SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE MEDICINAL PRODUCT
CLAFORAN 1 g in vials

2.QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains:

Active substance:
Cefotaxime sodium 1.048 g
(Equivalent to 1 g cefotaxime)

Excipients:
See Section 6.1 for excipients.

3.PHARMACEUTICAL FORM
Vials
White to slightly yellow powder.

4.CLINICAL PARTICULARS
4.1.Therapeutic indications
CLAFORAN is indicated in the treatment of the following serious infections caused by microorganisms that are susceptible to cefotaxime:

- **Curative treatment**

- Respiratory tract infections
- Urinary tract infections
- Genital infections
- Septicemia, bacteremia
- Endocarditis
- Abdominal infections including peritonitis
- Meningitis (except when caused by listeria) and other central nervous system infections
- Skin and soft tissue infections
- Bone and joint infections

- **Surgical prophylaxis**

- Gastrointestinal surgery
- Genitourinary surgery
- Obstetric or gynecological surgery.

4.2.Posology and method of administration
Posology/frequency and duration of administration:

– **Dosage for curative treatment**

CLAFORAN, an antibiotic administered by IM or IV route (by slow injection or infusion) and is prescribed as follows:

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- **Dosage in adults with normal renal function**

Table 1

Indication	Unit dose	Dosing interval	Method of administration	Daily dose
Uncomplicated gonorrhea	0.5 or 1 g	single dose	IM	0.5 to 1 g
Uncomplicated/moderate infections	1 to 2 g	8 or 12 hours	IM or IV	2 to 6 g
Serious infections	2 g	6 or 8 hours	IV	6 to 8 g

Where the infection is caused by strains that are not susceptible, antibiotic sensitivity tests must be carried out in order to confirm whether treatment with CLAFORAN is appropriate.

- **Dosage for surgical prophylaxis**

Normal dosage in adults

1 g of IV or IM cefotaxime is administered and repeated post-operatively, if required. The duration of this treatment must not exceed 24 hours.

Cesarean section

1 g of IV cefotaxime is administered when clamping the umbilical cord, followed by 1 g administered IV or IM, 6 and 12 hours after the first dose.

Method of administration:

IV administration (injection or infusion):

For administration as a solution for injection or infusion, dissolve cefotaxime in water for injection and use immediately.

For intermittent IV injections, the solution must be injected over a period of 3 to 5 minutes. During post-marketing surveillance, cases of potentially life-threatening arrhythmia have been reported in a very few patients who received rapid administration of cefotaxime through a central venous catheter.

IM administration

For IM administration, dissolve CLAFORAN in 1% lidocaine solution. In this case, caution must be exercised to ensure that the injection is not intravascular.

Additional information for specific populations:

Renal failure:

- **Dosage in adults with renal impairment**

Table 2

Creatinine clearance	Unit dose	Dosing interval	Daily dose
≤10 ml/min	Half the dose (see Table 1)	Same (see Table 1)	Half the dose (see Table 1)

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When creatinine clearance cannot be measured, it can be calculated based on serum creatinine levels using the following Cockcroft formula:

Men: Cl_{Cr} (ml/min) = $\frac{\text{weight (kg) x (140 – age in years)}}{\text{72 x serum creatinine (mg/dl)}}$

or

$\frac{\text{weight (kg) x (140 – age in years)}}{\text{0.814 x serum creatinine (µmol/l)}}$

Women: Cl_{Cr} (ml/min) = 0.85 x above result

Patients undergoing hemodialysis: 1 to 2 g daily, depending on the severity of the infection. On the day of hemodialysis, cefotaxime must be administered after dialysis.

Pediatric population:

- **Dosage in premature infants, newborns, infants and children with normal renal function**

Table 3

Patient	**Age or weight**	**Daily dose**	**Method of administration**	**Dosing interval**
Premature	0 to 1 week	50 to 100 mg/kg/day	IV	12 hours
Premature	1 to 4 weeks	75 to 150 mg/kg/day	IV	8 hours
Infants and children:	<50 kg	50 to 100 mg/kg/day For severe infections such as meningitis, the daily dose may be doubled	IV * or IM*	6 to 8 hours
Children	≥50 kg	adult dose		

*Do not exceed 2 g per 24 hours. The IM route with 1% lidocaine solvent must be used in children older than 30 months.

4.3.Contraindications

- Hypersensitivity to cephalosporins
- Hypersensitivity to cefotaxime or any of the ingredients of the medicinal product.

4.4.Special warnings and precautions for use

- **Superinfection**

As with other antibiotics, cefotaxime use, especially if long-term, may result in the overgrowth of non susceptible organisms. Repeated evaluation of the condition of the patient is essential. If superinfection occurs during treatment, appropriate measures should be taken.

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- **Anaphylactic reactions**

The prescription of cephalosporins necessitates preliminary enquiry into allergic diathesis, and particularly into hypersensitivity to beta-lactam antibiotics.
If a hypersensitivity reaction occurs, treatment must be discontinued.

The use of CLAFORAN is strictly contraindicated in patients with a previous history of immediate-type hypersensitivity to cephalosporins. If there is any doubt, it is essential that a doctor be present during the first administration to treat any anaphylactic reaction.

As cross allergy exists between penicillin and cephalosporins in 5% to 10% of cases, extreme caution must be exercised when penicillin-sensitive patients use cephalosporins; careful monitoring is essential for the first administration. Hypersensitivity reactions (anaphylaxis) that occur with these two types of antibiotic may be serious or even fatal (for emergency measures see "Emergency measures to take during anaphylactic shock")[1]. If a hypersensitivity reaction occurs, treatment must be discontinued.

- **Serious bullous reactions**

Serious skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime (see Section 4.8). Patients should be advised to contact their doctors before continuing treatment, if a skin and/or mucosal reaction occurs.

- ***Clostridium difficile* superinfection (e.g. pseudomembranous colitis)**

Severe and/or persistent diarrhea occurring during treatment or in the initial weeks following multiple antibiotic therapy, and especially with broad spectrum antibiotics, may be symptomatic of *Clostridium difficile* superinfection, the most severe form of which is pseudomembranous colitis. Though rarely diagnosed, this potentially fatal condition can be confirmed by endoscopy and/or histology. The best way to diagnose *Clostridium difficile* is to test for this pathogen, and more importantly for its cytotoxins, in the feces.

If a diagnosis of pseudomembranous colitis is suspected, CLAFORAN must be discontinued immediately, and appropriate antibiotic therapy (e.g. oral vancomycin or metronidazole) must be initiated without delay.

Clostridium difficile superinfection can be promoted by fecal stasis.
Medicinal products that inhibit peristalsis should not be used.

- **Hematological Reactions**

Leukopenia, neutropenia, and more rarely, agranulocytosis may develop during cefotaxime treatment, especially during long-term treatment. For treatment courses lasting longer than 7-10 days, the white blood cell count should be monitored and if neutropenia occurs, treatment should be discontinued.

Some cases of eosinophilia and thrombocytopenia, rapidly reversible after treatment discontinuation, have been reported. Cases of hemolytic anemia have also been reported (see Section 4.8).

- **Renal failure**

In patients with severe renal failure, dosage should be adjusted according to creatinine clearance. If needed, dosage can be adjusted based on serum creatinine.

[1] Translator's note: There is no such section in this document.

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- **Monitoring renal function**

Caution must be exercised if cefotaxime is administered in combination with aminoglycosides. Renal function must be monitored in these patients.

- **Sodium intake**

The sodium content of cefotaxime (48.2 mg/g cefotaxime) must be taken into account when prescribing to patients requiring sodium restriction.

- **Neurotoxicity**

High doses of beta-lactam antibiotics, including cefotaxime, may cause encephalopathy (loss of consciousness, abnormal movements and convulsions), especially in patients with renal failure (see Section 4.8). Patients should be advised to contact their doctor before continuing treatment if such reactions occur.

- **Precautions for administration**

During post-marketing surveillance, cases of potentially life-threatening arrhythmia have been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. Recommended injection or infusion durations must be followed (see Section 4.2).

- **Effects on laboratory tests**

As with other cephalosporins, a false-positive Coombs tests has been found in some patients treated with cefotaxime. This can interfere with blood cross-matching tests.
Urine glucose testing with non-specific reducing agents may yield false positive results. This is not seen when a glucose oxidase-specific method is used.

- **Neutropenia**

In treatments of more than 10 days' duration, the white blood cell count must be monitored, and if neutropenia occurs CLAFORAN treatment must be discontinued.

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

Aminoglycoside antibiotics and diuretics:
When using high doses of cephalosporins in patients treated with aminoglycoside antibiotics or potent diuretics such as furosemide, caution should be exercised against the possible side effects of these combinations on renal function. However, no increase in nephrotoxicity is expected at the recommended doses.

Probenecid prolongs the excretion of cephalosporins from renal tubules and causes an increase in plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of drugs known for their nephrotoxicity.

A false-positive Coombs tests may be seen during treatment with cephalosporins. This may occur during treatment with cefotaxime as well, and can interfere with blood cross-matching.

Urine glucose testing may yield false positive results with copper reduction methods (such as Benedict's, Fehling's or Clinitest) but not when using a specific glucose oxidase method.

Additional information for specific populations

No data are available.

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4.6. Pregnancy and lactation
General advice
Pregnancy category: B

Women of childbearing potential / Birth control (Contraception)
In women of childbearing potential the decision to use the medicinal product must be made by weighing the anticipated benefits against the potential risks. There are no data available concerning interference with birth control methods.

Pregnancy
Cefotaxime crosses the placental barrier.
Studies in a few animal species have shown no teratogenic or fetotoxic effects.
No clinical data are available regarding exposure to cefotaxime during pregnancy.
Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonic development, fetal development, parturition or postnatal development.
Nonetheless, the safety of cefotaxime has not been established in human pregnancy and the drug should not therefore be used during pregnancy.

Lactation
Cefotaxime passes into human breast milk, therefore patients should discontinue either breast-feeding or CLAFORAN treatment.

Reproduction / Fertility
Reproductive toxicity studies in mice, rats and rabbits have not shown any developmental or teratogenic effects. Fertility, prenatal and postnatal development were not affected (see Section 5.3).

4.7. Effects on ability to drive and use machines
Cefotaxime may cause dizziness and may affect the ability to drive or operate machinery.

4.8. Undesirable effects
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare < 1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon:
Eosinophilia and decreased platelet counts (thrombocytopenia) which were reversible after treatment discontinuation were reported.

Not known:
As with other beta-lactam antibiotics, neutropenia, and more rarely, agranulocytosis may develop during treatment, particularly if given over long periods.
Hemolytic anemia, and, after discontinuation of treatment, reversible neutropenia have been reported.
For treatment courses lasting longer than 10 days, blood counts must absolutely be monitored.

Immune system disorders
Uncommon:
Jarisch-Herxheimer reaction

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As reported with other antibiotics, Jarisch-Herxheimer reaction may develop in the first days of borreliosis treatment.
One or more of the following symptoms have been reported after several weeks of borreliosis treatment: Skin rash, itching, fever, leukopenia, increase in liver enzymes, difficulty breathing, joint discomfort. To a certain degree, these symptoms are consistent with those of the disease for which the patient is being treated.

Not known:
Hypersensitivity reactions have been reported. These include skin rash, itching, less frequently urticaria, elevated body temperature, and rarely anaphylaxis (angioedema possibly resulting in anaphylactic shock or bronchospasm) (see Section 4.4).

Nervous system disorders
Uncommon:
Convulsions

Not known:
Headache, dizziness
Administration of high doses of beta-lactam antibiotics including cefotaxime may cause encephalopathy, especially in patients with renal failure. (e.g. impaired consciousness, abnormal movements and convulsions).

Cardiac disorders
Not known:
Cases of potentially life-threatening arrhythmia have been reported in a very small number of patients who received rapid bolus injections of cefotaxime through a central venous catheter.

Respiratory, thoracic and mediastinal disorders
Not known:
Bronchospasm

Gastrointestinal disorders
Uncommon:
Diarrhea

Not known:
Nausea, vomiting, and abdominal pain may develop.
As with all other broad spectrum antibiotics, diarrhea, which may be accompanied by bloody stools, may be a symptom of enterocolitis. Pseudomembranous colitis is a particular form of enterocolitis which can develop due to antibiotics (in most cases due to *Clostridium difficile*) (see Section 4.4).
Hepatobiliary disorders
Uncommon:
Increase in liver enzymes (ALT, AST, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin levels. These laboratory abnormalities, which can also be explained by infection, rarely exceed twice the upper limits of the normal range, and generally lead to cholestatic, and most often asymptomatic liver disease.

Not known:
Hepatitis (sometimes with jaundice) has been reported.

Skin and subcutaneous tissue disorders
Uncommon:
Rash, pruritus, and less frequently urticaria.

Not known:
As with other cephalosporins, some cases of bullous eruption (erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity reactions have been reported.

Renal and urinary disorders
Uncommon:
Decreased renal function (increased creatinine) has been observed with cephalosporins including cefotaxime, particularly when used in combination with aminoglycosides.
Not known:
As with some other cephalosporins, interstitial nephritis may develop in patients treated with cefotaxime.

Reproductive system and breast disorders
Vaginal candidiasis

General disorders and administration site conditions
Very common:
Pain at the injection site (IM administration)

Uncommon:
Fever
Inflammation at the injection site
Phlebitis/thrombophlebitis was reported in a few patients who were administered cefotaxime intravenously. However, this rarely led to the discontinuation of treatment.

Not known:
Superinfection: As with other antibiotics, cefotaxime administration, especially long-term, may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during treatment, appropriate measures should be taken.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Turkey Pharmacovigilance Centre (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9. Overdose
Serum levels of cefotaxime may be reduced by peritoneal dialysis or hemodialysis. In the event of overdose, there is a risk of reversible encephalopathy, especially in patients with renal failure. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials
ATC code: J01DD01

Cefotaxime is a 2-aminothiazole cephalosporin antibiotic for parenteral use. It acts by inhibiting bacterial cell wall synthesis. It is stable against most beta-lactamases.

The microorganisms listed below are generally susceptible to cefotaxime:
Aeromonas hydrophila, Bacillus subtilis, Bordetella pertussis, Borrelia burgdorferi, Moraxella (Branhamella) catarrhalis, Citrobacter diversus, Citrobacter freundii*, Clostridium perfringens, Corynebacterium diptheriae, E.coli, Enterobacter* spp**, Erysipelothrix insidiosa, Eubacterium, Klebsiella pneumoniae,* including strains which do and do not produce Haemophilus ampicillin-resistant penicillinase, *Klebsiella oxytoca, Morganella morganii,* including strains which do and do not produce *methicillin-sensitive* Staphylococcal penicillinase, *Neisseria meningitidis,* including strains which do and do not produce Neisseria gonorrhoeae penicillinase, *Propionibacterium, Proteus mirabilis, vulgaris, Providencia, Streptococcus pneumoniae, Salmonella* spp, *Serratia* spp**, Shigella, Streptococci, Veillonella, Yersinia**

* The susceptibility to cefotaxime depends on the epidemiology and the level of resistance in the country concerned.

The microorganisms listed below are cefotaxime-resistant:
Acinetobacter baumanii, Bacteroides fragilis, Clostridium difficile Enterococcus, Gram-negative anaerobes, *Listeria monocytogenes,* methicillin-resistant *staphylococci, Pseudomonas aeruginosa, Pseudomonas cepacia, Stenotrophomonas maltophilia .*

5.2. Pharmacokinetic properties

Table 4
Pharmacokinetic properties in adults

	Healthy adults IV (5 minutes)	Healthy adults IM
1. Dose	1 g	1 g
2. Absorption		
Bioavailability (%)	100	90-95
3. Kinetic parameters		
T_{max} (h)		0.5
C_{max} (µg/ml)	100	20-30
Terminal half-life (h)	0.9-1.1	1.3
Volume of distribution (l/kg)	0.30	
Protein binding		
Type	Albumin	
%	25-40	
4. Metabolism		
Liver	+	
-Metabolites		
M1	Desacetylcefotaxime*	
M2	Lactamin form	
M3	Lactamin form	

5. Elimination	
Urine	90% Cefotaxime: 50% Desacetylcefotaxime: 15-25% M2 + M3 15-30%
Feces	10%

*The elimination half-life of desacetylcefotaxime in healthy subjects is around 2 hours. Its antibacterial effect is synergistic with that of cefotaxime.

Distribution:
Peak plasma concentrations of 100 µg/ml are reached 5 minutes after IV administration of 1 g cefotaxime. Peak plasma concentrations of 20 to 30 µg/ml are reached half an hour after IM administration of 1 g cefotaxime.

The elimination half-life is 1 hour (IV route) to 1-1.5 hours (IM route).

The volume of distribution is 0.31/kg.
The drug is 25-40% bound to plasma proteins, especially albumin.

Biotransformation:
Cefotaxime is metabolized in the liver.

Elimination:
About 90% of the administered dose is eliminated by the urinary route, 50% as the parent drug and about 20% as desacetylcefotaxime.

Pharmacokinetic patterns in special populations
Elderly patients: The elimination half-life of cefotaxime increases to a mean of 2.5 hours in patients over 80 years of age. The volume of distribution remains unchanged when compared with young people.

Adult patients with renal impairment:
The volume of distribution is virtually unchanged, the half life does not exceed 2.5 hours, even in end-stage renal failure.

Infants, children, newborns and premature infants:
In infants and children, the plasma levels and volume of distribution of cefotaxime are similar to those observed in adults receiving the same dose in mg/kg. The half-life ranges from 0.75 to 1.5 hours.

In newborns and premature infants, the volume of distribution is similar to that in infants and children. The average half-life ranges from 1.4 to 6.4 hours.

5.3 Preclinical safety data
Acute toxicity:
In animal studies, the acute toxicity of cefotaxime was low, with LD_{50} values approximately 10 g/kg following intravenous administration to mice and rats. Toxicity was even lower in these species when cefotaxime was administered intraperitoneally, subcutaneously or intramuscularly. The LD_{50} of cefotaxime in dogs was higher than 1.5g/kg.
Subacute toxicity studies were carried out in rats and dogs using doses of up to 300 mg/kg/day SC in rats for 13 weeks and of 1500 mg/kg/day IV in dogs.

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Chronic toxicity:
In chronic toxicity studies conducted over 6 months, doses of 250 mg/kg/day of cefotaxime were administered subcutaneously in rats and intravenously[2] in dogs. Toxicity was minimal in these studies. Cecal dilatation was observed in the small intestine of rats, and signs of mild renal toxicity were seen at high doses. These results demonstrate low cefotaxime toxicity.

Teratogenicity:
No evidence of developmental toxicity or teratogenicity was seen in reproductive toxicity studies in mice, rats and rabbits. Cefotaxime did not impair fertility, prenatal or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injection.

6.2. Incompatibilities

CLAFORAN must not be mixed with other antibiotics in the same syringe or infusion solutions. This applies to all antibiotics including aminoglycosides.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature, below 25°C, in the original packaging. Protect from light.

Solution prepared for injection or infusion with water for injection:

After reconstitution of cefotaxime sterile powder using water for injection, store under the following conditions:

- up to 12 hours at room temperature (not exceeding +25°C/in normal light)

- up to 24 hours in a refrigerator (+2°C to 8°C/protected from light)

If the solution is pale yellowish in color this does not mean that it is less effective as an antibiotic.

6.5. Nature and contents of container

One vial containing 1 g cefotaxime and one ampoule containing 4 ml of distilled water as solvent.
Cefotaxime is supplied in (clear glass) vials fitted with a metal cap and closed with a rubber stopper, packed in boxes.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the "Control of Medical Waste Regulations" and the "Control of Packaging and Packaging Waste Regulations".

[2] Translator's note : Should read « intramuscularly in dogs ».

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7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

197/79

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: August 10, 2001
Renewal of the authorization:

10. DATE OF REVISION OF THE TEXT

October 27, 2015.