SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicef Capsules 250mg / Cefradine Capsules 250mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient	**Per Capsule**
Cefradine Ph Eur	250 mg

3 PHARMACEUTICAL FORM

Capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefradine is indicated for the treatment of infections caused by sensitive Gram-positive and Gram-negative bacteria. These include upper respiratory tract infections such as sinusitis, pharyngitis, tonsillitis, laryngo-tracheo bronchitis and otitis media, and also lower respiratory tract infections such as bronchitis (acute and chronic), lobar pneumonia and bronchopneumonia.

Cefradine is effective in urinary tract infections including cystitis, urethritis and pyelonephritis. It is also active in skin and soft tissue infections such as abscess, cellulitis, furunculosis and impetigo.

The sensitivity of the infective agent to cefradine should be verified, however cefradine therapy may be commenced prior to this determination.

The following microorganisms are susceptible, *in vitro* to cefradine

Gram-positive *Staphylococci* (both penicillin sensitive and resistant strains and penicillinase-producing species)
- *Streptococci*
- *Streptococci pyogenes* (beta haemolytic)
- *Streptococcus pneumoniae*

Gram-negative - *Escherichia coli*
- *Klebsiella spp*
- *Proteus mirabilis*
- *Haemophilus influenzae*
- *Shigella spp*
- *Salmonella spp* (including *Salmonella typhi*)
- *Neisseria spp*

Many strains of *E.coli* and *Staphylococcus aureus* that produce the enzyme penicillinase and thus are ampicillin-resistant, are susceptible to cefradine which is unaffected by this enzyme.

4.2 Posology and method of administration

For oral administration.

Adults:
Urinary tract infections: 500mg four times daily or 1g twice daily. Infections which are severe or chronic may necessitate the administration of higher doses. Where complications arise including prostatitis and epididymitis, continued intensive treatment is required.

Respiratory tract infections : 250 to 500mg four times daily or 500mg to 1g twice daily, dependent on the site and severity of the infection.

Skin and soft tissue infections: 250 to 500mg four times daily or 500mg to 1g twice daily, again dependent on the site and severity of the infection.

Children:
Total daily dose of 25 to 50mg/kg given in two or four equal divided doses.
Otitis media: Total daily dose of 75 to 100mg/kg given in divided doses 6 to 12 hourly.

Maximum daily dosage: 4g

Elderly:
The normal adult dose is appropriate. Patients with impaired renal or hepatic function should be monitored during treatment.

Renal Impairment
The following doses are recommended (based on 500mg every 6 hours) for patients not on haemodialysis:

Creatinine Clearance	Dosage
> 20ml / min	500mg every 6 hours
5-20ml / min	250mg every 6 hours
< 5ml / min	250mg every 50-70 hours.

Recommendations for patients on chronic, intermittent haemodialysis:

250mg at the start of haemodialysis
250mg 6 to 12 hours after the start
250mg 36 to 48 hours after the start
250mg at the start of the next haemodialysis session if more than 30 hours have elapsed since the last dose.

Additional Information for all patients

Regardless of patient age or weight, higher doses of up to 1g four times daily may be required for infections which are chronic or severe. Treatment should continue for at least 2 to 3 days after symptoms have resolved or bacteria have been eradicated.

To reduce the possibility of rheumatic fever or glomerulonephritis resulting from infections with haemolytic streptococci, treatment should be continued for at least 10 days.

Throughout treatment of chronic urinary tract infections and for several months thereafter, regular bacteriological and clinical monitoring is required.

Doses below those recommended above should not be prescribed. Paediatric dosages should not exceed those specified for adults, regardless of severity of infection. It may be necessary to continue cefradine therapy for several weeks in persistent infections. Patients may be transferred from intramuscular/ intravenous cefradine therapy to oral treatment at the same dosage level.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Following administration of cefradine, a false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with reagent tablets such as Clinitest®. This does not occur with enzyme based tests such as Clinistix® or Diastix®.

Prolonged use of antibiotics may result in overgrowth of non-susceptible organisms.

Dosage should be reduced in renal failure (see section 4.2).

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Loop diuretics may increase nephrotoxicity of cephalosporins.

Probenecid has been seen to raise serum concentrations of cefradine, by reducing renal clearance of the cephalosporins.

There is evidence of partial cross-allergenicity between the penicillins and the cephalosporins. Therefore, cefradine should be used with caution in those patients with known hypersensitivity to penicillin. There have been instances of patients who have had reactions to both drug classes (including anaphylaxis)

4.6 Fertility, pregnancy and lactation

Fertility

Although animal studies have shown no teratogenic effects, safety in

pregnancy has not been established.

Pregnancy

As with all medicines, use should be avoided in pregnancy especially in the first trimester, unless considered essential by the physician

Breast-feeding

Cefradine is excreted in breast milk and should be used with caution in lactating mothers.

4.7 Effects on ability to drive and use machines

Since the medicine may cause dizziness, patients should be cautioned about operating hazardous machinery, including automobiles.

4.8 Undesirable effects

Undesirable effects are uncommon and mainly mild in nature. They are limited essentially to gastrointestinal disturbances and on occasion to hypersensitivity phenomena.

Infections and infestations
Rarely: Antibiotic-associated colitis
Frequency unknown: Vaginitis, candidal overgrowth, candidiasis

Blood and lymphatic system disorders
Frequency unknown: Eosinophilia, blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia)

Immune system disorders
Frequency unknown: Fever, arthralgia, serum sickness-like reactions, anaphylaxis

Psychiatric disorders
Frequency unknown: Confusion, sleep disturbances

Nervous system disorders
Frequency unknown: Hypersensitivity, hyperactivity, hypertonia, dizziness, nervousness
Rarely: Headache

Gastrointestinal disorders
Frequency unknown: Diarrhoea, nausea, glossitis, heartburn
Rarely: Vomiting, abdominal discomfort

Hepatobiliary disorders
Frequency unknown: Liver, enzyme disturbances, transient hepatitis, cholestatic jaundice

Skin and subcutaneous tissue disorders

Frequency unknown: Rashes, toxic epidermal necrolysis, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, oedema

Renal and urinary disorders
Frequency unknown: Reversible interstitial nephritis

General disorders and administration site conditions
Frequency unknown: Tightness in the chest

Investigations
Frequency unknown: Elevation of blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, positive direct Coombs' test

Musculoskeletal and connective tissue disorder
Frequency unknown: Joint pain

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continues monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The symptoms of cefradine overdose are non-specific and are generally nausea, vomiting, diarrhoea and gastric upsets. Treatment is mainly supportive although gastric lavage will be necessary if a large amount has been ingested.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: first generation cephalosporin, ATC code: J01DB09

Mechanism of action

Cefradine is a broad-spectrum first generation cephalosporin antibiotic active against both Gram-positive and Gram-negative bacteria. It is also highly active against most strains of penicillinase producing Staphylococci. The anti-bacterial action of cefradine is through inhibition of bacterial cell wall synthesis, probably by acylation of membrane – bound transpeptidase enzymes. This prevents cross-linkage of peptidoglycan chains which is necessary for bacterial cell wall strength and rigidity.

Susceptibility: The following organisms have shown in vitro sensitivity to Cefradine.

Gram-positive Aerobes: Staphylococci (both penicillin sensitive and resistant strains), Streptococci, Streptococcus pneumoniae and Streptococcus pyogenes (beta haemolytic).

Gram-negative Aerobes: Escherichia coli, Haemophilus influenzae, Klebsiella spp, Neisseria spp., Proteus mirabilis, Salmonella spp.(including Salmonella typhi) and. Shigella spp.

Because Cefradine is unaffected by penicillinase, many strains of Escherichia coli and Staphylococcus aureus which produce this enzyme are susceptible to Cefradine but resistant to ampicillin.

Insusceptible microorganisms:

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.

In general, bacterial resistance to cephalosporins usually results both from the production of a β-lactamase and the presence of permeability barriers to the drug.

5.2 Pharmacokinetic properties

Absorption

Cefradine has a high degree of stability to many beta-lactamases. It has a low degree of protein binding and a large volume of distribution. Therefore, tissue levels are generally found to be high. Oral cefradine can be given twice or four times daily. Cefradine is acid stable and is rapidly absorbed following oral administration in the fasting state.

Distribution

Following doses of 250mg, 500mg and 1000mg average peak serum levels of approximately 9, 16.5, and 24.2 micrograms/ml, respectively, were obtained at one hour. The presence of food in the gastrointestinal tract delays the absorption but does not affect the total amount of cefradine absorbed. Measurable serum levels are present six hours after administration.

Elimination

Over 90% of the drug is excreted unchanged in the urine within 6 hours. Peak urine concentrations are approximately 1600 micrograms/ml following a 250mg dose, 3200 micrograms/ml following a 500mg dose, and 4000 micrograms/ml following a 1000mg dose. After 48 hours administration of 100 mg/kg/day of cefradine for the treatment of otitis media, cefradine has been measured in the middle ear exudate at an average level of 3.6 microgram/ml.

5.3 Preclinical safety data

No further information additional to that already contained in this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Lauryl Sulphate
Povidone
Colloidal Silicon Dioxide
Magnesium Stearate
Lactose Monohydrate

Capsule Shell Components

Sunset Yellow (E110) FD
& C Blue 2 (E132)
Titanium Dioxide (E171)
Gelatin

Overprint Ink Constituients

Shellac
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C (at room temperature).

6.5 Nature and contents of container

PVC blisters (250 micron) backed by hard temper aluminium foil (20micron) containing 2, 4, 10, 14, 20, 28, 30, 50, 56, 60, 84, 100, 500 or 1000 capsules. The capsules are size 2 hard gelatin shells with orange body and blue cap overprinted CEPHR250 in black.

6.6 Special precautions for disposal

Not Applicable.

7 MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
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Watford
Herts
WD18 9SS
Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0167

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE

AUTHORISATION
28 September 1998

10 DATE OF REVISION OF THE TEXT

16/05/2017