SUMMARY OF PRODU CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Protec 1 g IM/IV Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Cefepime Hydrochloride for Injection with L-Arginine equivalent to 1 g Cefepime

3. PHARMACEUTICAL FORM

Before constitution:
Glass vial containing white to Pale yellow powder sealed with rubber closure aluminum seal with nip off.

After reconstitution:
Clear, pale yellow to amber colored solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Protec is indicated in the treatment of the following infections:
-Pneumonia (moderate to severe) including cases associated with concurrent bacteremia.
-Empiric Therapy for Febrile Neutropenic Patients.
-Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis).
-Uncomplicated Skin and Skin Structure Infections.
-Complicated Intra-abdominal Infections.

4.2 Posology and method of administration

Protec should be administered over approximately 30 minutes when given intravenously.

Recommended Dosage schedule for Protec in Patients with CrCL > 60 mL/min

Site and type of infection	Dose	Frequency	Duration (days)
Adults:			
Moderate to Severe Pneumonia 1-2 g IV q12h 10 including cases associated with concurrent bacteremia	1-2 g IV	q12h	10
Empiric Therapy for Febrile Neutropenic Patients	2 g IV	q8h	7 or until resolution of neutropenia
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections including pyelonephritis, Including cases	0.5-1 g IV/IM	q12h	7-10

associated with concurrent bacteremia			
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, Including cases associated with concurrent bacteremia	2 g IV	q12h	10
Moderate to severe Uncomplicated Skin and Skin Structure Infections	2 g IV	q12h	10
Complicated Intra-abdominal Infections (used in combination with metronidazole)	2 g IV	q12h	7-10
Pediatric patients (2 months up to 16 years) The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients is 50 mg/kg/dose, administered every 12 hours (every 8 hours for febrile neutropenic patients), for duration as given above			

4.3 Contraindications

Cefepime is contraindicated in patients with known hypersensitivity to any of its components, or to cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

4.4 Special warnings and precautions for use

Before therapy with (Cefepime hydrochloride) for injection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to Cefepime, cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to cefepime occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, corticosteroids, intravenous fluids, intravenous antihistamines, pressor amines, and airway management, as clinically indicated.
In patients with impaired renal function (creatinine clearance < 60 ml/min), the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefepime, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents

4.5 Interaction with other medicinal products and other forms of interaction

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with cefepime because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. The administration of Cefepime may result in a false-positive reaction for glucose in the urine with copper reduction tests. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

4.6 Pregnancy and lactation

There is no adequate and well-controlled studies of Cefepime use in pregnant women, this drug should be used during pregnancy only if clearly needed (Pregnancy Category B).

Cefepime is excreted in human breast milk in very low concentrations (0.5 μg/ml). Caution should be exercised when Cefepime is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Cefepime is not known to affect the ability to drive or use machines.

4.8 Undesirable effects

>10%: Hematologic: Positive Coomb's test without hemolysis.
1% to 10%: Central nervous system: Fever (1%), headache (1%).
Dermatologic: Rash, pruritus.Gastrointestinal: Diarrhea, nausea, vomiting.
Local: Pain, erythema at injection site

4.9 Overdose

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of Cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01DE01

Mechanism of action

Microbiology

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.
Cefepime is a bactericidal agent that has a spectrum of activity against a range of Gram-positive and Gram-negative bacteria.
Cefepime is highly resistant to hydrolysis by a number of beta-lactamases, has a low affinity for chromosomally encoded beta-lactamases, and exhibits rapid penetration into Gram-negative bacterial cells.
Cefepime minimum bactericidal concentrations were $\leq$2 times the minimum inhibitory concentration for the majority of organisms tested.
Cefepime has been shown to be active against most strains tested of the following organisms both in vitro and in clinical infections.

Gram-positive aerobes:

Staphylococcus aureus (including penicillinase-producing strains but excluding methicillin-resistant staphylococci), *Streptococcus agalactiae* (Group B streptococci), *Streptococcus pneumoniae* (formerly Diplococcus pneumoniae), *Streptococcus pyogenes* (Group A streptococci), other beta-haemolytic streptococci (Groups C, G, F).

Gram-negative aerobes:

Acinetobacter calcoaceticus (subsp. *anitratus, lwoffi*), Enterobacter spp.(*including E. aerogenes, E. agglomerans, E. cloacae, E. sakazakii*), *Escherichia coli*, *Haemophilus influenzae*, (including strains of beta-lactamase producing *H. influenzae*), *Haemophilus parainfluenzae*, Klebsiella

spp.(including *K. oxytoca, K. ozaenae, K. pneumoniae*), *Moraxella catarrhalis* (formerly *Branhamella catarrhalis*), *Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa* (not all strains), *Serratia marcescens*.
Cefepime exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 8 mcg/mL or less against 90% or more of the strains of the following micro-organisms: however, *in vitro* activity does not necessarily imply clinical efficacy.
Gram-positive aerobes:
Note: Enterococci like *Enterococcus faecalis* and methicillin-resistant staphylococci, are resistant to cefepime.
Staphylococcus aureus (including beta-lactamase-producing strains but excluding methicillin-resistant staphylococci), *Staphylococcus epidermidis* (including beta-lactamase-producing strains), *Staphylococcus hominis, Staphylococcus saprophyticus*, Group D streptococci (*Streptococcus bovis*), Viridans streptococci.
Gram-negative aerobes:
Pseudomonas putida, P. stutzeri, Proteus vulgaris, Aeromonas hydrophila, Capnocytophaga spp., Citrobacter spp. including *C. freundii, Campylobacter jejuni, Gardnerella vaginalis, Haemophilus ducreyi, Hafnia alvei, Neisseria gonorrhoeae* (including beta-lactamase-producing strains), *Neisseria meningitidis*, Providencia sp. including *P. rettgeri, P. stuartii*, Salmonella spp., *Serratia liquefaciens*, Shigella spp., *Yersinia enterocolitica*.
Note: Cefepime is inactive against most strains of *Xanthomonas maltophilia* (*Pseudomonas maltophilia*). Not all pseudomonas strains are susceptible.
Anaerobes:
Clostridium perfringens, Mobiluncus spp.
Note: Cefepime is inactive against *Bacteroides fragilis* and *Clostridium difficile*.

5.2 Pharmacokinetic properties

Adults
Following intramuscular injection, cefepime is completely absorbed. Therapeutic concentrations are found in various body fluids such as urine, bile, peritoneal fluid, blister fluid and sputum, and tissues such as bronchial mucosa, prostate, appendix and gallbladder, following intravenous administration of a single dose of cefepime.
The average elimination half-life of cefepime is approximately two hours.
There is no evidence of accumulation in healthy subjects receiving doses up to 2 g intravenously every 8 hours for a period of 9 days. Total body clearance averages 120 mL/min.

The average renal clearance of cefepime is 110 mL/min, demonstrating that cefepime is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration.
Urinary recovery of unchanged cefepime represents approximately 85% of dose, resulting in high concentrations of cefepime in the urine.
The serum protein binding of cefepime averages 16,4% and is independent of concentration in the serum.

Healthy volunteers 65 years old or older, who received a single 1g intravenous dose of cefepime had higher area under the concentration-time curve and lower renal clearance values compared to younger healthy adults. Dosage adjustments in the elderly are recommended if renal function is compromised.
The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1g dose.

Elimination half-life is prolonged in patients with various degrees of renal insufficiency with a linear relationship between total body clearance and creatinine clearance. This serves as the basis for dosage adjustment recommendations in this group of patients.
Average half-life in severely impaired patients requiring dialysis therapy is 13 hours for haemodialysis and 19 hours for continuous ambulatory peritoneal dialysis.

Paediatrics
Single and multiple-dose pharmacokinetics of cefepime were evaluated in patients ranging in age from 2 months to 16 years who received 50 mg/kg doses administered by IV infusion or IM injection: multiple doses were administered every 8 or 12 hours for at least 48 hours.
Mean plasma concentrations of cefepime after the first dose were similar to those at steady state, with only slight accumulation seen upon repeated dosing.
Following IM injection under steady state conditions, mean peak cefepime plasma concentrations of 68 mcg/mL were achieved at a median time of 0,75 hours, compared to 185,6 mcg/mL after IV. The mean trough concentration after IM injection at steady state was 6,0 mcg/mL at 8 hours. Bioavailability averaged 82% after IM injection.
Other pharmacokinetic parameters in infants and children were not different between first-dose and steady-state determinations, regardless of dosing schedule (q12h or q8h). There were also no differences in pharmacokinetics among various patient ages or between males and female patients.

Following a single IV dose, total body clearance (in children over 6 months) averaged 3,4 mL/min/kg and average volume of distribution was 0,3 L/kg. The overall mean elimination half-life was 1,6 hours**.** The urinary recovery of unchanged cefepime was 60,4% of the administered dose, and renal clearance was the primary pathway of elimination, averaging 2,0 mL/min/kg. Elimination was slower in children 2 - 6 months (t½1,89 hours, clearance 2,97 mL/min/kg).

Concentrations of cefepime in cerebrospinal fluid relative to those in plasma are shown in Table 1.

TABLE 1
Mean (SD) Plasma (PL) and CSF Concentrations, and CSF/PL Ratios of Cefepime in Infants and Children*

Sampling Time (hr)	N	Plasma concentration (mcg/mL)	CSF concentration (mcg/mL)	Ratio CSF/PL
0,5	6	70,4 (55,4)	5,7 (8)	0,12 (0,14)
1	4	44,1 (7,8)	4,3 (1,5)	0,10 (0,04)
2	5	23,9 (12,9)	3,6 (2,0)	0,17 (0,09)
4	5	11,7 (15,7)	4,2 (1,1)	0,87 (0,56)
8	5	4,9 (5,9)	3,3 (2,8)	1,02 (0,64)

* Patients ranged in ages from 3,1 months to 14,7 years, with a mean (SD) age of 2,9 (3,9) years. Patients with suspected central nervous system infection were treated with cefepime at a dose of 50 mg/kg administered as an IV infusion over 5 to 20 minutes every 8 hours.

Single plasma and CSF samples were collected from selected patients at the sampling times shown relative to the end of infusion on day 2 or 3 of cefepime treatment.

5.3 Preclinical safety data

Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable

6.2 Incompatibilities

Not known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep at store below 30°C

6.5 Nature and contents of container

One labelled 15R tubular clear glass vial containing powder; closed with rubber stopper and sealed with aluminium flip-off seal packed in a printed carton with folded leaflet

6.6 Special precautions for disposal and other handling

For I.V infusion, constitute the vial, and add an appropriate quantity of the resulting solution to an I.V. container with one of the following I.V. fluids: 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, M/6 Sodium lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection, Normosol-R®, and Normosol-M® in 5% Dextrose Injection.
The resulting solution should be administered over approximately 30 minutes.
For I.M administration, constitute the vial 1 g in 2.4 ml with one of the compatible diluents (ex. Sterile water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Sterile Bacteriostatic Water for injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine Hydrochloride).

Single-Dose vial for I.V/I.M administration	Amount of Diluent to be added (ml)
2 g (IV)	10
1 g (IV)	10
1 g (IM)	2.4

These solutions maybe stored up to 24 hours at controlled room temperature or 7 days in a refrigerator

7. MARKETING AUTHORISATION HOLDER

Tabuk Pharmaceutical Manufacturing Company
P.O. Box 3633
Tabuk - Saudi Arabia
Tel: 00966144283030
Fax: 00966144283031

8. MARKETING AUTHORISATION NUMBER(S)

Marketing Authorization Number in Ethiopia: **08119/08550/REN/2022**

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization in Ethiopia: **29/10/2014**

Date of latest renewal in Ethiopia: **13/11/2022**

10. DATE OF REVISION OF THE TEXT

August 2023