CLAFORAN DATA SHEET

1. TRADE NAME OF THE MEDICINAL PRODUCT

Claforan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Claforan 1.0 g vial contains 1.048 g cefotaxime sodium, equivalent to 1 g cefotaxime.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder with solvent for solution for injection or infusion.

White to yellowish-white powder and colourless solution as solvent.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Properties: Claforan is a broad-spectrum bactericidal cephalosporin antibiotic. Claforan is exceptionally active *in vitro* against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive organisms.

Indication: Claforan is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity.

Septicaemias

Respiratory Tract Infections such as acute and chronic bronchitis, bacterial pneumonia, infected bronchiectasis, lung abscess and post-operative chest infections.

Urinary Tract Infections such as acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria.

Soft-Tissue Infections such as cellulitis, peritonitis and wound infections.

Bone and Joint Infections such as osteomyelitis, septic arthritis.

Obstetric and Gynaecological Infections such as pelvic inflammatory disease.

Gonorrhoea particularly when penicillin has failed or is unsuitable.

Other Bacterial Infections such as meningitis and endocarditis.

PROPHYLAXIS:

Prophylaxis of infections in patients with reduced resistance.

Pre-operative prophylaxis in patients who are at increased risk from infection.

The administration of Claforan prophylactically may reduce the incidence of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated or in clean operations where infection would have serious effects.

Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. Claforan should therefore be administered immediately prior to surgery and if necessary continued in the immediate post-operative period.

Administration should usually be stopped within 24 hours since continuing use of any antibiotic in the majority of surgical procedures does not reduce the incidence of subsequent infection.

BACTERIOLOGY:

The following organisms have shown *in vitro* sensitivity to Claforan.

***GRAM-POSITIVE*:**

Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains.

Beta-haemolytic and other streptococci such as *Streptococcus mitis* (*viridans*) (many strains of enterococci, e.g., *Streptococcus faecalis*, are relatively resistant).

Streptococcus (*Diplococcus*) *pneumoniae*.

Clostridium spp.

***GRAM-NEGATIVE*:**

Escherichia coli.

Haemophilus influenzae including ampicillin-resistant strains.

Klebsiella spp.

Proteus spp. (both indole positive and indole negative).

Enterobacter spp.

Neisseria spp. (including β-lactamase producing strains of *N. gonorrhoea*).

Salmonella spp. (including *S. typhi*).

Shigella spp.

Providencia spp.

Serratia spp.

Citrobacter spp.

Claforan has frequently exhibited useful *in vitro* activity against *Pseudomonas* and *Bacteroides* species although some strains of *Bacteroides fragilis* are resistant.

There is *in vitro* evidence of synergy between Claforan and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of *Pseudomonas*. No *in vitro* antagonism has been noted. In severe infections caused by *Pseudomonas* spp. the addition of an aminoglycoside antibiotic may be indicated.

4.2 Posology and Method of Administration

DOSAGE:

Claforan may be administered intravenously, by bolus injection, by infusion or intramuscularly. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

***Adults*:** The recommended dosage for mild to moderate infections is 1 g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

In severe infections dosage may be increased up to 12 g daily given in 3 or 4 divided doses. For infections caused by sensitive *Pseudomonas* spp. daily doses of greater than 6 g will usually be required.

***Children*:** The usual dosage range is 100-150 mg/kg/day in 2 to 4 divided doses. However, in very severe infections doses of up to 200 mg/kg/day may be required.

***Neonates*:** The recommended dosage is 50 mg/kg/day in 2 to 4 divided doses. In severe infections 150-200 mg/kg/day, in divided doses, have been given.

***Dosage in Gonorrhoea*:** A single injection of 1 g may be administered intramuscularly or intravenously.

***Dosage in Renal Impairment*:** Because of extra-renal elimination, it is only necessary to reduce the dosage of Claforan in severe renal failure (GFR <5 ml/min = serum creatinine approximately 751 micromol/l). After an initial loading dose of 1 g, daily dose should be halved without change in the frequency of dosing, i.e., 1 g in 12 hourly becomes 0.5 g 12 hourly, 1 g 8 hourly becomes 0.5 g 8 hourly, 2 g 8 hourly becomes 1 g 8 hourly, etc. As in all other patients, dosage may require further adjustment according to the course of the infection and the general condition of the patient.

ADMINISTRATION:

***Intravenous Administration*:**

For Intravenous injection Claforan 1.0 g should be dissolved in at least 4 ml Water for Injections.

Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

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

***Intravenous infusion*:** Claforan may be administered by intravenous infusion. 1-2 g are dissolved in 40-100 ml of Water for Injections Ph. Eur. or in the infusion fluids listed under "Pharmaceutical Particulars". The prepared infusion may be administered over 20-60 minutes. To produce an infusion using vials with an infusion connector, remove the safety cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solvent into the vial. Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

***Intramuscular Administration*:**

For intramascular injection Claforan 1.0 g should be dissolved in 4 ml Water for Injections and then administered by deep intragluteal injection. Pain on I.M. injection can be avoided by dissolving Claforan 1.0 g in 4 ml lidocaine solution 1%. An intravascular injection should be avoided because lidocaine can cause restlessness, tachycardia, conduction disturbances, vomiting and convulsions following intravascular administration. (See 4.3 contraindications)

It is advisable not to inject a volume greater than 4 ml on one side. If the daily dose exceeds 2 g, or more than two daily injections are required, the dose should be administered intravenously.

4.3 Contraindications

- Due to the risk of anaphylactic shock Claforan is contraindicated in patients with known hypersensitivity reactions of immediate type or severe hypersensitivity to cefotaxime or other cephalosporins or anaphylaxis to penicillins or other beta-lactam antibiotics.
- Claforan constituted with lidocaine must never be used:
  - by the intravenous route
  - in infants aged less than 30 months of age
  - in subjects with a known history of hypersensitivity to lidocaine or other local anesthetics of the amide type
  - in patients who have non-paced heart block
  - in patients with severe heart failure

4.4 Special Warnings and Special Precautions for Use

• Anaphylactic reactions

During cefotaxime therapy, severe acute (and even fatal) hypersensitivity reactions may occur (e.g., angioedema, bronchospasm, anaphylaxis and even shock) (see sections 4.3 and 4.8). In these cases, cefotaxime must be discontinued and appropriate treatment initiated (e.g., shock therapy).

Particular precaution for use of Claforan is required in patients with any hypersensitivity to penicillin and other beta-lactam antibiotics as a parallel allergy may exist (for contraindications in patients with known hypersensitivity reactions, see section 4.3).

Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

In patients with allergic reactivity of any other kind (e.g., with hay fever or bronchial asthma), Claforan should likewise be used with particular caution, as there is an increased risk of serious hypersensitivity reactions in these cases.

• Severe bullous reactions

Severe bullous skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, have been reported with Claforan therapy (see section 4.8). Patients should be urged to consult a doctor immediately if mucocutaneous reactions occur.

• *Clostridium difficile*-associated disease (e.g., pseudomembranous colitis)

Severe and persistent diarrhoea during or within the first few weeks of treatment may be due to *Clostridium difficile*-associated disease which, in its most severe form as pseudomembranous colitis, may have a fatal outcome. Diagnosis can be confirmed by endoscopic or histological tests. At the mere suspicion of pseudomembranous colitis, cefotaxime treatment must be discontinued immediately and appropriate treatment promptly instituted (e.g., administration of specific antibiotics/chemotherapeutic agents with clinically proven efficacy). Antiperistaltic agents must not be taken. *Clostridium difficile*-associated disease can be promoted by coprostasis.

• Haematological reactions

Leukopenia, neutropenia or, more rarely, bone marrow failure, pancytopenia or agranulocytosis may occur, especially after prolonged use. Blood count monitoring should therefore be performed in cases where treatment lasts for more than 7 to 10 days. Treatment with cefotaxime should be discontinued in case of abnormal results.

A few cases of eosinophilia and thrombocytopenia, rapidly reversible upon discontinuation of cefotaxime, have been reported, as well as cases of haemolytic anaemia (see also section 4.8).

• Neurotoxicity

Especially in patients with renal insufficiency, encephalopathy may occur after high doses of beta-lactam antibiotics, including cefotaxime, which may lead to conditions such as clouded consciousness, movement disorders and seizures (see section 4.8). Patients should be urged to consult a doctor immediately at the onset of such reactions. If seizures occur, the usual emergency measures are indicated and treatment with Claforan may, upon consideration of the benefits and risks, have to be discontinued.

• Patients with renal insufficiency

For patients with severely impaired renal function (glomerular filtration rate below 10 ml/min), the dose should be adjusted to creatinine clearance (see section 4.2). Renal function must be monitored if nephrotoxic medications (e.g., aminoglycosides) are co-administered (see also section 4.5). Monitoring of renal function is also indicated in elderly patients and in those with pre-existing impairment of renal function.

• Precautions for use

In individual patients, potentially life-threatening cardiac arrhythmias have been reported to occur after rapid injection of Claforan via a central venous catheter (CVC). The recommended rate of injection must therefore be respected (see section 4.2).

• Monitoring

As with any use of antibiotics, administration of Claforan (especially over long periods of treatment) can lead to a proliferation of pathogens which are insensitive to the medication being used. Vigilance is required for signs of a possible secondary infection with such pathogens. Secondary infections are to be treated accordingly.

As with other beta-lactam antibiotics, granulocytopenia and, more rarely, agranulocytosis may develop during treatment with Claforan, particularly if given over long periods. For courses of treatment lasting longer than 10 days, blood counts should therefore be monitored.

Claforan is not suitable for the treatment of syphilis.

There is insufficient clinical experience with infections caused by *Salmonella typhi*, paratyphi A and paratyphi B.

• Effect on laboratory diagnostic tests

As with other cephalosporins, the Coombs' test may prove positive in some patients during cefotaxime treatment. This can also affect cross matching.

Urinary glucose tests using non-specific reducing agents may yield false-positive results. This phenomenon does not occur with tests based on glucose oxidase.

• Sodium uptake

1 bottle of Claforan 1.0 g contains about 2.1 mmol (48 mg) sodium. To be taken into consideration by patients on a controlled sodium (low-sodium/low-salt) diet.

• Formulation containing lidocaine

See 4.3 Contraindications.

• Speed of I.V. Injection

See section 4.2 Posology and Method of Administration.

• Neutropenia

For treatment courses lasting longer than 10 days, the white blood cell count should be monitored and treatment stopped in the event of neutropenia.

• Other

Claforan, like other parenteral anti-infective drugs, may be locally irritating to tissues. In most cases, perivascular extravasation of Claforan responds to changing of the infusion site. In rare instances, extensive perivascular extravasation of Claforan may result in tissue damage and require surgical treatment. To minimize the potential for tissue inflammation, infusion sites should be monitored regularly and changed when appropriate.

4.5 Interactions with Other Medicines and Other Forms of Interaction

Other antibiotics

Cefotaxime should not be combined with bacteriostatic agents (e.g., tetracyclines, erythromycin, chloramphenicol or sulphonamide), as, in terms of *in vitro* antibacterial activity, an antagonist effect has been observed. A synergistic effect may occur when combined with aminoglycosides.

Probenecid

Concomitant administration of probenecid causes higher, longer-lasting serum cefotaxime concentrations, due to inhibition of renal excretion.

Potentially nephrotoxic medications and loop diuretics

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs, such as furosemide, aminoglycosides and NSAIDs.

Renal function should be monitored when combined with potentially nephrotoxic medications (e.g., aminoglycoside antibiotics, polymyxin B and colistin) or loop diuretics, as the nephrotoxicity of these substances may be enhanced.

4.6 Pregnancy and Lactation

Pregnancy

The safe use of cefotaxime during pregnancy has not been demonstrated. Animal studies have shown no reproductive toxicity. However, there are no adequate controlled studies in pregnant women.

Cefotaxime crosses the placenta. Hence, cefotaxime should not be used during pregnancy unless absolutely necessary.

Breastfeeding

Cefotaxime is excreted into human milk.

In nursing infants, use of Claforan during lactation can lead to interference with the physiological intestinal flora, diarrhoea, colonisation by yeast-like fungi and possible sensitisation. A decision must be made as to whether to discontinue breastfeeding or to abstain from Claforan therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on Ability to Drive and Use Machines

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired.

Very rarely (<1/10,000), cases of encephalopathy (e.g., with clouded consciousness, seizures [tonic/clonic] and movement disorders) have been reported with the use of high doses and particularly in patients with concurrent renal dysfunction. Moreover, vertigo may occur. Under these circumstances, patients should refrain from driving or using machines (see also section 4.4).

4.8 Undesirable Effects

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known (cannot be estimated from the available data)*
Infections and infestations			Superinfections (see section 4.4), e.g., oral or vaginal candidiasis	
Blood and lymphatic system disorders			Granulocytopenia, leukocytopenia, leukopenia, eosinophilia, thrombocytopenia	Bone marrow failure, pancytopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction**	Anaphylactic reactions, angioedema, bronchospasm, malaise possibly culminating in shock, anaphylactic shock
Nervous system disorders			Seizures (see section 4.4)	Headache, dizziness, encephalopathy (e.g., clouded consciousness, central nervous excitation, myoclonus, movement disorders) (see section 4.4)
Cardiac disorders				Tachycardia, arrhythmias following rapid bolus administration via a CVC

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known (cannot be estimated from the available data)*
Gastrointestinal disorders			Diarrhoea, anorexia, nausea, vomiting, abdominal pain	Enterocolitis (also haemorrhagic), pseudomembranous colitis (see section 4.4), candidiasis
Hepatobiliary disorders			Elevation of liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/ or bilirubin***	Hepatitis* (possibly with jaundice)
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria		Bullous eruptions (Erythema multiforme), Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4), acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Joint-related complaints (e.g., swelling)		
Renal and urinary disorders		Impairment of renal function/ elevation of creatinine and urea (especially on co-medication with aminoglycosides)	Interstitial nephritis	Acute renal failure (see section 4.4)
General disorders and administration site conditions	Pain at the injection site; I.M. administration: induration	Fever, inflammatory reactions at the administration site, including phlebitis/ thrombophlebitis		Rapid I.V. injection: hot flushes and vomiting

* Post-marketing experience

** During treatment of spirochetal infections (e.g., borreliosis), a Jarisch-Herxheimer reaction may develop, with fever, chills, headache and joint-related complaints.
After several weeks of borreliosis treatment, one or more of the following symptoms has been reported to occur: skin rash, pruritus, fever, leukopenia, liver enzyme elevations, respiratory complaints, joint-related complaints. To some extent, these phenomena are consistent with the symptoms of the underlying disease of the treated patient.

*** Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been reported. These laboratory abnormalities, which may also be explained by the infection, may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Superinfection:

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

For I.M. formulations: if the solvent contains lidocaine, systemic reactions to lidocaine may occur, especially in the event of inadvertent intravenous injection or injection into highly vascularized tissue or in the event of an overdose.

4.9 Overdose

In the event of an overdose, measures to accelerate elimination may be required in addition to discontinuing the medicinal product (e.g., haemodialysis or peritoneal dialysis). There is no antidote.

a) Symptoms of an overdose

Cases of intoxication in the strictest sense are unknown in humans. The symptoms largely correlate to the adverse effect profile. With certain risk constellations and administration of very high doses, reversible encephalopathy may occur, with central nervous excitation, myoclonus and seizures, as has been described for other beta-lactams. The risk for developing these adverse effects is greater in patients with severely impaired renal function, epilepsy and meningitis.

b) Emergency measures

Centrally mediated seizures can be treated with diazepam or phenobarbital, but not with phenytoin. In the event of anaphylactic reactions, the usual emergency measures are to be instituted, preferably at the first sign of shock. Otherwise, symptomatic treatment of the side effects is recommended, if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Cefotaxime is a parenteral beta-lactam antibiotic belonging to the cephalosporin group.

ATC code

J01DD01.

Mode of action

The mechanism of action of cefotaxime is based on an inhibition of bacterial cell wall synthesis (during the growth phase) through blockade of the penicillin-binding proteins (PBPs), such as transpeptidases. This results in a bactericidal effect.

Relationship between pharmacokinetics and pharmacodynamics

The efficacy depends mainly upon the length of time that the active substance level remains above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanism of resistance

Resistance to cefotaxime may be due to the following mechanisms:

- Inactivation through beta-lactamases:

Cefotaxime can be hydrolysed by certain beta-lactamases, particularly through extended-spectrum beta-lactamases (ESBLs), which occur in strains such as *Escherichia coli* or *Klebsiella pneumoniae* or through constitutively expressed beta-lactamases of the AmpC type, which have been confirmed in such strains as *Enterobacter cloacae*. In infections caused by bacteria with inducible AmpC beta-lactamase and *in vitro* susceptibility to cefotaxime, there is a risk that, during treatment, mutants with constitutive (derepressed) AmpC beta-lactamase expression may be selected.

- Reduced affinity of PBPs for cefotaxime:

Acquired resistance of pneumococci and other streptococci is due to modifications of existing PBPs as a result of mutation. However, the formation of an additional PBP with reduced affinity for cefotaxime is responsible for resistance in methicillin (oxacillin)-resistant staphylococci.

- Insufficient penetration of cefotaxime through the outer cell wall of Gram-negative bacteria can result in an insufficient inhibition of the PBPs.

Cefotaxime can be actively transported out of the cell by efflux pumps.

There is complete cross-resistance between cefotaxime and ceftriaxone and partial cross-resistance with other penicillins and cephalosporins.

Breakpoints

Testing of cefotaxime is performed with the usual dilution series. The following minimum inhibitory concentrations were determined for susceptible and resistant micro-organisms:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Pathogen	Susceptible	Resistant
Enterobacteriaceae	≤1 mg/l	>2 mg/l
Staphylococcus spp.[1)]	—[1)]	—[1)]
Streptococcus spp. (groups A, B, C, G)[2)]	—[2)]	—[2)]
Streptococcus pneumoniae	≤0.5 mg/l	>2 mg/l
Haemophilus influenzae	≤0.12 mg/l	>0.12 mg/l
Moraxella catarrhalis	≤1 mg/l	>2 mg/l
Neisseria gonorrhoeae	≤0.12 mg/l	>0.12 mg/l
Neisseria meningitidis	≤0.12 mg/l	>0.12 mg/l
Non-species-specific breakpoints*	≤1 mg/l	>2 mg/l

1) For *Staphylococcus* spp., the test result for oxacillin is used. Methicillin (oxacillin)-resistant staphylococci are considered to be resistant, regardless of the test result.

2) For *Streptococcus* spp. (group A, B, C, G) the test result for penicillin G is used.

* Mainly based on serum pharmacokinetics.

Prevalence of acquired resistance in Germany

The prevalence of acquired resistance in individual species may show local and temporal variations. Local information on the resistance situation is thus required, particularly for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of cefotaxime is questionable, expert therapeutic advice should be sought.

Particularly in cases of serious infection or unsuccessful therapy, a microbiological diagnosis with confirmation of the pathogen and its susceptibility to cefotaxime should be undertaken.

Prevalence of acquired resistance in Germany on the basis of data from the past 5 years from national resistance monitoring projects and studies (last revised December 2010):

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (methicillin-sensitive)
Streptococcus agalactiae
Streptococcus pneumoniae (including penicillin-resistant strains)
Streptococcus pyogenes
Aerobic Gram-negative micro-organisms
Borrelia burgdorferi°
Haemophilus influenzae
Moraxella catarrhalis°
Neisseria gonorrhoeae°
Neisseria meningitidis°
Proteus mirabilis%
Proteus vulgaris
Species in which acquired resistance may present a problem for use
Aerobic Gram-positive micro-organisms
Staphylococcus aureus$
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis+
Aerobic Gram-negative micro-organisms
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli%
Klebsiella oxytoca%
Klebsiella pneumoniae%
Morganella morganii
Serratia marcescens
Anaerobic micro-organisms
Bacteroides fragilis
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus spp.
Listeria monocytogenes
Staphylococcus aureus (methicillin-resistant)
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Clostridium difficile
Other micro-organisms
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.
Treponema pallidum

° At the time of publication of the table, no current data were available. Susceptibility is assumed in the primary literature, standard works and therapy recommendations.

+ In at least one region, the resistance rate is over 50%.

% Strains producing extended-spectrum beta-lactamases (ESBL) are always resistant.

$ On an out-patient basis, the resistance rate is <10%.

5.2 Pharmacokinetic properties

Cefotaxime is administered via the parenteral route. Following intravenous injection of 1 g cefotaxime, serum concentrations are approximately 81-102 mg/l after 5 minutes and 46 mg/l after 15 minutes.

8 minutes after I.V. injection of 2 g cefotaxime, serum concentrations of 167-214 mg/l were measured.

Following intramuscular administration, peak serum concentrations (approximately 20 mg/l after 1 g) are reached within 30 minutes.

Distribution

Cefotaxime has good tissue penetration, crosses the placental barrier and reaches high concentrations in foetal tissue (up to 6 mg/kg). Only a small percentage is excreted in human milk (breast milk concentrations: 0.4 mg/l after 2 g).

When the meninges are inflamed, cefotaxime and desacetylcefotaxime penetrate the subarachnoid space, where they subsequently reach therapeutically effective concentrations (e.g., in infections caused by Gram-negative bacteria and pneumococci).

The apparent volume of distribution ranges between 21-37 l. Serum protein binding is approximately 25-40%.

Metabolism

Cefotaxime is extensively metabolised in humans. Around 15-25% of a parenteral dose is excreted as O-desacetylcefotaxime. The metabolite has good antibacterial activity against a wide range of pathogens.

In addition to desacetylcefotaxime, there are two further inactive lactones. From desacetylcefotaxime, a lactone is formed as an intermediate product with a short life-cycle, which is not detectable in either the urine or plasma, as it undergoes rapid conversion into open-ring (beta-lactam ring) lactone stereoisomers. These are also excreted in the urine.

Excretion

Cefotaxime and desacetylcefotaxime are predominantly excreted via the renal route. A small percentage (approximately 2%) is excreted with the bile. In urine collected after 6 hours, 40-60% of a dose was recovered in its unchanged form and approximately 20% was recovered as desacetylcefotaxime. After I.V. administration of radioactively-labelled cefotaxime, just over 80% was recovered in the urine, of which 50-60% was unchanged parent substance and the remainder a mixture of three metabolites.

The total clearance of cefotaxime is 240-390 ml/min and renal clearance is 130-150 ml/min.

The serum half-life is between 50-80 minutes. In geriatric patients, the half-life was 120-150 minutes.

In cases of severe renal dysfunction (creatinine clearance: 3-10 ml/min), the half-life of cefotaxime may be prolonged to 2.5-10 hours.

Unlike the active and inactive metabolites, cefotaxime only accumulates to a small extent under these conditions.

Both cefotaxime and desacetylcefotaxime are largely removed from the blood by haemodialysis.

5.3 Preclinical safety data

The toxicity of Claforan is very low. Depending on the species, the LD_{50} varies after I.V. administration in animal trials. In mice and rats, it is 9-11 g/kg body weight. Following subcutaneous administration, the LD_{50} values in one-week-old mice and rats were 6.1 to 7.4 g/kg body weight and 18.7 g/kg body weight in female mice.

Mutagenic potential

In vivo studies on the bone marrow of rats and mice did not indicate a mutagenic potential for Claforan.

Reproductive toxicity

Cefotaxime crosses the placenta. Following intravenous administration of 1 g Claforan during labour, values of 14 µg/ml were measured in the umbilical cord serum within the first 90 minutes post-dose, which fell to about 2.5 µg/ml by the end of the second hour post-dose. In the amniotic fluid, peak concentrations of 6.9 µg/ml were measured after 3-4 hours; this value exceeds the MIC for most Gram-negative pathogens.

Animal studies on rats and mice did not indicate teratogenic properties for Claforan. Fertility of the exposed animals was not impaired.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for Injections as solvent.

6.2 Incompatibilities

The following are not compatible with Claforan:

- sodium hydrogen carbonate solution
- solutions for infusion with a pH value over 7
- aminoglycosides

If immiscibility has not been proven, Claforan should not be mixed with other medicinal products (for compatibility with solutions for infusion, see section 6.3).

Incompatibility with other antibiotics/chemotherapeutic agents:

Due to physical/chemical incompatibility with all aminoglycosides, cefotaxime should not be administered in an injection or solution for infusion containing aminoglycosides. The two antibiotics should be injected at separate sites using separate devices.

6.3 Special Precautions for Storage

Finished Product:

Do not store above 30ºC. Keep the container in the outer carton, in order to protect from light.

Reconstituted Solution:

The chemical and physical stability of the reconstituted solution is 12 hours at 25ºC. For microbiological reasons, the solution should be administered immediately. If the solution is not used straight away, the user is responsible for in-use storage times and conditions. Even if reconstitution has taken place under controlled and validated conditions, the storage time should not normally exceed 24 hours at 2-8ºC.

Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, Claforan is compatible with several commonly used intravenous infusion fluids and will retain satisfactory potency for up to 24 hours refrigerated (2-8ºC) in the following:

- Water for Injections Ph. Eur.
- Sodium Chloride Injection BP.
- 5% Dextrose Injection BP.
- Dextrose and Sodium Chloride Injections BP.
- Compound Sodium Lactate Injection BP. (Ringer-lactate Injection)

After 24 hours any unused solution should be discarded.

Claforan is also compatible with 1% lidocaine; however, freshly prepared solutions should be used.

Claforan is also compatible with metronidazole infusion (500 mg/100 ml) and both will maintain potency when refrigerated (2-8ºC) for up to 24 hours. Some increase in colour of prepared solutions may occur on storage. However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

6.4 Nature and Contents of Container

Each box includes:

1 vial of dry powder for the preparation of a solution for injection or infusion + 1 ampoule of 4 ml Water for Injections.

6.5 Preparation and Handling

In order to avoid septic complications on injection, it is recommended that care should be taken during reconstitution to ensure aseptic handling and that the solution should be used immediately after reconstitution. Aseptic handling is particularly important if the solution is not intended for immediate use.

7. MANUFACTURER:

S.C. ZENTIVA S.A., ROMANIA

8. LICENSE HOLDER:

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The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in July 2015

CLAF POWD SOLV PHY SH 130715