SWIPIP-T (PIPERACILLIN AND TAZOBACTAM FOR INJECTION USP, 4.5G)

1.3.1 Summary Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

SWIPIP-T (Piperacillin and Tazobactam for injection USP 4.5 g), Powder for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains
Piperacillin Sodium (Sterile) USP
Equivalent to Piperacillin 4 gm
Tazobactam Sodium (Sterile) USP
Equivalent to Tazobactam 500 mg

Kindly refer section 6.1 for full list of Excipients.

3 PHARMACEUTICAL FORM

Powder for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and adolescents
- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.
Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.
Children 2 to 12 years of age
- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

4.2 Posology and method of administration

The dose and frequency of Piperacillin/Tazobactam depends on the severity and localisation of the infection and expected pathogens.
Adult and adolescent patients
Infections
The usual dose is 4 g piperacillin / 0.5 g tazobactam given every 8 hours.
For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.

The following table summarises the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:

Treatment frequency	**Piperacillin/Tazobactam 4 g / 0.5 g**
Every 6 hours	Severe pneumonia
	Neutropenic adults with fever suspected to be due to a bacterial infection.
Every 8 hours	Complicated urinary tract infections (including pyelonephritis)
	Complicated intra-abdominal infections
	Skin and soft tissue infections (including diabetic foot infections)

Renal impairment

The intravenous dose should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of substance toxicity; medicinal product dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	**Piperacillin/Tazobactam (recommended dose)**
> 40	No dose adjustment necessary
20-40	Maximum dose suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dose suggested: 4 g / 0.5 g every 12 hours

For patients on haemodialysis, one additional dose of piperacillin / tazobactam 2 g / 0.25 g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours.

Hepatic impairment

No dose adjustment is necessary.

Dose in elderly patients

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 40 ml/min.

Paediatric population (2-12 years of age)

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	**Indication / condition**
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	Neutropenic children with fever suspected to be due to bacterial infections*
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	Complicated intra-abdominal infections*

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam/kg should be administered following each dialysis period.Use in children aged below 2 years

The safety and efficacy of piperacillin/ tazobactam in children 0-2 years of age has not been established.

Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen and the patients clinical and bacteriological progress.

4.3 Contraindications

Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

4.4 Special warnings and precautions for use

Before initiating therapy with Piperacillin/Tazobactam, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Piperacillin/Tazobactam, should be discontinued.

Therapy with Piperacillin/Tazobactam may result in the emergence of resistant organisms, which might cause super-infections.

Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

Leukopenia and neutropenia may occur, especially during prolonged therapy; therefore, periodic assessment of haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

This medicinal product contains 9.4 mmol (216 mg) of sodium per vial of powder for solution for injection or infusion. To be taken into consideration by patients on a controlled sodium diet

Hypokalaemia may occur in patients with low potassium reserves or who are receiving concomitant medicinal products that may lower potassium levels; periodic electrolyte determinations may be performed in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were conducted.

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided.

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 normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of Piperacillin/Tazobactam in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic.

Piperacillin and tazobactam cross the placenta. Piperacillin / tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in breast milk. Tazobactam concentrations in human milk have not been studied.. Women who are breast feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The most commonly reported adverse reactions (occurring in 1 to 10 patients in 100) are diarrhoea, vomiting, nausea and rash.
In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000),
Infections and infestations:		Candidal superinfection		
Blood and lymphatic system disorders:		leucopenia, neutropenia, thrombocytopenia	anaemia, purpura, epistaxis, bleeding time prolonged) eosinophilia, haemolytic anaemia	agranulocytosis, Coombs direct test positiv, pancytopenia, activated partial thromboplastin time prolonged, prothrombin time prolonged, thrombocythaemia
Immune system disorders:		hypersensitivity	anaphylactic / anaphylactoid reaction (including shock)	
Metabolism and nutrition disorders				blood glucose decreased, blood albumin decreased, blood protein total decreased hypokalaemia
Nervous system disorders		headache, insomnia		
Vascular disorders		hypotension, phlebitis, thrombophlebitis	Flushing	
Gastrointestinal disorders	diarrhoea, nausea, vomiting	constipation, dyspepsia, jaundice, stomatitis	abdominal pain, pseudomembra-nous colitis,	
Hepatobiliary		alanine	Blood bilirubin	

disorders		aminotransferase increased, aspartate aminotransferase increased	increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatitis	
Skin and subcutaneous tissue disorders	Rash including maculopapular rash	pruritus, urticaria,	bullous dermatitis, erythema multiforme, exanthema	Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders		blood creatinine increased	tubulointerstitial nephritis, renal failure	blood urea increased
General disorders and administration site conditions		pyrexia,, injection site reaction	chills	

4.9 Overdose

Symptoms

There have been post-marketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced including nausea, vomiting, and diarrhoea have also been reported with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

In the event of an overdose, piperacillin/tazobactam treatment should be discontinued.

No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, combinations of penicillin's, including beta-lactamase inhibitors

ATC code: J01CR05

Mechanism of action:

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillin's, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillin's and cephalosporins but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactum extends the antibiotic

spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone

PK/PD relationship:

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major pharmacodynamic determinant of efficacy for piperacillin

Mechanism of resistance

The two main mechanisms of resistance to piperacillin / tazobactam are:

• Inactivation of the piperacillin component by those beta-lactamases that are not inhibited by tazobactam: beta-lactamases in the Molecular class B, C and D. In addition, tazobactam does not provide protection against extended-spectrum beta-lactamases (ESBLs) in the Molecular class A and D enzyme groups.

5.2 Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 μg/ml and 34 μg/ml respectively.

Distribution

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and tazobactam are widely distributed in tissue and body fluids including intestinal mucosa, gall bladder, lung, bile and bone. Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillin's.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite, that has been found to be micro-biologically inactive.

Elimination

Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion.

Piperacillin is excreted rapidly as unchanged substance, with 68% of the administered dose appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose appearing as unchanged substance, and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Following single or multiple doses of piperacillin / tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0.7 to 1.2 hours and was unaffected by dose or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance.

There are no significant changes in piperacillin pharmacokinetics due to tazobactam. Piperacillin appears to slightly reduce the clearance of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects.

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 ml/min compared to patients with normal renal function.

Haemodialysis removes 30% to 50% of piperacillin / tazobactam, with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 18% of the tazobactam dose removed as the tazobactam metabolite.

Paediatric population

In a population PK analysis, estimated clearance for 9 month-old to 12 year-old patients was comparable to adults, with a population mean (SE) value of 5.64 (0.34) ml/min/kg. The piperacillin clearance estimate is 80% of this value for paediatric patients 2-9 months of age. The population mean (SE) for piperacillin volume of distribution is 0.243 (0.011) l/kg and is independent of age.

Elderly patients

The mean half-life for piperacillin and tazobactam were 32% and 55% longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

Race

No difference in piperacillin or tazobactam pharmacokinetics was observed between Asian (n=9) and Caucasian (n=9) healthy volunteers who received single 4 g / 0.5 g doses.

5.3 Preclinical safety data

No inhouse preclinical safety data has been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dark, dry place, Not exceeding 30˚C temp.
keep out of the reach and sight of children.

6.5 Nature and contents of container <an special equipment for use, administration or implantation>

One Vial of Piperacillin and Tazobactam for Injection USP, 4.5 g

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/ MANUFACTURER

APPLICANT:

M/s EXCEL CHARIS PHARMACEUTICAL CHEMICAL LTD.
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