

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protec 2 g IV Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Cefepime Hydrochloride for injection with L-Arginine equivalent Cefepime 2 g.

3. PHARMACEUTICAL FORM

Before reconstitution: Glass vial containing white to pale yellow powder sealed with rubber closure aluminum seal with flip 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 associated with concurrent bacteremia	0.5-1 g IV/IM	q12h	7-10

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

Hypersensitivity to cefepime, to any other cephalosporin or to any of the excipients listed in section 6.1.

History of severe hypersensitivity reaction (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

As with all beta-lactam antibacterial agents, severe and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefepime must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefepime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefepime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately.

Serious hypersensitivity reactions may require epinephrine and other supportive therapy. Antibiotics should be administered with caution to patients that have shown some form of allergy, particularly to drugs. If there is an allergic reaction to Cefepime, the medicine should be stopped and adequate treatment applied.

Antibacterial activity of cefepime

Due to the relatively limited spectrum of antibacterial activity of Cefepime it is not suitable for the treatment of some 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 with cefepime (see section 5.1).

As with other antibiotics, the use of Cefepime can lead to the development of resistant micro-organisms. If superinfection occurs during treatment, adequate measures should be taken.

Renal impairment

In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organisms (see sections 4.2 and 5.2).

During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure (see section 4.8 - Undesirable effects). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommendations.

In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis, however, some cases included a fatal outcome.

Clostridium difficile associated diarrhea

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including cefepime and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of cefepime. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including cefepime, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

It is known that cefepime is excreted substantially by the kidney and the risk of toxic reactions to this drug can be higher in the patients with renal insufficiency. Because elderly patients are more susceptible to have a decreased renal function, caution should be taken in the selection of the

dose and renal function should be monitored (see section 5.2). In elderly patients with renal failure to whom the usual dose of cefepime was administered, severe adverse events occurred (see section 4.8) including reversible encephalopathy (consciousness disturbance, including confusion, hallucinations, stupor and coma), myoclonus, convulsions (including non-convulsive status epilepticus) and/or renal failure.

Interference with serological testing

A positive Coombs test, without evidence of haemolysis, has been described in patients treated with cefepime twice daily.

Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta-lactam antibiotics.

The monitoring of renal function is recommended during the treatment with Cefepime if other drugs that have nephrotoxic potential are administered (i.e., aminoglycosides and potent diuretics).

Cephalosporins can potentiate the action of coumarin anticoagulants.

Interaction with diagnostic tests

In patients treated with Cefepime positive Coombs test was described with no evidence of haemolysis.

In the glycosuria test, a false positive result may occur due to reduction of copper (the enzymatic method should preferably be used).

4.6 Pregnancy and lactation

Pregnancy

In what concerns cefepime there are no sufficient data on its exposure in pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, labour or post-natal development (see section 5.3).

This medicinal product should only be prescribed to pregnant women with great caution.

Breastfeeding

Cefepime is excreted in human milk in very low quantities, so caution is recommended when administered to the breast-feeding woman.

Fertility

There are no data on the use of cefepime in human fertility. Reproduction studies in animals did not reveal any effects on fertility.

4.7 Effects on ability to drive and use machines

The effects of the medicinal product on the ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, Confusional state or hallucinations may alter the ability to drive and use machines (see sections 4.4, 4.8 e 4.9).

4.8 Undesirable effects

In clinical trials (N=5598), the more common adverse events were gastrointestinal symptoms and hypersensitivity reactions. The undesirable effects considered as definitively, probably or possibly related to cefepime are listed.

The frequency of adverse reactions listed below, reported during the clinical experience or post-marketing experience, is defined using the following convention:

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).

The side effects are presented by decreasing order of severity within each class of frequency.

System organ class	Frequency	MedDRA term
Infections and Infestations	Uncommon	Oral candidiasis, vaginal infection
	Rare	Candidiasis
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia
	Uncommon	Thrombocytopenia, leukopenia, neutropenia
	Not known	Aplastic anaemia ^a , haemolytic anaemia ^a , agranulocytosis
Immune system disorders	Rare	Anaphylactic reaction, angioedema
	Not known	Anaphylactic shock
Psychiatric disorders	Not known	State of confusion, hallucination
Nervous system Disorders	Uncommon	Headaches
	Rare	Convulsions, paraesthesia, dysgeusia, dizziness

	Not known	Coma, stupor, encephalopathy, altered state of conscience, myoclonus
Vascular disorders	Common	Phlebitis at the infusion site
	Rare	Vasodilatation
	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea
Gastrointestinal Disorders	Common	Diarrhoea
	Uncommon	Pseudomembranous colitis, colitis, nausea, vomiting
	Rare	Abdominal pain, constipation
	Not known	Gastrointestinal disorder
Skin and subcutaneous tissue disorders	Common	Skin rash
	Uncommon	Erythema, urticaria, pruritus
	Not known	Toxic epidermal necrolysis ^a , Stevens-Johnson syndrome, erythema multiforme
Renal and urinary disorders	Uncommon	blood urea increased, blood creatinine increased
	Not known	Renal failure, toxic nephropathy ^a
Reproductive system and breast disorders	Rare	Genital pruritus
General disorders and administration site conditions	Common	Infusion site reaction, injection site inflammation and pain
	Uncommon	Pyrexia, infusion site inflammation
	Rare	Chills
Investigations	Very common	Positive Coombs test
	Common	Alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, prothrombin time prolonged, partial thromboplastin time prolonged
	Not known	False positive glycosuria

^a – Adverse reactions generally accepted as being attributable to other compounds of the same class.

The safety profile of cefepime in infants and children is similar to that seen in the adult.

As with other drugs of the class of cephalosporins, encephalopathy (conscience disorder, including confusion, hallucinations, stupor and coma), convulsions, myoclonus and/or renal failure were reported. Most cases occurred in patients with renal impairment which received cefepime doses that exceeded those recommended (see section 4.4).

Such as with other cephalosporins, anaphylaxis, including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia were reported.

During clinical tests, changes in laboratory tests were transient in the patients with normal baseline values. The changes that occurred with a frequency between 1% and 2% (except when indicated other frequency) were: increased alanine aminotransferase (3.6%), aspartate aminotransferase (2.5%), alkaline phosphatase, total bilirubin, anaemia, eosinophilia, increased prothrombin time and thromboplastin time (2.8%) and positive Coombs test with no haemolysis (18.7%). The transient increases of uraemia, serum creatinine and thrombocytopenia were observed in 0.5% to 1% of the patients. Transient leukopenia and neutropenia were observed (< 0.5%).

4.9 Overdose

In case of severe overdose, especially in patients with renal function impairment, haemodialysis can help remove cefepime from the body (peritoneal dialysis is not useful).

Accidental overdose occurred with the administration of high doses to patients with decreased renal function (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Fourth-generation cephalosporins, ATC code: J01DE01

Mechanism of action

Cefepime is a broad-spectrum, bactericidal antibiotic, with activity against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to aminoglycosides or third generation cephalosporins.

It is highly resistant to hydrolysis caused by most beta-lactamases. It has a reduced affinity for beta-lactamases changed via chromosomes and has a rapid penetration in the cells of the Gram-negative bacteria.

Resistance

The bacterial resistance to cefepime can depend on one or several mechanisms:

- Hydrolysis via beta-lactamases. Cefepime is stable to most beta-lactamases changed by plasmids and via chromosomes, but it can be hydrolysed effectively by certain beta-lactamases with broad-spectrum which are present mostly in *Escherichia coli* and *Klebsiella pneumoniae* and by enzymes changed by the chromosomes.
- Reduced affinity of the penicillin-binding proteins (PBPs) to cefepime. The resistance developed to *Streptococcus pneumoniae* and other streptococci caused by PBPs mutation; resistance of the staphylococci to methicillin caused by the production of additional PBPs with reduced affinity to cefepime.

- Non penetrable exterior membrane.

- Drugs efflux pumps.

There may be simultaneously more than one mechanism of resistance in each cell wall. Depending on the mechanism(s) present, there may be crossed resistance to several or to all other beta-lactam and/or antibacterial drugs of other types.

During treatment, resistance to the following species can develop: *Citrobacter*, *Pseudomonas* (especially *P. aeruginosa*), *Morganella* and *Serratia*.

Critical concentration values (Breakpoints)

The critical concentration values to differentiate susceptible (S) pathogens from resistant (R) pathogens, in accordance with EUCAST (2009-05-25) are:

Microorganism	Susceptible	Resistant
Critical concentration values related to species	non S \leq 4 mg/l	R > 8 mg/l
<i>Enterobacteriaceae</i>	S \leq 1 mg/l	R > 8 mg/l
<i>Pseudomonas</i> ^a	S \leq 8 mg/l	R > 8 mg/l
<i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i>	S \leq 0.25 mg/l	R > 0.25 mg/l
<i>Streptococcus pneumoniae</i>	S \leq 1 mg/l	R > 2 mg/l
<i>Streptococci</i> A, B, C and G ^b		
<i>Staphylococcus</i> ^c		

^a Critical concentration value is valid in high dose (2g x3).

^b Based on the critical concentration value for benzylpenicillin.

^c Based on the critical concentration value for methicillin.

The prevalence of acquired resistance may vary geographically and with time for selected species and it is desirable to have local information on resistance, 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.

Commonly susceptible species	
Gram-positive aerobes	<i>Staphylococcus aureus</i> and coagulase negative staphylococci including beta-lactamase producing strains Streptococci. Pneumococci
Gram-negative aerobes	<i>Acinetobacteria</i> <i>Aeromonas spp</i> <i>Citrobacter</i> Enterobacteriae <i>Escherichia coli</i>

	<i>Haemophilus influenzae</i> including beta-lactamase producing strains <i>Klebsiella</i> <i>Moraxella catarrhalis</i> including beta-lactamase producing strains <i>Morganella morganii</i> <i>Proteus</i> <i>Providencia</i> <i>Pseudomonas</i> <i>Serratia</i>
--	---

Species with acquired resistance	
Gram-positive aerobes	<i>Enterococos</i> <i>Listeria</i>
Gram-negative aerobes	<i>Burkholderia cepacia</i> <i>Legionella</i> <i>Stenotrophomonas maltophilia</i>
Anaerobes	Anaerobic bacteria including <i>Bacteroides</i> and <i>Clostridium difficile</i>
Other microorganisms	<i>Chlamydia</i> <i>Mycoplasma</i>

5.2 Pharmacokinetic properties

Absorption

Cefepime is completely absorbed after IM administration.

Distribution

Adults: Average plasma concentrations of cefepime observed in the male adult, after a single IV infusion (30 minutes) or after the IM injection of doses of 500 mg, 1 g and 2 g are summarized in table 1; in table 2 are presented the average concentrations in the tissues and biological fluids. After the intramuscular administration, cefepime is completely absorbed.

Table 1: Average plasma concentrations of cefepime (micrograms/ml)

Cefepime dose	0.5 h	1 h	2 h	4 h	8 h	12 h
500 mg IV	38.2	21.6	11.6	5.0	1.4	0.2
1 g IV	78.7	44.5	24.3	10.5	2.4	0.6
2 g IV	163.1	85.8	44.8	19.2	3.9	1.1
500 mg IM	8.2	12.5	12.0	6.9	1.9	0.7
1 g IM	14.8	25.9	26.3	16.0	4.5	1.4
2 g IM	36.1	49.9	51.3	31.5	8.7	2.3

Cefepime concentrations in specific tissues and biological fluids are in Table 2.

The binding of cefepime to serum proteins is, on average, 16.4% and is independent of the serum concentration.

Table 2: Average concentrations of cefepime in several tissues (micrograms/g) and biological fluids (micrograms/g)

Tissue or Fluid	Dose (IV)	Time after the collection (h)	Average concentration
Urine	500 mg	0 – 4	292
	1 g	0 – 4	926
	2 g	0 – 4	3120
Bile	2 g	9.4	17.8
Peritoneal fluid	2 g	4.4	18.3
Blister fluid	2 g	1.5	81.4
Bronchial mucosa	2 g	4.8	24.1
Expectoration	2 g	4.0	7.4
Prostate	2 g	1.0	31.5
Appendix	2 g	5.7	5.2
Gall bladder	2 g	8.9	11.

Biotransformation

Cefepime is metabolised in N-methylpyrrolidinium, being converted quickly in N-oxide. About 85% of the administered dose is eliminated unchanged; high concentrations of unchanged cefepime are detected in urine. Less than 1% of the administered dose is eliminated in urine as N-methylpyrrolidinium, 6.8% as N-oxide and 2.5% as cefepime epimer.

Elimination

The elimination average half-life of cefepime is about 2 hours, and is independent of the dose for the range of 250 mg to 2 g. There is no evidence of accumulation in the healthy individuals receiving doses up to 2 g IV every 8 hours for 9 days. The total body clearance is 120 ml/min. The average renal clearance of cefepime is 110 ml/min, suggesting an elimination almost exclusively via the kidneys, mainly by glomerular filtration.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

The antibacterial activity depends on the time during which the free concentration serum/urine exceeds the minimum inhibitory concentration (MIC).

Special populations

Renal dysfunction: The elimination half-life is increased in patients with several degrees of renal failure, so the dosage adjustment is recommended.

Liver dysfunction: Cefepime pharmacokinetics was not changed in patients with hepatic insufficiency that received a dose of 1 g. It is not necessary to change the posology of cefepime

in this population.

Elderly: healthy voluntary individuals of 65 years old or more that received a single dose of 1 g IV of cefepime presented higher AUC values and lower renal clearance values when compared with younger adults.

It is recommended the dose adjustment in the elderly patient with renal function impairment (see sections 4.2 and 4.4).

From the more than 6400 adults treated with cefepime in clinical studies, 35% were aged 65 years old or more and 16% were aged 75 years old or more. In clinical studies when the elderly patient received the recommended dose for the adult patient, the clinical efficacy and safety were comparable to the clinical efficacy and safety in the non-elderly adult patient, unless the patient had renal failure. There was a mild increase in the elimination half-life time and lower renal clearance values when compared with those seen in younger individuals. Dose adjustments are recommended if the renal function is impaired (see section 4.2).

Children: Cefepime pharmacokinetics with single and multiple doses was assessed in patients aged between 2.1 months and 11.2 years, with doses 50 mg/kg in IV infusion or IM injection; multiple doses were administered with intervals of 8 or 12 hours for at least 48 hours.

After the single IV administration, the total clearance was 3.3 ml/min/kg, with a distribution value of 0.3 l/kg. The elimination half-life was 1.7 hour, with an average recovery in urine of unchanged cefepime around 60.4% of the administered dose, being the renal clearance the main route of elimination (2.0 ml/min/kg).

The average plasma concentrations of cefepime in steady state after the administration of multiple IV doses were similar to those seen after the 1st dose, only with mild accumulation after repeated doses.

After the IM administration in steady state conditions, maximum cefepime plasma concentrations around 68 micrograms/ml were obtained in average in 0.75 hours. The bioavailability was in average 82% after intramuscular administration.

The cefepime concentrations in cerebrospinal fluid (CSF) in relation to plasma are the following:

Table 3: Average concentrations in plasma and in CSF in children*

Sample collection (h)	N	Plasma concentration (micrograms/ml)	CSF concentration (micrograms/ml)	CSF/plasma relation
0.5	7	67.1 (51.2)	5.7 (7.3)	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)

* The age of the patients ranged from 3.1 month to 12 years. The patients with suspicion of CNS infection received 50 mg/kg every 8 hours, in 5 to 20 minutes infusion. The plasma and CSF were collected in the times determined in relation to the end of the infusion on the 2nd or 3rd day of treatment.

Other: clinical improvement was seen with cefepime in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. Pharmacokinetics of cefepime did not change in patients with hepatic function impairment which received a single dose of 1 g and in patients with cystic fibrosis. No dose adjustment of cefepime is required in this population.

5.3 Preclinical safety data

No long term studies were performed in the animal to assess the carcinogenic potential. In *in vitro* and *in vivo* genotoxicity tests, cefepime did not show to be genotoxic. In the rat no decreased fertility was seen.

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 room temperature (15 - 30 °C), protect from light.

6.5 Nature and contents of container

One labelled 20R tubular clear glass vial containing powder; closed with rubber stopper and sealed with aluminum 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 may be 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: 04566/06846/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First authorization in Ethiopia: 25/02/2015

Date of latest renewal in Ethiopia: 24-07-2021

10. DATE OF REVISION OF THE TEXT

August 2023