Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Claforan Powder for Solution for Injection 500mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 500mg cefotaxime base.

Excipient(s) with known effect
Sodium 24mg (see section 4.4)

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

A white to pale yellow-white crystalline powder.

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, meningitis and other sensitive infections suitable for parenteral antibiotic therapy.

Prophylaxis:
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 infections 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.

Claforan may also be used prophylactically along with orally administered non-absorbable antibiotics to reduce the incidence of infection among selected patients undergoing intensive therapy, whose duration of stay in Intensive Care Unit is anticipated to exceed 48 hours.

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) pneumonia.

Clostridium spp.

Gram Negative

Escherichia coli.
Haemophilius influenzae including ampicillin resistant strains.
Klebsiella spp.
Proteus spp. (both indole positive and indole negative).
Enterobacter spp.
Neisseria spp. (including B-lactamase producing strains of N.gonorrhoea).
Salmonella spp. (including Sal. 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 cause 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 or by slow injection or infusion or intramuscularly. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organism 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 1g 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 12g daily given in 3 or 4 divided doses. For infections caused by sensitive Psuedomonas spp. daily doses of greater than 6 g will usually be required.

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

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

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

Dosage in Renal Impairment:

In patients with a creatinine clearance less than 10 ml/minute, after an initial normal dose, the maintenance doses have to be reduced to one half of the normal dose, without change of the dose interval.

In haemodialysed patients: 1 to 2 g daily, depending on the severity of the infection; on the day of haemodialysis, cefotaxime must be administered after the dialysis session.

In patients undergoing peritoneal dialysis: 1 to 2 g daily, depending on the severity of the infection; cefotaxime is not removed by peritoneal dialysis.

ADMINISTRATION:

Intravenous and Intramuscular administration:

Intravenous administration (Injection or infusion):
Reconstitute Claforan with Water for Injection as given in the Dilution Table. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Dilution Table:

Vial Size	Diluent to be added
500mg	2ml
1g	4ml

Claforan may be administered by intravenous infusion. 1-2g are dissolved in 40-100ml of Water for Injection or in the infusion fluids listed under "Pharmaceutical Particulars" in Section 6.6 Instructions for use/handling.

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.

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.

Cefotaxime and aminoglycosides should not be mixed in the same syringe or infusion fluid.

Intramuscular administration:

In case of intramuscular administration, re-constitute Claforan with Water for Injection or 1% lidocaine solution as per the Dilution Table above. When using lidocaine solution as diluent, intravascular injection must be strictly avoided.

Intramuscular administration		
	Volume of diluent	Nature of diluent
Cefotaxime 0.50g Cefotaxime 1g	2 ml 4 ml	{water for injection {or {1 % lidocaine solution

4.3 Contraindications

Hypersensitivity to cephalosporins
In patients with a history of hypersensitivity to Cefotaxime and/or to any component of Claforan Powder for Solution for Injection 500mg

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4 Special Warnings and Precautions For Use)

Claforan reconstituted with lidocaine is contraindicated in patients with:
Known history of hypersensitivity to lidocaine or other local anesthetics of the amide type
Non-paced heart block
Severe heart failure
Administration by the intravenous route
Infants aged less than 30 months of age

4.4 Special warnings and precautions for use

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 (see Section 4.8).

· Anaphylactic reactions
Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8).

If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contra-indicated in subjects with a previous history of immediatetype hypersensitivity to cephalosporins.

Since cross allergy exists between penicillins and cephalosporins, use of the latter should be undertaken with extreme caution in penicillin sensitive subjects. Hypersensitivity reactions (anaphylaxis) occurring with these two antibiotic families may be serious or even fatal.

. Severe skin reactions
Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime treatment.

At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

If signs and symptoms suggestive of these reactions appear, cefotaxime should be withdrawn immediately. If the patient has developed AGEP, SJS, TEN or DRESS with the use of cefotaxime, treatment with cefotaxime must not be restarted and should be permanently discontinued.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to cefotaxime in children that develop symptoms of rash and fever during therapy with cefotaxime.

· *Clostridium difficile* associated disease (e.g. pseudomembranous colitis)
Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of *Clostridium difficile* associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudo-membranous colitis.
The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.
If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay. *Clostridium difficile* associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given.

· Blood disorders
Leukopenia, neutropenia and, more rarely, bone marrow failure, pancytopenia or agranulocytosis may develop during treatment with cefotaxime. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia.
Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolytic anemia have also been reported. (see section 4.8)

· Patients with renal insufficiency
The dosage should be modified according to the creatinine clearance calculated.
Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with pre-existing renal impairment.

Encephalopathy
Beta-lactams, including cefotaxime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

· Precautions for administration
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. The recommended time for injection or infusion should be followed (see section 4.2).

See section 4.3 for contraindications for Claforan when reconstituted with lidocaine.

· Effects on Laboratory Tests
As with other cephalosporins a positive Coombs' test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood. Urinary glucose testing with non-specific reducing agents may yield false-positive results. This phenomenon is not seen when a glucose-oxydase specific method is used.

· Sodium
This medicinal product contains 24mg sodium per vial, equivalent to 1.2% of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid interferes with the renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4 Special Warnings and Precautions for Use).

4.6 Fertility, pregnancy and lactation

Pregnancy: The safety of cefotaxime has not been established in human pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
There are, however, no adequate and well controlled studies in pregnant women.
Cefotaxime crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risks.

Lactation:
Cefotaxime passes into human breast milk.
Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonization by yeast-like fungi, and sensitisation of the infant cannot be excluded. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding 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 adverse reactions such as dizziness or encephalopathy (which may include convulsions, confusion, impairment of consciousness, movement disorders) the patient should not operate machines or drive a vehicle.
High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

System organ class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (< 1/10,000)**	**Not known (cannot be estimated from available data)***
Infections and infestations						Superinfection (see section 4.9)
Blood and the lymphatic system disorders			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 Anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy* (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central venous catheter
Gastrointestinal disorders			Diarrhea			Nausea Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-bilary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis** (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4) Acute generalised

						exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Renal and Urinary disorders			Decrease in renal function/ increase of creatinine (particularly when coprescribed with aminoglycosides)			Acute renal failure (See Section 4.4) Interstitiitial nephritis
General disorders and administration site conditions	*For IM formulations:* Pain at the injection site		Fever Inflammatory reactions at the injection site, including phlebitis/ thrombophlebitis			*For IM formulations (where lidocaine is used for re-constitution):* Systemic reactions to lidocaine

* Beta-lactams, including cefotaxime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.
** postmarketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment.
The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been reported. These laboratory abnormalities 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 IM Formulations:
Since the solvent contains lidocaine, systemic reactions to lidocaine may occur, especially in the event of inadvertent intravenous injection or injection into highly vascularised tissue or in the event of an overdose.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is 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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms of overdose may largely correspond to the profile of side effects.
There is a risk of encephalopathy in cases of administration of beta-lactam antibiotics including cefotaxime, particularly in case of overdose or renal impairment.

In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).
No specific antidote exists. Cefotaxime may be removed by haemodialysis. Peritoneal dialysis is ineffective in removing cefotaxime.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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 bacteria.

5.2 Pharmacokinetic properties

Pharmacokinetics: After a 1000mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102 microg/ml. Doses of 500mg and 2000mg produce plasma concentrations of 38 and 200 microg/ml, respectively. There is no accumulation following administration of 1000mg intravenously or 500mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of cefotaxime is 21.6L/1.73m^2 after 1g intravenous 30 minute infusion.

Concentrations of cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30 microg/ml in children with meningitis.

Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 microg/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principle metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390ml/minute and renal clearance 145 to 217ml/minute.

After intravenous administration of cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Prolonged use of an anti-infective may result in the development of superinfection due to organisms resistant to that anti-infective.
Aminoglycosides are incompatible with cephalosporins in parenteral mixtures.

6.3 Shelf life

Unopened: 2 years.
Reconstituted solution: See Section 6.4 and 6.6.

6.4 Special precautions for storage

Unopened: Do not store above 25°C. Keep the vial in the outer carton.

Injection: Use immediately after reconstitution.

Infusion: Some reconstituted or mixed solutions will retain satisfactory potency for up to 24 hours refrigerated (at 2 - 8°C) – See Section 6.6. for further information.

After 24 hours any unused solution should be discarded.

From a microbiological point of view, the product should be used immediately. If not used immediately, in–use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Claforan is supplied in type III colourless glass vials, closed with a grey elastomer stopper sealed with either an aluminium cap fitted with a detachable flip top, or an infusion connector closure.

The bottles are boxed individually and in packs of 10, 25 or 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.

When dissolved in Water for Injections, a straw-coloured solution is formed which is suitable for intravenous or intramuscular injection.

Reconstituted Solution: 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 (2-8 °C) in the following:

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

Claforan is also compatible with 1% lignocaine, 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 (2-8 °C) 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.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
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3 Burlington Road
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8 MARKETING AUTHORISATION NUMBER

PA1142/041/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th May 1981

Date of last renewal: 18th December 2009

10 DATE OF REVISION OF THE TEXT

May 2024