SmPC

Miradroxil (Cefadroxil 500mg)

1. Name of the medicinal product

Miradroxil (Cefadroxil) 500 mg Capsules

2. Qualitative and quantitative composition

One capsule contains 500 mg of cefadroxil (as monohydrate).

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Capsules, hard gelatin

Description: Maroon -White Coloured hard gelatin capsule contains white granular powder.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of following infections caused by cefadroxil-susceptible organisms (see section 5.1), when an oral therapy is indicated:

- Streptococcal pharyngitis and tonsillitis

- Bronchopneumonia, bacterial pneumonia

- Uncomplicated urinary tract infections: pyelonephritis, cystitis

- Skin and soft tissue infections: abscesses, furunculosis, impetigo, erysipelas, pyoderma, lymphadenitis

Consideration should be given to official local guidance regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dosage depends on the susceptibility of the pathogens, the severity of the disease and on the clinical status of the patient (renal and hepatic function).

Indications	Adults and adolescents > 40 kg with normal renal function	Children (< 40 kg) with normal renal function
Streptococcal pharyngitis / tonsillitis	Dosage may be decreased to 1000 mg once a day over at least 10 days	30 mg/kg/day once a day over at least 10 days
Bronchopneumonia, bacterial pneumonia	1000 mg twice a day	30-50 mg/kg/day divided into two daily doses
Urinary tract infections	1000 mg twice a day	30-50 mg/kg/day divided into two daily doses

Skin & soft tissue infections	1000 mg twice a day	30-50 mg/kg/day divided into two daily doses

Children may benefit of increased posology up to 100 mg/kg/day.

Depending on the severity of the infection, adults may require increased posology. The dosage maximum is 4 g per day. Chronic urinary tract infection may require a prolonged and intensive treatment with continued testing of susceptibility and clinical monitoring.

Miradroxil 500 mg capsules is not recommended for infants and children under 6 years. For younger children and children with a body weight < 40 kg, liquid oral forms (Miradroxil 250 mg/ 5 ml or 500 mg/ 5 ml suspension) are available.

• Renal impairment:

The dosage should be adjusted according to creatinine clearance rates to prevent accumulation of cefadroxil. In patients with creatinine clearance of 50 ml/min or less, the following reduced dosage schedule is recommended as a guideline for adults:

Creatinine clearance (ml/ min/ 1.73 m^2)	Serum Creatinine (mg/100ml)	Initial dose	Following dose	Dosage interval
50 - 25	1.4 – 2.5	1000 mg	500 mg – 1000 mg	every 12 hours
25 - 10	2.5 – 5.6	1000 mg	500 mg – 1000 mg	every 24 hours
10 - 0	> 5.6	1000 mg	500 mg – 1000 mg	every 36 hours

• Children (< 40 kg) with renal impairment:

Cefadroxil is not indicated in children suffering from renal insufficiency and children requiring haemodialysis.

• Dosage for haemodialysis patients:

Haemodialysis eliminates 63% of 1000 mg of cephalosporin after 6 to 8 hours of haemodialysis. Elimination half-time of cephalosporin is about 3 hours during dialysis.

Patients with haemodialysis receive one additional dose of 500 mg - 1000 mg at the end of the haemodialysis.

Hepatic impairment:

No adjustment of posology is necessary.

• Elderly:

As cefadroxil is excreted by renal route, the dosage should be adjusted if necessary as described under impaired renal function.

Mode of administration

Bioavailability is not affected by food and cefadroxil may be taken with meals or on an empty stomach. In case of gastro-intestinal disturbances, it may be administered with food.

The capsules are taken unchewed with a liberal quantity of fluid.

Duration of therapy

Treatment should be applied for 2 to 3 further days after regression of the acute clinical symptoms or evidence of bacterial eradication has been obtained. In infections caused by Streptococcus pyogenes up to 10 days treatment may be considered.

4.3 Contraindications

- Hypersensitivity to cefadroxil, to any of the cephalosporins or to any of the excipients listed in section 6.1.

- History of severe reactions to penicillins or to any other beta-lactam drugs.

4.4 Special warnings and precautions for use

- 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.

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

- In patients with a history of non severe hyper-sensitivity to penicillins, or other non-cephalosporin beta –lactam drugs, cefadroxil should be used with special caution as cross allergies occur (incidence 5-10%).

- 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).

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

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

- 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).

- 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.

- 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.

- 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. This also applies to Coombs' tests carried out in newborns whose mothers received treatment with cephalosporins before delivery.

- Forced diuresis leads to a decrease of cefadroxil blood levels.

- Urinary sugar should be determined enzymatically (e.g. with test strips) during treatment with cefadroxil since reduction tests can furnish falsely elevated values.

- Cefadroxil contains sodium

This medicinal product contains less than 1 mmol (23 mg) sodium per hard capsule, that is to say essentially 'sodium-free'.

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

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

- The concomitant administration of probenecid reduces the renal elimination of cefadroxil; therefore, plasma concentrations of cefadroxil may be increased when given in combination with probenecid.

-4.6 Fertility, pregnancy and lactation

Pregnancy

Although animal studies and clinical experience have not shown any evidence of teratogenicity, the safe use during pregnancy has not been established.

Breast-feeding

Cefadroxil is present 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

Cefadroxil may cause headache, dizziness, nervousness, sleeplessness and fatigue, therefore the ability to drive and use machines may be influenced (see section 4.8).

4.8 Undesirable effects

The adverse events are ranked under headings of frequency, using the following convention:

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 form the available data).

Adverse drug reactions occur in about 6% to 7%* of treated patients.

System Organ Class

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

Infections and infestations

Clinical pictures due to a growth of opportunistic organisms (fungi), such as vaginal mycoses, thrush (see section 4.4).

Blood and lymphatic system disorders

Eosinophilia, thrombocytopenia, leukopenia, neutropenia, agranulocytosis: rare cases during prolonged used, which subside upon discontinuation of therapy.

Haemolytic anaemia of immunologic origin.

Immune system disorders

Serum sickness-like reactions.

Immediate allergic reaction (anaphylactic shock) (see section 4.4).

Nervous system disorders

Headache, sleeplessness, dizziness, nervousness.

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, glossitis (see section 4.4).

Pseudo-menbranous colitis has been reported (may range in severity from mild to life threatening) (see section 4.4).

Hepatobiliary disorders

Cholestase and idiosyncratic hepatic failure have been reported.

Minor elevation of serum transaminases (ASAT, ALAT) and alkaline phosphatases.

Skin and subcutaneous tissue disorders

Pruritus, rash, allergic exanthema, urticaria.

Angioneurotic edema.

Stevens Johnson syndrome and erythema multiforma have been reported.

Musculoskeletal and connective tissue disorders

Arthralgia.

Renal and urinary disorders

Interstitial nephritis (see section 4.4).

General disorders and administration site conditions

Drug fever.

Fatigue.

Investigations

Direct and indirect positive Coombs tests (see section 4.4).

*incidence of suspected adverse reactions in an observational post-marketing study in 904 patients.

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 Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC classification

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

S ≤

R >

Enterobacteriaceae (uncomplicated UTI only)

Staphylococcus spp.

Streptococcus groups A, B, C, and G

Non-species related breakpoints

Note1: 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.

Note2: 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 influenza $ 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

Myko plasma spp

Legionella spp

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

$ Species with natural intermediate susceptibility

5.2 Pharmacokinetic properties

Absorption

After oral administration cefadroxil is practically completely absorbed. Simultaneous intake of food has practically no effect on absorption (AUC).

Distribution

After oral doses of 500 mg (1000 mg) peak plasma concentrations of about 16 (30) µg/ml are obtained after 1-1,3 hours. Between 18 and 20% of cefadroxil is bound to plasma proteins. Cephalosporins do not penetrate in the CSF and should not be used for treatment of meningitis (see section 4.1)

Biotransformation

Cefadroxil is not metabolised.

Elimination

Cefadroxil is eliminated far more slowly than comparable oral cephalosporins (half life: about 1,4 h to 2,6 h) so that intervals between doses can be prolonged to 12-24 hours. Roughly 90% of the substance is eliminated in unchanged form through the kidneys within 24 hours. Cefadroxil may be eliminated from the organism through haemodialysis.

Characteristics in patients with reduced creatinine clearance, a sign for renal functional impairment

Elimination is retarded, so that interval between doses must be prolonged (see section 4.2).

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Magnesium stearate

Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

(ALU/ALU)--Packs

7. Marketing authorisation holder

MIRAFLASH NIGERIA LIMITED (pharmaceuticals)
Ogun State, Nigeria

8. Marketing authorization number(s)

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