IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/037/004
Case No: 2059853

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA0006/024/004.

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Claforan Powder for solution for Injection 2 g

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/01/2009** until **17/12/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Claforan Powder for solution for Injection 2 g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 2g cefotaxime base.

Each gram of Claforan contains approximately 48 mg (2.09 mmol) of sodium.

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 of 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 bolus 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 or divided doses. For infections caused by sensitive Pseudomonas spp. daily doses of greater than 6 g will usually be required.

Dosage in Gonorrhoea: A single injection of 1 g 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:
Because of extra-renal elimination, it is only necessary to reduce the dosage of Claforan in severe renal failure (GFR < 5ml/min = serum creatinine approximately 751 micromol/1). After an initial loading dose of 1g, daily dose should be halved without change in the frequency of dosing, i.e. 1g in 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 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 and Intramuscular administration:

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
2g	10ml

Intravenous Injection:

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". 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.

4.3 Contraindications

Known or suspected allergy to cephalosporins.

4.4 Special warnings and precautions for use

Preliminary enquiry about allergy to penicillin and other beta-lactam antibiotics is necessary before prescribing cephalosporins since cross allergy occurs in 5-10% of cases.

Hypersensitivity reactions (anaphylaxis) occurring with the two types of antibiotics can be serious and occasionally fatal. Hypersensitivity requires that treatment be stopped.

Patients with severe renal dysfunction should be placed on the dosage schedule recommended under "Posology and

Method of Administration".

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

Claforan reconstituted with Lignocaine must never be used:
By the intravenous route
In infants under 30 months
In subjects with a previous history of hypersensitivity to this product
In patients who have an unpaced heart block
In patients with severe heart failure.

The sodium content of Claforan (2.09mmol/g) should be taken into account when prescribing to patients requiring sodium restriction.

Claforan may predispose patients to pseudo-membranous colitis. Although any antibiotic may predispose to pseudo-membranous colitis, the risk is higher with broad spectrum drugs, such as cephalosporins.

This side effect, which may occur more frequently in patients receiving higher doses for prolonged periods, should be considered as potentially serious. The presence of C.Difficile should be investigated, and treatment with Claforan stopped in cases of suspected colitis.

The diagnosis should be confirmed by sigmoidoscopy and specific antibiotic therapy (e.g. oral vancomycin or Metronidazole) initiated if considered clinically necessary. The administration of products which cause faecal stasis should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Cephalosporin antibiotics at high dosage should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as frusemide as these combinations are suspected to adversely affect renal function.

However, at the recommended doses, enhancement of nephrotoxicity is unlikely to be a problem with Claforan.

Probenecid interferes with renal tubular transfer of Claforan, delaying its excretion and increasing the plasma concentration.

Interference with Laboratory Tests:
A positive Coombs test may be seen during treatment with Cephalosporins. This phenomenon may occur during treatment with Claforan.

A false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidose methods.

4.6 Pregnancy and lactation

Pregnancy: It is known that Claforan crosses the placental barrier. Although studies in animals have not shown an adverse effect on the developing foetus, the safety of Claforan in human pregnancy has not been established. Consequently, Claforan should not be administered during pregnancy especially during the first trimester, without carefully weighing the expected benefit against possible risks.

Lactation: Claforan is excreted in the milk.

4.7 Effects on ability to drive and use machines

There is no evidence that Claforan directly impairs the ability to drive or to operate machines.

4.8 Undesirable effects

Adverse reactions to Claforan have occurred relatively infrequently and have generally been mild and transient. Effects reported include candidiasis, nausea, vomiting, abdominal pain, diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis (see warnings)), transient rises in liver transaminases, alkaline phosphatase and/or bilirubin.

As with other Cephalosporins, changes in renal function have been observed with high doses of Claforan, particularly when co-prescribed with aminoglycosides. Rare cases of interstitial nephritis have been reported in patients treated with Claforan.

Administration of high doses of Cephalosporins, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions).

Hypersensitivity reactions have been reported. These include skin rashes, pruritus and less frequently urticaria, drug fever and very rarely anaphylaxis (e.g. angioedema & bronchospasm possibly culminating in shock).

As with other cephalosporins, occasional cases of bullous reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme have also been reported.

As with other beta-lactam antibiotics, granulocytopenia and more rarely agranulocytosis may develop during treatment with Claforan, particularly if given over long periods. A few cases of eosinophilia and neutropenia have been observed, reversible when treatment is ceased. Some cases of rapidly reversible eosinophilia and thrombocytopenia on stopping treatment have been reported. Rare cases of haemolytic anaemia have been reported. For cases of treatment lasting longer than 10 days, blood count should therefore be monitored.

Transient pain may be experienced at the site of injection. This is more likely to occur with higher doses. Occasionally, phlebitis has been reported in patients receiving intravenous Claforan. However, this has rarely been a cause for discontinuations of treatment.

A very small number of cases of arrhythmias have occurred following rapid bolus infusion through a central venous catheter.

The following symptoms have occurred after several weeks of treatment for borreliosis: skin rash, itching, fever, leucopenia, increases in liver enzymes, difficulty of breathing, joint discomfort. To some extent these manifestations are consistent with the symptoms of the underlying disease, for which the patient is being treated.

4.9 Overdose

Serum levels of Claforan may be reduced by peritoneal dialysis or haemodialysis. In the case of overdosage, particularly in renal insufficiency there is a risk of reversible encephalopathy.

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 102µg/ml. Doses of 500mg and 2000mg produce plasma concentrations of 38 and 200µg/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 30μg/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 μg/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 Sections 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

sanofi-aventis Ireland Ltd
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA540/37/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th May 1981

Date of last renewal: 18th December 2004

10 DATE OF REVISION OF THE TEXT

January 2009