SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCTS

ROXIPIME 2 g Powder for Solution for IV Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each vial contains cefepime hydrochloride equivalent to 2 g cefepime as powder.

Excipients:

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Sterile Powder for injection.

Light yellow -white coloured powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROXIPIME is used in the treatment of the following infections mentioned, if the causative organism is susceptible.

- Severe pneumonia;
- Empirical treatment in febrile neutropenia; in patients at high risk for severe infections (for example, patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients
- Treatment for complicated and uncomplicated Urinary Tract Infections, including pyelonephritis,
- It is used for intra-abdominal infections treatment.

Culture and susceptibility tests should be performed to determine susceptibility of infection factor organism against cefepime. Empirical treatment with ROXIPIME can be started without

waiting results of susceptibility tests and it should be regulated according to antibiotic treatment result when results of these tests are determined.

In patient with aerobic-anaerobic mix infection risk, if there is especially bacteria which is insusceptible to cefepime, in initial of treatment, anaerobic drug addition to treatment is recommended until determining effective microorganism. When the results are appeared, it is decided whether ROXIPIME may be administered as in combination with other anti-infective agents according to sensitivity profile.

4.2. Posology and method of administration

Posology/Frequency of administration and duration:

Adults and children over 40 kg

In adults with normal renal function and in children over 40 kg body weight, ROXIPIME dose administration scheme is shown in Table 1.

TABLE 1

Recommended Dosage Schedule for Adults with normal renal function and children over 40 kg (12 years and older) *

The severity of infection	**Dose and route of administration**	**Dose range**
Severe infections	2 g IV	q12h
Very severe and life-threatening infections	2 g IV	q8h

*Normal treatment duration is 7-10 days. For more severe infections, longer duration treatment may be required. Empirical treatment duration of febrile neutropenia is 7 days or continue until neutropenia disappears.

It is used in children 12 years old and over

For pediatric patients with body weight more than 40kg, adult recommendation doses in the table above may be administered (*see; Table 1)*. Child doses should be administered in patients who are older than age of 12 and have less than 40 kg of body weight. Dose in child patients should not pass over recommended maximum dose of adults (2 g in 8 hourly). Limited experiences are available regarding intramuscular administration in child patient.

Method of Administration:

ROXIPIME is administered intravenously (See section 6.6). The dosage and route of administration vary according to the susceptibility degree of infection effective organisms, the severity of the injection, and the condition and renal function of the patient.

Information regarding specific populations:

Renal Impairment:

In patients with renal insufficiency, the dose of Cefepime should be adjusted to compensate the slower rate of renal elimination. The recommended initial dose of Cefepime in patients with mild to moderate renal insufficiency should be the same as in patients with normal renal function.

The recommended maintenance dose according to creatinine clearance in adult patients with renal insufficiency is presented in Table 2.

If only serum creatinine values are available Creatinine clearance can be determined by the following formula (Cockcroft and Gault equation).

$$\text{In Males: Creatinine Clearance (mL /min)} = \frac{\text{Weight (kg)} \times (140\text{-age})}{72 \times \text{serum creatinine (mg/dl)}}$$

Females: 0.85 × above value

TABLE 2

Maintenance dosing schedule in adult patients with renal insufficiency *

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule	
	Very serious or life-threatening infections	Severe infections
>50	2 g every 8 hours	2 g every 12 hours
30 - 50	2 g every 12 hours	2 g every 24 hours
11 - 29	2 g every 24 hours	1 g every 24 hours
≤10	1 g every 24 hours	500 mg every 24 hours
Hemodialysis*	500 mg every 24 hours	500 mg every 24 hours
*Pharmacokinetic modeling shows that reduced dosage is necessary for these patients. Dosage on hemodialysis patients taken cefepime should be as follows: First day of cefepime treatment, 1g loading dose and following this 500 mg /day for all infections. On dialysis days, Cefepime should be administered following dialysis.		

Dialysis Patients: In patients undergoing hemodialysis, approximately 68% of the cefepime present in the body at the start of dialysis is removed during 3-hour dialysis period. In patients performed ambulatory peritoneal dialysis, cefepime may be administered at the same doses recommended for patients with normal renal function, (i.e., 250 mg, 500 mg, 1 g or 2 g depending on the severity of the infection at every 48 hours).

Children with Renal Impairment: Since urinary excretion is the primary route of elimination of cefepime in pediatric patients (see; section 5.2), an adjustment of the dosage of ROXIPIME is necessary in this population. If only serum creatinine is available, creatinine clearance may be estimated using either of the following methods:

Creatinine clearance (mL/min./1.73 m^2) = 0.55 × height (cm) / serum creatinine (mg/dl) or

Creatinine clearance (ml/min./1.73 m^2) = 0.52 × height (cm) / serum creatinine (mg/dl) – 3.6

Hepatic Impairment: Dosage adjustments is not required in hepatic impairment.

Pediatric population: For detailed information, please see section regarding children in '' Posology/ frequency of administration and duration" section.

Geriatric population: In clinical studies, in case of not existing renal impairment, in elderly patients taken the usual recommended adult dose, it is recorded that clinical efficacy and safety of ROXIPIME are not different from adults (See, Section 4.4).

4.3. Contraindications

It is contraindicated in patients allergic to Cephalosporin group of antibiotics, penicillins and beta-lactam antibiotics or any of the excipients.

4.4 Special warnings and precautions for use

In patients decreasing in urinary excretion due to renal failure (creatinine clearance ≤ 50 mL / min) or in patients with other diseases suppressing renal function, dose of ROXIPIME should be adjusted to compensate the slower rate of renal elimination. Because high and prolonged antibiotic concentrations may occur from usual dosages in patients with renal impairment or other conditions that may compromise renal function, the maintenance dosage should be reduced when Cefepime is administered to patients. Maintenance dosage should be determined according to degree of renal impairment, severity of infection, and susceptibility of the causative organism *(see, section 4.2).* In safety research after drug is presented to use, back-reflexive encephalopathy (loss of consciousness including confusion, hallucinations, stupor and coma), myoclonus, seizures (including non-convulsive epileptic state), and / or renal impairment has been recorded *(see, section 4.8).* Many of these cases occurred in patients with renal impairment and who are taken doses of ROXIPIME that exceeded the recommended dosages. In general, symptoms of neurotoxicity disappears after discontinuation of cefepime and/or after hemodialysis but some cases have been fatal.

In patients (adult and pediatric) at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying haematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
Cefepime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. If neutropenia occurs as a result of prolonged therapy, cefepime should be discontinued and alternative antibiotic therapy used.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ROXIPIME, and may range in severity from mild diarrhea to fatal colitis. Because up to two months after the use of antibacterial agents, diarrhea related with *C. difficile* has been reported, conscious drug use is needed in this duration. If CDAD is diagnosed or this diagnosis is suspected, continuing and not directed against *C. difficile* antibiotic use may need to be discontinued.

Renal function should be monitored carefully if drugs with a nephrotoxic potential such as aminoglycosides and potent diuretics are administered with ROXIPIME.

Particularly in patients showing allergic reaction to drugs, antibiotics should be administered carefully. If an allergic reaction occurs in administration of ROXIPIME, drug should be discontinued immediately and the necessary treatment should be administered to the patient. If serious hypersensitivity reactions are seen, epinephrine or other supporting treatment may be required.

As with other antibiotics, ROXIPIME may lead to overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Use in the elderly: In clinical studies, 16% of more than 6400 adults treated with cefepime were 75 years old and older and 35% of them are 65 years and older. In clinical studies, in

elderly patients received the usual recommended adult dose, in case of not have renal impairment, clinical efficacy and safety of cefepime is reported not to be different from adults. Compared to younger patients, a little prolongation in the elimination half-life and decrease in renal clearance values are observed. Dose adjustment in elderly patients with reduced renal function is recommended. *(See;Section 4.2).*

Cefepime is known to be substantially excreted by the kidney, and the risk of toxic reactions of this drug may be greater in patients with impaired renal function.

In patients with creatinine clearance less than 60 mL/min, dose of cefepime should be decreased absolutely.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal functions should be monitored *(See, Section 4.4 and 4.8 and 5.2).*

Back-reflexive encephalopathy (loss of consciousness including confusion, hallucinations, stupor), myoclonus, seizures (including non-convulsive epileptic state), and / or renal impairment have occurred with normal doses of Cefepime in elderly patients with renal insufficiency (See, Section 4.4 and 4.8).

If the findings of non-compulsive status epileticus (mental status change, confusion and reaction- including extension of time of response) or seizure are occurred, it should be evaluated that stopping cefepime or dose adjustment should be done.

4.5. Interaction with other medicinal products and other forms of interaction

Solutions of ROXIPIME like many beta-lactam antibiotics should not be mixed to metronidazole, vancomycin, gentamicin, tobramycin sulfate and netilmicin sulfate solution due to potential interaction. Because physical or chemical instability are possible. However, if concurrent therapy with ROXIPIME is necessary, these antibiotics should be administered separately.

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with ROXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Probenecid reduces kidney tubular secretion and cause to increase elimination life of cephalosporins excreted by this way and toxicity risk. Nephrotoxicity has been reported following concomitant administration of cephalosporins with potent diuretics such as furosemide.

In patients treated with ROXIPIME, false positive glycosuria reactions may occur. False positive reactions with methods suppressing glucose oxidase have not been observed.

4.6. Pregnancy and Lactation

General Advice

Pregnancy Category: B

Women of childbearing potential / Contraception

In organogenesis period, in rats up to 1000mg/kg/day dose (1.6 times of maximum recommended daily human dose calculated on the basis mg/m^2), in mice up to 1200mg/kg/day dose (maximum recommended daily human dose calculated on the basis mg/m^2) or in rabbits up to100mg/kg/day dose (0.3 times of maximum recommended daily human dose calculated on the basis mg/m^2), administered cefepime is not teratogenic or embryocidal.

ROXIPIME may reduce the effectiveness of birth control pills and cause pregnancy.

Pregnancy period

There are no adequate clinical data for cefepime for exposure in pregnancy.

Studies on animals does not show that there are direct or indirect harmful effects regarding pregnancy / embryonal / fetal development / birth or postnatal development.

Caution should be taken when prescribing to pregnant women.

Lactation period

Cefepime is excreted by breastmilk in very low concentrations. Care should be taken while cefepime is administered to nursing women.

Reproductive ability/ Fertility

No lack of fertility was observed in rats.

4.7. Effects on ability to drive and use machines

Effects of ROXIPIME on ability to drive and use machines have not been examined.

4.8. Undesirable Effects

ROXIPIME is generally well tolerated. In clinical trials (N=5598) the most common side effects regarding to ROXIPIME were gastrointestinal symptoms and hypersensitivity reactions.

Side effects associated with ROXIPIME are as follows:

Following frequency groups are used:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders

Very common: redness, rash, urticaria

Nervous system disorders

Very common: Headache

Common: dizziness, paresthesia

Vascular disorders

Common: Vasodilation

Respiratory, thoracic disorders and mediastinal disorders

Common: Dyspnea

Gastrointestinal disorders

Very common: Nausea, vomiting, oral moniliasis, diarrhea, colitis (including pseudomembranous colitis)

Common: abdominal pain, constipation

General disorders and administration site disorders

Very common: Fever, vaginitis, erythema

Common: genital pruritus, taste disorders, tremors and non-specific moniliasis

Clinically significant events seen less frequently than 0.05% are anaphylaxis and seizures.

Local reactions such as phlebitis (2.9%) and inflammation (0.1%) at the site of I.V. infusion may occur. These reactions occurred in 5.2% of patients.

Post marketing Experience

In addition to the side effects reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide post marketing experience. However, because of the uncontrolled spontaneous reports, these side effects could not be determined whether or not it is connected to ROXIPIME.

As with other drugs in the same class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor and coma), seizures, myoclonus, and / or renal impairment

have been recorded. Many of these are occurred in patients with renal impairment and received doses of ROXIPIME that exceeded the recommended dosage.

As in other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia has been recorded.

Side effects were registered when the cephalosporin group of antibiotics is used and varying laboratory findings are as follows: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage and false positive test for urine glucose.

Effects on Laboratory Tests

Laboratory Test Abnormalities that developed during clinical trials in patients with normal baseline values were transient. Temporary laboratory test abnormalities occurred at a frequency between 1% and 2% (unless otherwise noted) are: alanine aminotransferase (3.6%), aspartate aminotransferase (2.5%), alkaline phosphatase, total bilirubin, anemia, eosinophilia, prolonged prothrombin time, partial thromboplastin time (2.8%); positive Coombs' test without hemolysis (18.7%). Transient elevations of blood urea nitrogen and/or serum creatinine and transient thrombocytopenia were observed in 0.5% to 1% of patients. Transient leukopenia and neutropenia were also seen (< 0.5%).

Additional Information regarding to Special Populations

Pediatric patients

ROXIPIME safety profile recorded in children are similar in adults.

In clinical trials, the most common recorded side effect is rash.

4.9. Overdose and Treatment

In cases of severe overdose, especially in patients with renal dysfunction, cefepime may be removed from the body by hemodialysis. The peritoneal dialysis is not helpful. Accidental overdosing has occurred when high doses were given to patients with impaired renal function.

(See, Section 4.2, 4.2 and 4.8). Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.

5.PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other beta-lactam antibiotics

ATC code: J01DE01

Mechanism of action:

Cefepime is an antibiotic with its broad spectrum that acts by inhibition of bacterial cell wall synthesis.

Microbiology:

It shows effect on Gram-positive and Gram-negative bacteria including many strains resistant to aminoglycosides or third-generation cephalosporins. Cefepime is highly resistant to hydrolysis by most beta-lactamases and has a low affinity for chromosomally-encoded beta-lactamases. It exhibits rapid penetration into Gram-negative bacterial cells.

In studies using *Escherichia coli* and *Enterobacter cloacae*, cefepime bound with highest affinity to penicillin binding proteins (PBP) 3 followed by PBP 2, then it was followed by PBPs 1a and 1b. Binding to PBP 2 occurs with significantly higher affinity than that of other parenteral cephalosporins. This may enhance its antibacterial activity. The moderate affinity of cefepime for PBPs 1a and 1b probably also contribute to its overall bactericidal activity.

Cefepime has been shown to be bactericidal by time-kill analysis (killing-curves) and by determination of minimum bactericidal concentrations (MBC) for a wide variety of bacteria. The cefepime MBC/MIC ratio was ≤ 2 for more than 80% of isolates of all Gram-positive and Gram-negative species tested. Synergy with aminoglycosides has been demonstrated *in vitro*, primarily with *Pseudomonas aeruginosa* isolates.

Cefepime has been shown to be active against most strains of the following microorganisms:

Gram-Positive Aerobes:

Staphylococcus aureus (including beta-lactamase producing strains), *Staphylococcus epidermidis* (including beta-lactamase producing strains) and other staphycoccus including *S. hominis and S. Saprophyticus*

Streptococcus pyogenes (A class staphycoccus),

Streptococcus agalactiae (B class staphycoccus),

*Streptococcus pneumoniae (*including moderately penicillin resistant strains, between MIC 0.1 and 1 mg/ml),

Other beta-hemolytic streptococcus (group C, F, G),

S.bovis (group D)

Viridans streptococci.

Note: Most strains of enterococci, e.g., *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to many cephalosporins including cefepime.

Gram-Negative Aerobes:

Acinetobacter calcoaceticus (anitratus, lwoffi subspecies),

Aeromonas hydrophila,

Capnocytophage species,

Citrobacter species including *C. diversus and C. Freundü* ,

Campylobaster jejuni,

Enterobacter species including *E. cloacae, E. Areogenes, E. Sakazakü,*

Escherichia coli, Gardnerella vaginalis, Haemophilus ducreyi,

Haemophilus influenzae (including beta-lactamase producing strains)

Haemophilus parainfluenzae, Hafnia alvei,

Klebsiella species including *K. pneumoniae, K. Oxytoca, K. Ozaenae,*

Legionella species,

Morganella morganii,

Moraxella catarrhalis (Branhamella catarrhalis) (including beta-lactamase producing strains),

Neisseria gonorrhoeae (including beta-lactamase producing strains),

Neisseria meningitidis,

Pantoea agglormerans (Known as Enterobacter agglomerans),

Proteus species including *P. mirabilis, P. Vulgaris,*

Providencia species including *P.rettgeri, P. Stuartü*

Pseudomonas species including *P. aeruginosa, P. putida, P. stutzeri*

Salmonella species

Serratia species including *S. marcescens, S. Liquefaciense,*

Shigella species,

Yersinia enterocolitica.

Note: Cefepime is inactive against many strains of *Xanthomonas maltophilia (Pseudomonas maltophilia).*

Anaerobes:

Bacteroides species,

Clostridium perfringens, Fusobacterium species,

Mobiluncus species, *Peptostreptococcus* species, *Veillonella* species and

Prevotella melaninogenica known as Bacteroides melaninogenicus

Note: Cefepime is inactive against *Bacteroides fragilis* and *Clostridium difficile*. Synergy with Aminoglycoside antibiotics has been demonstrated.

5.2. Pharmacokinetics properties

General Properties

Cefepime that is active substance of ROXIPIME is a broad spectrum cephalosporin antibiotic.

Adults

Absorption:

The average plasma concentrations of Cefepime observed in normal male adults at various times following single 30-minutes infusions (IV) or 500 mg, 1 g, and 2 g infusions (I.M.) are summarized in Table 3.

TABLE 3

Average Plasma Concentrations of Cefepime (mcg/mL) in healthy adult male volunteers

Cefepime Dose	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr
500 mg I.V.	38.2	21.6	11.6	5.0	1.4	0.2
1 g I.V.	78.7	44.5	24.3	10.5	2.4	0.6
2 g I.V.	163.1	85.8	44.8	19.2	3.9	1.1

Distribution:

Concentrations of Cefepime achieved in specific tissues and body fluids are listed in Table 4. The ratio of binding to serum proteins is approximately 16.4% and is independent of its concentration in serum.

TABLE 4

Average Concentrations of Cefepime in Different Body Fluids (mcg/mL) or Tissues (mcg/g) in Healthy adult male volunteers

Tissue or Fluid	Dose (I.V.)	Average Time of Sampling Post-Dose (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
Sputum	2 g	4.0	7.4
Prostate	2 g	1.0	31.5
Appendix	2 g	5.7	5.2
Gallbladder	2 g	8.9	11.9

Biotransformation:

Cefepime is metabolized to N-methylpyrolidine which is rapidly converted to the N-oxide. Approximately 85% of the administered dose is excreted as unchanged in the urine; cefepime is found in urine in high concentrations. Less than 1% of the administered dose exits in urine as N-methylpyrolidine, 6.8% of it as N-oxide, and 2.5% of it as an epimer of Cefepime.

Elimination:

Average elimination half-life of cefepime in blood is 2 hours and 250 mg – 2 g. In healthy individuals, accumulation was not observed in body at 2 g intravenous solutions administered every 8 hours during 9 days. Average total body clearance is 120 mL/min. Average renal clearance of cefepime is 110 mL / min, cefepime is mainly excreted by the kidneys mainly by glomerular filtration.

Linearity/Non-linear case:

Average elimination half-life of cefepime in the blood does not show changes according to the dosage.

Characteristic Properties in Patients

Pediatric patients: Cefepime single and multiple doses pharmacokinetics have been evaluated in patients between 2.1 months to 11.2 years of age and 50 mg/kg doses administered with I.V. infusion or I.M. injection; multiple doses has been applied for at least 48 hours every 8 or 12 hours.

Following a single intravenous dose in children, total body clearance is average 3.3 mL/min/kg; average volume of distribution is 0.3 l / kg, and average elimination half-life is 1.7 hours. 60.4% of the administered dose is excreted as unchanged in the urine, renal clearance is the major route of excretion as 2.0 ml / min / kg.

Following Multiple IV doses, the mean plasma concentrations of cefepime after the first dose were similar to those at steady state, with only slight accumulation seen upon repeated dosing.

Geriatric patients: In healthy volunteers 65 years and older, AUC value of cefepime that is administered as single dose of 1 g IV, is higher and renal clearance value is lower compared to young volunteers. If renal function is suppressed, dose adjustment is recommended for elderly patients *(see, section 4.2 and 4.4)*

Hepatic impairment: The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1 g dose. The pharmacokinetics of cefepime were unaltered significantly in cystic fibrosis patients. In these patient populations, changing of ROXIPIME dosage is not necessary.

Renal impairment: The half-life in patients with varying degrees of renal impairment is prolonged, there is a linear relationship between creatinine clearance and body clearance. Therefore, dosage adjustment is recommended for patients in this group. The average half-life in patients requiring hemodialysis was 13 hours and in patients requiring continuous peritoneal dialysis was 19 hours.

Other: The pharmacokinetics of cefepime do not change to a clinically significant degree in patients with cystic fibrosis.

Clinical Studies

Febrile Neutropenic Patients: The safety and efficacy of Cefepime monotherapy of febrile neutropenic patients have been assessed in two multicenter, randomized trials comparing Cefepime monotherapy (at a dose of 2 g intravenously every 8 hours) to ceftazidime monotherapy (at a dose of 2 g intravenously every 8 hours). These studies comprised 317 evaluable patients. Table 5 describes the characteristics of the evaluable patient population.

TABLE 5

Demographic properties of Evaluable Patients

(First Episodes Only)

	Cefepime	***Ceftrazidime***
Total	164	153
Median age (yr)	56.0 (range, 18 to 82)	55.0 (range 16 to 84)
Male	86 (52%)	85 (56%)
Female	78 (48%)	68 (44%)
Leukemia	65 (40%)	52 (34%)
Other hematologic malignancies	43 (26%)	36 (24%)
Solid tumor	54 (33%)	56 (37%)
Median ANC nadir (cells/microliter)	20 (range, 0 to 500)	20.0 (range 0 to 500)
Median duration of neutropenia (days)	6 (range, 0 to 39)	6.0 (range, 0 to 32)
Indwelling venous catheter	97 (59%)	86 (56%)
Prophylactic antibiotics	62 (38%)	64 (42%)
Bone marrow graft	9 (5%)	7 (5%)
SBP less than 90 mm Hg at entry	7 (4%)	2 (1%)

ANC = absolute neutrophil count; SBP = systolic blood pressure

The clinical response rates have been given on Table 6. For all outcome measures, Cefepime was found as therapeutically equivalent to ceftazidime:

TABLE 6

Pooled Response Rates for Empiric Therapy of Febrile Neutropenic Patients

	% Response	
Result Measures	Cefepime (n=164)	Ceftazidime (n=153)
First attack was resolved with no treatment modification, no new febrile episodes or infection, and oral antibiotics were used for completion of treatment		
First attack was resolved with no treatment modification, no new febrile episodes or infection and oral antibiotics were not used after treatment.		
Survival, treatment modification was allowed.	93	97
First attack was resolved with no treatment modification and oral antibiotics were used for completion of treatment	62	67

First attack was resolved with no treatment modification and oral antibiotics were not used after treatment.	46	51

Insufficient data exist to support the efficacy of Cefepime monotherapy in patients at high risk for severe infection (patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy or with severe or prolonged neutropenia). No data are available in patients with septic shock.

5.3. Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

For evaluating the carcinogenic potential, long-term study have not been conducted in animals. *In vitro* and *in vivo* genotoxicity tests showed that cefepime is not genotoxic. No lack of fertility was observed in rats.

6.PHARMACEUTICAL PROPERTIES

6.1. List of excipients

L-arginine

Water for Injection

6.2. Incompatibilities

Solutions of ROXIPIME like many beta-lactam antibiotics should not be mixed to metronidazole, vancomycin, gentamicin, tobramycin sulfate and netilmicin sulfate solution due to potential interaction. Because of physical or chemical incompatibility are present. However, if concurrent therapy with ROXIPIME is necessary, each of these antibiotics should be administered separately.

It is recommended not to mix ROXIPIME and other drugs, when administering intravenously.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 30ºC as powder.

Store in the original package in order to protect from light.

It should be used in 24 hours below 30ºC at room temperature, in 7 days at 2-8 ºC (refrigerator) after reconstituted.

6.5 Nature and contents of container

25 ml type II transparent glass vial with gray coloured bromobutyl rubber stopper fixed with transparent aluminum / plastic flip-off cap and ampoule containing 10 ml water for injection.

In addition, 10 vials hospital packaging is also available.

6.6 Special precautions for disposal and other handling

Preparation of Solutions and Route of Administration:

ROXIPIME powder should be prepared by using diluent volumes indicated in Table 7.

TABLE 7

Preparation of Solutions of ROXIPIME

	Amount to be added for reconstitution (ml)	Approximate volume to be obtained (ml)	Approximate Cefepime Concentration (mg/ml)
Intravenous			
500 mg vial	5	5.6	100
1 g vial	10	11.3	100
2 g vial	10	12.5	160
1 g vial	50	50	20
1 g vial	100	100	10
2 g vial	50	50	40
2 g vial	100	100	20

Intravenous Administration:

The I.V. administration is preferable for patients with severe or life- threatening infections, particularly if the possibility of shock is present.

In direct IV. Administration, ROXIPIME is applied by dissolving in the amounts shown in the table above with sterile water for injection, 5% dextrose injection or 0.9% sodium chloride. It is applied directly to the vein within 3-5 minutes or it is injected to the application set in patients undergoing an appropriate IV solution infusion.

For intravenous infusion, 500 mg, 1 g and 2 g ROXIPIME vial should be prepared as indicated above, as for direct IV administration. Then, add required quantity of the solution obtained to an intravenous administration set including suitable I.V. fluid. The obtained solution should be administered over a period of approximately 30 minutes.

Compatibility and Stability

Intravenous: ROXIPIME is compatible at concentrations between 1 mg per mL and 40 mg per mL with the following intravenous infusion 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. These solutions should be used in 24 hours below 30ºC at room temperature, in 7 days (in a refrigerator) at 2- 8°C after reconstituted.

Note: Visual partıculate matter control should be performed in parenteral drugs before administration and if there is particulate matter, drug should not be used.

As with other cephalosporins, the color of ROXIPIME powder and solution can get darker; however, this does not affect the drugs potency.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MANUFACTURER

Pharma Vision San. Ve Tic. A.Ş.
Davutpaşa Caddesi No: 145
Topkapı-İSTANBUL
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11. DATE OF REVISION OF THE TEXT

14.09.2020

NOT ALL PRESENTATIONS MAY BE MARKETED.