NAME OF THE MEDICINAL PRODUCT
Cefradine, 500 mg, capsules, hard

QUALITATIVE AND QUANTITATIVE COMPOSITION

Cefradine, 500 mg, capsules, hard
Each hard capsule contains cefradine dihydrate equivalent to 500 mg of cefradine anhydrous.

Excipients
Cefradine, 500 mg, capsules, hard
Magnesium stearate, Empty hard gelatin capsule shell (Size ‘0’)

PHARMACEUTICAL FORM
Cefradine, 500 mg, capsules, hard
Hard gelatine, locking-type, size No. 2 capsule, evenly filled with free flowing granular off-white powder, odourless to a mild characteristic odour, light-blue opaque cap and body, printed “squibb” on both halves in white, with mild characteristic odour of gelatine or
A hard gelatine capsule (size No. 0) with a yellowish grey coloured body and a green coloured locked cap, printed with “Kefdrin 500” and ‘GW’ logo in white

CLINICAL INFORMATION
Indications
Cefradine is indicated for the treatment of infections of the urinary and respiratory tracts and of skin and soft tissues, these include:

• upper respiratory infections: pharyngitis, sinusitis, otitis media, tonsillitis, laryngo-tracheo bronchitis,
• lower respiratory infections : acute and chronic bronchitis, lobar and bronchopneumonia,
• urinary tract infections: cystitis, urethritis, pyelonephritis,
• skin and soft tissue infections: abscess, cellulitis, furunculosis, impetigo.
Cefradine has been shown to be effective in reducing the incidence of post-operative infections in patients undergoing surgical procedures associated with a high risk of infection. It is also of value where post-operative infections would be disastrous and where patients have a reduced host resistance to bacterial infection. Protection is best ensured by achieving adequate local tissue concentrations at the time contamination is likely to occur. Thus, cefradine should be administered immediately prior to surgery and treatment should be continued during the post-operative period.

Bacteriological studies to determine the causative organisms and their sensitivity to cefradine should be performed. Therapy may be instituted prior to receiving the results of the sensitivity test.

**Cefradine, parenteral formulations**

For the treatment of:

- bone and joint infections,
- septicemia and endocarditis.

Sterile cefradine for injection is indicated primarily for those patients unable to tolerate oral medication. It is also indicated for intravenous use either by direct injection or by intravenous infusion for the treatment of serious and life threatening infections.

**Dosage and Administration**

As with antibiotic treatment in general, therapy should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. In infections caused by group A beta-hemolytic streptococci, a minimum of 10 days of treatment is recommended to guard against the risk of rheumatic fever or glomerulo-nephritis. In the treatment of chronic urinary tract infections, frequent bacteriologic and clinical appraisal is necessary during therapy and may be necessary for several months afterwards. Persistent infections may require treatment for several weeks. Doses smaller than those indicated above should not be used.

**Cefradine, oral formulations**

In all patients, regardless of age and weight, doses up to 1 g every 6 hours may be given for severe or chronic infections.
Oral cefradine may be utilised following clinical improvement achieved with parenteral therapy for the continuation of therapy for persistent or severe infections where prolonged therapy is indicated. Cefradine may be given without regard to meals.

Cefradine, parenteral formulations
Parenteral therapy may be followed by oral cefradine either as capsules, tablets or oral suspension.

Route of Administration
Cefradine, oral formulations
For oral use

Adults
Cefradine, oral formulations
Respiratory tract infections (other than lobar pneumonia) and skin and soft tissue infections
The usual dose is 250 mg every 6 hours or 500 mg every 12 hours. Severe infections may require larger doses.

Lobar pneumonia
The usual dose is 500 mg every 6 hours or 1 g every 12 hours.

Uncomplicated urinary tract infections
The usual dose for uncomplicated infections is 500 mg every 12 hours. For more serious infections including prostatitis, 500 mg every 6 hours or 1 g every 12 hours is recommended.
Prolonged intensive therapy is recommended for prostatitis and epididymitis.

Children
Cefradine, oral formulations
In mild to moderately severe infections the usual daily dose is from 25 to 50 mg/kg/day administered in equally divided doses every 6 or 12 hours.
For otitis media due to *H. influenzae*, daily doses from 75 to 100 mg/kg administered in equally divided doses every 6 or 12 hours is recommended. The maximum dose should not exceed 4 g per day.

Doses for children should not exceed doses recommended for adults.

**Elderly**

There are no specific dosage recommendations or precautions for use in the elderly except, as with other drugs, to monitor those patients with impaired renal or hepatic function.

**Renal impairment**

*Patients not on dialysis*

The following dosage schedule based on a dosage of 500 mg every 6 hours and on creatinine clearance is suggested as a guideline. Further modification in the dosage schedule may be required because of the dosage selected and individual variation.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose</th>
<th>Time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20 ml/min</td>
<td>500 mg</td>
<td>6 hours</td>
</tr>
<tr>
<td>5-20 ml/min</td>
<td>250 mg</td>
<td>6 hours</td>
</tr>
<tr>
<td>&lt; 5 ml/min</td>
<td>250 mg</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

*Patients on chronic, intermittent haemodialysis*

- 250 mg start,
- 250 mg at 12 hours,
- 250 mg 36-48 hours (after start).

Children may require dosage modification proportional to their weight and severity of infection.

See also *Section Warnings and Precautions.*

**Hepatic impairment**

There are no relevant data available.

**Contraindications**

Cefradine is contraindicated in:
• Patients with known hypersensitivity to the cephalosporin antibiotics or to any component of the formulation.

Warnings and Precautions

Renal impairment
Use of cefradine in patients with renal dysfunction should be monitored intensively. A modified dosage schedule in patients with decreased renal function is necessary (see Section Dosage and Administration).

False positive reaction for glucose
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, but not with enzyme-based tests such as Clinistix or Diastix.

Prolonged use
As with all antibiotics, prolonged use may result in overgrowth of non-susceptible organisms.

Hypersensitivity phenomena
Hypersensitivity phenomena are more likely to occur in individuals who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever or urticaria (see Section Adverse Reactions).

History of colitis/gastrointestinal disorders
Cefradine should be used with caution in those patients with a known history of colitis/gastrointestinal disorders.

Lactose
This product contains Lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take these medicines.
Interactions

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

Loop diuretics
Loop diuretics may increase nephrotoxicity of cephalosporins.

Probenecid
Probenecid has been seen to raise serum concentrations of cefradine, by reducing renal clearance of the cephalosporins. Active drug substances of high molecular weight are incompatible with cephalosporins in parenteral mixtures.

Oral contraceptives
In common with other antibiotics, cefradine may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Warfarin
The concomitant use of cefradine with warfarin may result in increased INR and thereby increase the risk for bleeding. The mechanism of the interaction appears to involve alterations in intestinal flora that synthesise vitamin K. In a nested case-control study, there was an association between cephalosporin use in patients on warfarin therapy and an increased risk of bleeding. When possible, substitute an antibiotic with a low-risk profile for bleeding. If concomitant use is deemed necessary, more frequent monitoring of INR is recommended especially during initiation and discontinuation of the antibiotic.

Live typhoid vaccine
Cefradine, like other antibiotics with antibacterial activity against Salmonella typhi organisms, may interfere with the immunological response to the live typhoid vaccine. The appropriate period of time (24 hours or more) should elapse between the administration of the last dose of the antibiotic and the live typhoid vaccine.
Pregnancy and Lactation

**Fertility**
There are no relevant data available.

**Pregnancy**
Cefradine should not be used during pregnancy unless considered essential by the physician.
Although animal studies have not demonstrated any teratogenicity, safety in pregnancy has not been established.

**Lactation**
Cefradine should not be used during breast-feeding unless considered essential by the physician.
Cefradine is excreted in breast milk. *(see Section Warnings and Precautions)*.

**Ability to perform tasks that require judgement, motor or cognitive skills**
Since this medicine may cause dizziness, patients should be cautioned about operating hazardous machinery, including automobiles.

**Adverse Reactions**

**Clinical Trial Data**
Not relevant for this product.

**Post Marketing Data**
Adverse reactions are ranked under headings of frequency using the following convention:
- Very common $\geq 1/10$
- Common $\geq 1/100$ to $<1/10$
- Uncommon $\geq 1/1000$ to $<1/100$
- Rare $\geq 1/10000$ to $<1/1000$
- Very rare $<1/10000$
- Not known (cannot be estimated from the available data).
Infections and infestations
*Not known:* vaginal infection, candidiasis, pseudomembranous colitis

Blood and lymphatic system disorders
*Not known:* eosinophilia, leukopenia, neutropenia, Coombs direct test positive

Immune system disorders
*Not known:* hypersensitivity (see Skin and subcutaneous tissue disorders), anaphylactic reaction

Nervous system disorders
*Not known:* dizziness, headache

Gastrointestinal disorders
*Not known:* glossitis, dyspepsia, nausea, vomiting, diarrhoea, abdominal pain, gastrointestinal disorder

Hepatobiliary disorders
*Not known:* hepatitis, jaundice cholestatic, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood alkaline phosphatase increased

Renal and urinary disorders
*Not known:* tubulointerstitial nephritis, blood urea increased, blood creatinine increased

Skin and subcutaneous tissue disorders
*Not known:* erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, rash, pruritus

Musculoskeletal and connective tissue disorders
*Not known:* arthralgia

General disorders and administration site conditions
Not known: chest discomfort, oedema, pyrexia

**Overdosage**

There are no relevant data available.

**Clinical Pharmacology**

**Pharmacodynamics**

**Pharmacotherapeutic group**

Antiinfectives for systemic use, first generation cephalosporins

**ATC Code**

J01DB09

**Mechanism of Action and Pharmacodynamic effects**

Cefradine is a broad-spectrum, bactericidal antibiotic active against both Gram-positive and Gram-negative bacteria. It is also highly active against most strains of penicillinase-producing Staphylococci.

**Microbiology**

The following organisms have shown in vitro sensitivity to cefradine.

**Gram-positive**

Staphylococci (both penicillin sensitive and resistant strains), Streptococci, *Streptococcus pyogenes* (beta haemolytic) and *Streptococcus pneumoniae*.

**Gram-negative**

*Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Haemophilus influenzae*, *Shigella* spp., *Salmonella* spp. (including *Salmonella typhi*) and *Neisseria* 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.

**Pharmacokinetics**

**Absorption**

Cefradine, oral formulations
Cefradine is acid stable and is rapidly absorbed following oral administration in the fasting state. Following doses of 250 mg, 500 mg, and 1 g in normal adult volunteers, average peak serum levels of approximately 9, 16.5 and 24.2 μg/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.

Distribution

Measurable serum levels are present 6 hours after administration. 48 hours after the administration of 100 mg/kg/day of cefradine for treatment of otitis media, the average concentration of cefradine in middle ear exudate was 3.6 μg/ml. Cefradine does not cross the blood-brain barrier to any appreciable extent.

Cefradine is minimally bound to serum proteins (8 to 17%). Assays of bone and cardiac tissue (atrial appendage) obtained at surgery have shown that cefradine penetrates these tissues.

Elimination

Cefradine, oral formulations

Over 90% of the drug is excreted unchanged in the urine within 6 hours. Peak urine concentrations are approximately 1600 μg/ml following a 250 mg dose, 3200 μg/ml following a 500 mg dose, and 4000 μg/ml following a 1 g dose.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

There are no relevant data available.

PHARMACEUTICAL INFORMATION

Shelf-Life

As registered locally.

Storage

As registered locally.
Nature and Contents of Container
As registered locally.

Incompatibilities
There are no relevant data available.

Use and Handling
Cefradine, oral formulations
There are no special requirements for use or handling of these products.

Version number: 03
Version date: 05 July 2013