SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefadroxil 500 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains cefadroxil monohydrate equivalent to 500 mg anhydrous cefadroxil.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard Capsules

Deep blue/light blue, hard gelatin, self-locked capsules of size '0' imprinted with '500' in black edible ink on both cap and body, containing white or almost white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefadroxil is a cephalosporin antibiotic bactericidal in vitro against a wide range of Gram-positive and Gram-negative microorganisms. Cefadroxil is indicated in the treatment of the following infections when due to susceptible microorganisms.

Respiratory tract infections: Tonsillitis, pharyngitis, lobar and bronchopneumonia, acute and chronic bronchitis, pulmonary abscess, empyema, pleurisy, sinusitis, laryngitis, otitis media.

Skin and soft-tissue infections: Lymphadenitis, abscesses, cellulitis, decubitus ulcers, mastitis, furunculosis, erysipelas.

Genitourinary tract infections: Pyelonephritis, cystitis, urethritis, gynaecological infections.

Other infections: Osteomyelitis, septic arthritis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Adults and children weighing more than 40 kg (6 st. and 4 lbs):

One to tow capsules (500 mg to 1 g) twice a day, depending upon the severity of infection.

Alternatively, in skin and soft tissue and uncomplicated urinary tract infections, 1 g once a day.

In the treatment of beta-haemolytic streptococcal infections, Cefadroxil should be administered for at least 10 days.

Adults and children (7years & above) weighing less than 40 kg (6 st. and 4lbs):

One capsule (500 mg) twice a day.

Elderly:

No specific dosage recommendations or precautions for use in the elderly except to monitor those patients with impaired renal function.

The bioavailability and consequent chemotherapeutic effects of cefadroxil are unaffected by food. It may, therefore, be taken with meals or on an empty stomach.

Renal Impairment Dosage:

In patients with renal impairment, the dosage should be adjusted according to creatinine clearance rates to prevent drug accumulation and serum levels should be monitored. A modified dosage schedule is unnecessary in patients with creatinine clearance rates of greater than 50 ml/min. In those patients with creatinine clearance rates of 50 ml/min or less, the following reduced dosage schedule is recommended as a guideline, based upon the creatinine clearance rate (ml/min/1.73m^2).

Patients with renal insufficiency may be treated with an initial dose of 500 mg to 1000 mg of cefadroxil. Subsequent doses may be administered according to the following table:

Creatinine clearance	Dose	Dose Interval
0-10 ml/min/1.73m^2	500-1000 mg	36 hrs
11-25 ml/min/1.73m^2	500-1000 mg	24 hrs
26-50 ml/min/1.73m^2	500-1000 mg	12 hrs

Cefadroxil can be removed from the body by haemodialysis.

4.3 Contraindications

Cefadroxil is contraindicated in patients with:

- History of hypersensitivity to cefadroxil, to any other cephalosporin or to any of the excipients of this product.
- History of severe reactions to penicillins or to any other beta-lactam drugs

4.4 Special warnings and precautions for use

Pseudomembranous colitis

As with other broad spectrum antibiotics, pseudomembranous colitis has been reported. In case of severe and persistent diarrhoea, an antibiotic-associated pseudomembranous colitis should be considered. In that case Cefadroxil must be discontinued immediately and a suitable therapy should be started (e.g. oral vancomycin, 250 mg q.i.d.). Antiperistaltics are contraindicated.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefadroxil, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated

History of gastro-intestinal disturbances

Cefadroxil should be used with caution in patients with a history of gastro-intestinal disturbances particularly colitis.

Cefadroxil does not penetrate in the CSF and is not indicated for the treatment of meningitis (see section 5.2).

Penicillin is the first drug of choice for the treatment of the Streptococcus pyogenes and for the prevention of rheumatic fever. Data for cefadroxil are not sufficiently substantial for prophylaxis therapy.

As experience in premature infants and neonates is limited, the use of cefadroxil in these patients should only be undertaken with caution.

Patients with history of allergies

Special caution should be exercised in patients with history of severe allergies or asthma.

In patients with a history of non severe hypersensitivity to penicillins, or other non-cephalosporin beta–lactam drugs, cefadroxil should be used with special caution as cross allergies occur (incidence 5-10%). There is evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Should an allergic reaction to cefadroxil occur, the drug should be discontinued and the patient treated with the usual agents (pressor amines, corticosteroids and/or antihistamines), depending on the severity of the reaction.

Patients who are allergic to aspirin have greater chances of developing an allergic reaction to one of the ingredients (colouring agent) in this medicine, namely Carmoisine (E122).

Allergic reactions

Treatment must be discontinued at once if allergic reactions occur (urticaria, exanthema, pruritus, fall of blood pressure and increased heart rate, respiratory disturbances, collapse, etc.) and suitable countermeasures should be taken (sympathomimetics, corticosteroids and/or antihistaminics).

Renal impairment

Caution is necessary in patients with renal impairment; the dosage must be adjusted according to the grade of renal impairment (see section 4.2 Posology).

Prolonged use

Particularly on prolonged use frequent checks on the blood count and regular hepatic and renal function tests are advisable. Superinfections with fungi (e.g. *candida*) can occur on prolonged treatment with cefadroxil.

Severe life-threatening infections or those which require higher posology or repetitive administrations per day may benefit of parenteral cephalosporins.

The result of the Coombs' test can be transiently positive during or after treatment with cefadroxil. In haematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs’ testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs’ test may be due to the drug

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use

Cefadroxil should not be combined with bacteriostatic antibiotics (e.g. tetracycline, erythromycin, sulfonamides, chloramphenicol) since an antagonistic effect is possible.

Treatment with Cefadroxil in combination with aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics should be avoided since such combinations can potentiate nephrotoxic effects.

Concomitant use not recommended

Frequent checks on coagulation parameters are necessary during concomitant long term use of anticoagulants or thrombocyte aggregation inhibitors to avoid haemorrhagic complications.

Precautions to be exercised

The concomitant administration of probenecid can produce higher and sustained concentrations of cefadroxil in the serum and in the bile.

The occurrence of diarrhoea may impair the resorption of other medicaments and therefore lead to an impairment of their efficacy.

Forced diuresis leads to a decrease of cefadroxil blood levels.

Cefadroxil may attenuate the effect of oral contraceptives.

Cefadroxil binds to cholestyramine which may lead to reduced bioavailability of cefadroxil.

Laboratory tests

The result of the direct Coombs' test can be transiently positive during or after treatment with cefadroxil. This also applies to Coombs' tests carried out in newborns whose mother received treatment with cephalosporins before delivery.

Urine from patients treated with cefadroxil may give a false-positive glycosuria reaction when tested with Benedict's or Fehling's solutions. This does not occur with enzyme based tests. Urinary sugar should be determined enzymatically (e.g. with test strips) during treatment with cefadroxil

4.6 Fertility, Pregnancy and lactation

Pregnancy

Although animal studies and clinical experience have not shown any evidence of teratogenicity, the safe use of cefadroxil during pregnancy has not been established. Reproduction studies have been performed in mice and rats at doses up to 11 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to Cefadroxil. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Cefadroxil is excreted in low concentrations in breast milk sensitization, diarrhoea or colonization of the infants' mucosa with fungi are possible.

The use of cefadroxil during pregnancy and in lactating mothers should therefore be handled very strictly.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that cefadroxil has any effect on the ability to drive and/or use machines.

4.8 Undesirable effects

The most commonly reported side-effects are gastrointestinal disturbances and hypersensitivity phenomena.
Undesirable effects reported are listed per System Organ Class and per frequency.
Very common: (>1/10)
Common: (>1/100, <1/10)
Uncommon: (>1/1000, <1/100)
Rare: (>1/10000, <1/1000)
Very rare: (<1/10000), including isolated cases

Infections and infestations
Uncommon: Clinical pictures due to a growth of opportunistic organisms (fungi), such as vaginal mycoses (genital candidiasis), thrush

Blood and the lymphatic system disorders

Rare: Eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis: rare cases during prolonged use, which subside upon discontinuation of therapy.
Very rare: Isolated cases of haemolytic anaemia of immunologic origin.

Immune system disorders
Rare: Serum sickness-like reactions
Very rare: immediate allergic reaction (anaphylactic shock)

Nervous and psychiatric system disorders
Very rare: dizziness, headache, nervousness, sleeplessness
Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, dyspepsia, abdominal discomfort, abdominal pain, glossitis
Very rare: Isolated cases of pseudo-membranous colitis
Unknown frequency: Colitis has been reported.

Hepato-biliary disorders
Rare: minor elevations of serum transaminases (ASAT, ALAT) and alkaline phosphatase
Cases of cholestasis and idiosyncratic hepatic failure have been reported.

Skin and subcutaneous tissue disorders
Common: Rash, pruritus, allergic exanthema, urticaria
Rare: Angioneurotic oedema
Very rare: Stevens Johnson syndrome and erythema multiforma have been reported

Musculoskeletal and connective tissue disorders
Rare: Arthralgia,

Renal and urinary disorders
Rare: Interstitial nephritis

General disorders and administration site conditions
Rare: Drug fever
Very rare: Fatigue

Investigations
*Very rare:*Direct and indirect positive Coombs tests(see section 4.4)

4.9 Overdose

No clinical reports are as yet available on cefadroxil in this respect. However in view of experience gained with other cephalosporins the following symptoms are possible: nausea, hallucinations, hyperreflexia, extrapyramidal symptoms, clouded consciousness, or even coma and renal functional impairment. First aid after intake of toxic doses: induce vomiting at once or gastric lavage, if necessary haemodialysis. Monitor and if necessary correct the water and electrolyte balance, monitor renal function.

Ingestion of <250 mg/kg in children under six years of age was not associated with significant outcomes. The patient should be observed and treated symptomatically. For amounts >250 mg/kg, gastric lavage or stimulation of vomiting is appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

ATC-Code: **J01DB05**

Pharmacotherapeutic group: Other beta-lactam antibacterials. First generation cephalosporins.

Mode of action

Cefadroxil is a cephalosporin for oral administration which inhibits bacterial wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins. The result is formation of a defective cell wall that is osmotically unstable, and bacterial cell lysis.

Mechanisms of resistance

Cefadroxil may be active against organisms producing some types of beta-lactamase, for example TEM-1, in low to moderate quantities. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes.

Cefadroxil cannot be expected to be active against bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam drugs. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

In vitro, oral first generation cephalosporins are less active than penicillins G and V on Gram-positive microorganisms and are less active than aminopenicillins on *H. influenzae*.

Breakpoints

The following breakpoint recommendations for cefadroxil according to the European Committee on Antimicrobial Susceptibly Testing (EUCAST) have been defined (Breakpoint tables for interpretation of MICs and zone diameters, Version 1.0, December 2009):

Cefadroxil (EUCAST Clinical Breakpoint Table)	**MIC breakpoints**	
	S ≤	**R >**
Enterobacteriaceae (uncomplicated UTI only)	16	16
Staphylococcus spp.	Note[1]	Note[1]
Streptococcus groups A, B, C, and G	Note[2]	Note[2]
Non-species related breakpoints	IE	IE

Note[1]: Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility except for ceftazidime and cefixime and ceftibuten, which do not have breakpoints and should not be used for staphylococcal infections.

Note[2]: The beta-lactam susceptibility of beta-haemolytic streptococci groups A, B, C and G is inferred from the penicillin susceptibility.

IE: indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such, that the utility of the agent in at least some types of infections is questionable.

Species

Commonly susceptible species

Gram-positive aerobes

Streptococci Group B, C and G

Streptococcus pyogenes *

Gram-negative aerobes

Moraxella catarrhalis *

Species for which acquired resistance may be a problem

Gram-positive aerobes

Staphylococcus aureus (methicillin-susceptible) *

Staphylococcus epidermidis

Streptococcus pneumoniae *

Gram-negative aerobes

Citrobacter diversus[$] *Escherichia coli* [$] *Haemophilus influenzae* [$] *Klebsiella pneumoniae*[$] *Klebsiella oxytoca* [$] *Proteus mirabilis** [$]

Inherently resistant species

Gram-positive aerobes

Enterococcus spp.

Staphylococcus aureus (Methicillin-resistant)

Staphylococcus epidermidis (Methicillin-resistant)

Streptococcus pneumoniae (penicillin-resistant)

Gram-negative aerobes

Acinetobacter spp.

Citrobacter freundii

Enterobacter spp.

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Serratia marcescens

Other species

Chlamydia spp

Mykoplasma spp

Legionella spp

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

$ Species with natural intermediate susceptibility

5.2 Pharmacokinetic properties

Cefadroxil is rapidly absorbed after oral administration. The bioavailability is unaffected by food. Following single doses of 500 mg and 1000 mg average peak serum levels were approximately 16 and 28 □g/ml respectively. Measurable levels were present 12 hours after administration. Over 90% of the drug is excreted unchanged in the urine within 24 hours. Peak urine concentrations are approximately 1,800 □g/ml after a 500 mg dose. Increases in dose generally produce a proportionate increase in cefadroxil urinary concentration. Oral dosing produces effective tissues penetration in lungs, tonsil, liver, gall bladder, bile duct, prostate, bone, muscle and synovial fluid. The half-life is approximately 80 – 120 minutes, and protein binding is approximately 20%. Cefadroxil can be removed from the body by haemodialysis.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction. Although, tests for mutagenicity and carcinogenicity of cefadroxil in animals have not been reported, there is no published evidence to suggest that potential carcinogenicity and mutagenicity is a concern with the cephalosporin-class of compounds.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents:

Microcrystalline cellulose

Magnesium stearate

Crospovidone

Talc

Capsule Shell/Body:

Gelatin
Carmoisine E 122
Patent blue V E131
Titanium dioxide E171

Printing Ink:
Shellac
Potassium hydroxide
Black iron oxide E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original pack.

6.5 Nature and contents of container

Blister strip comprising of clear transparent PVC film (coated uniformly with PVdC on the inner side) with a backing of aluminium foil (coated with heat seal lacquer). Strips of 7 capsules each or 10 capsules each are enclosed in a cardboard carton. Not all pack sizes may be marketed.

Packs are available as:
14 capsules (2 strips of 7 capsules)
20 capsules (2 strips of 10 capsules)
100 capsules (10 strips of 10 capsules)

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Gaelic Laboratories Limited
Waterford Road, Clonmel,
County Tipperary,
E91 CD92,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 57395/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 October 2001

10 DATE OF REVISION OF THE TEXT

12/01/2023