate USP (Sterile) added as Buffer (Sodium 90.2 mg)

3. PHARMACEUTICAL FORM

Dry powder for Injection

4. Clinical particulars

4.1 Therapeutic indications

It 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

Lastpen-1gm 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.

4.2 Posology and method of administration

Posology

The dose recommendations for Lastpen-1gm represent the quantity of imipenem/cilastatin to be administered.

The daily dose of Lastpen-1gm 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 .

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. 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.

Table 1

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 Lastpen-1gm 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 Lastpen-1gm 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, Lastpen-1gm is recommended only when the benefit outweighs the potential risk of seizures.

Currently there are inadequate data to recommend use of Lastpen-1gm 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

Lastpen-1gm 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.

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 Lastpen-1gm, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to Lastpen-1gm 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.

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. 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

Lastpen-1gm 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

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 Lastpen-1gm should be decreased or discontinued.

Patients with creatinine clearances of <15 ml/min should not receive Lastpen-1gm unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, Lastpen-1gm is recommended only when the benefit outweighs the potential risk of seizures.

Paediatric population

Clinical data are insufficient to recommend the use of Lastpen-1gm 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.

Lastpen-1gm 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 Lastpen-1gm. 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 Lastpen-1gm 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 Lastpen-1gm was administered with probenecid. Concomitant administration of Lastpen-1gm 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.

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. The potential risk for humans is unknown.

Lastpen-1gm 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 Lastpen-1gm 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

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%), 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 (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥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 Not Known	aggravation of myasthenia gravis, headache 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 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 Lastpen-1gm
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation
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 Lastpen-1gm 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 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.

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 Lastpen-1gm. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems,

ATC code: J01DH51

Mechanism of action

Lastpen-1gm 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/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that imipenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy.

Mechanism of resistance

Resistance to imipenem may be due to the following:

• Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins)

• Imipenem may be actively removed from the cell with an efflux pump.

• Reduced affinity of PBPs to imipenem

• Imipenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolysing beta-lactamases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target-based cross-resistance between imipenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes.

5.2 Pharmacokinetic properties

Imipenem

Absorption

In normal volunteers, intravenous infusion of Lastpen-1gm 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 15-20% 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 Lastpen-1gm. 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 Lastpen-1gm, 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 Lastpen-1gm, 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 70-80% of the dose of cilastatin was recovered unchanged in the urine as cilastatin within 10 hours of administration of Lastpen-1gm. 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, 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 sodium at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem-cilastatin sodium (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.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 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.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

The vial should be stored below 30ºC. Protect from moisture. Keep out of reach of children.

6.5 Nature and contents of container

30 ml clear glass vial packed in unit carton along with package insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Name	**Brawn Laboratories Limited.**
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8. Marketing authorization number(s)

06828/08154/REN/2021

9. Date of first authorization/renewal of the authorization

Nov 28, 2021

10. Date of revision of the text

N/A