Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Velosef Syrup 250 mg/5ml, Powder for oral suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted contains 250 mg cefradine per 5 ml

Excipients: Each 5ml contains 2.8g of sucrose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for oral suspension.
White to pale cream, moderately coarse powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of infections of the urinary, respiratory and of the 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 postoperative infections in patients undergoing surgical procedures associated with a high risk of infection. It is also of value where postoperative infections would be disastrous and where patients have a reduced host resistance to bacterial infections. 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 continued during the postoperative period.

Bacteriology 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.

4.2 Posology and method of administration

Cefradine may be given without regard to meals.

<u>Adults and children over 10 years</u>:

For urinary tract infections the usual dose is 500mg twice daily; severe or chronic infections may require larger doses. Prolonged intensive therapy is needed for complications such as prostatitis and epididymitis. For respiratory tract infections and skin and soft tissue infections the usual dose is 250mg or 500mg four times daily or 500mg or 1g twice daily depending on the severity and site of infections.

Children under 10 years:

The usual dose is from 25 to 50mg/kg/day total, administered in equally divided doses every 6 or 12 hours. For otitis media daily doses from 75 to 100mg/kg administered in equally divided doses every 6 to 12 hours are recommended. The maximum dose should not exceed 4g per day.

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.

All patients, irrespective of age and weight

Larger doses (up to 1g four times daily) may be given for severe or chronic infections. Therapy should be continued for a minimum of 48-72 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. In infections caused by haemolytic strains of streptococci, a minimum of 10 days' treatment is recommended to guard against the risk of rheumatic fever or glomerulonephritis. In the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisal is necessary during therapy and may be necessary for several months afterwards. Persistent infections may require treatment for several weeks. Smaller doses than those indicated above should not be used. Doses for children should not exceed doses recommended for adults. As cefradine is available in both injectable and oral form, patients may be changed from the cefradine injectable to cefradine oral at the same dosage level.

Renal Impairment Dosage

Patients not on dialysis:

The following dosage schedule is suggested as a guideline based on a dosage of 500mg Q6H and on creatinine clearance. Further modification in the dosage schedule may be required because of the dosage selected and individual variation.

Creatinine Clearance	Dose	Time Interval	
more than	20 ml/min	500 mg	6 hours
	5-20 ml/min	250 mg	6 hours
less than	5 ml/min	250 mg	12 hours

Patients on chronic, intermittent haemodialysis:

250 mg	At start of haemodialysis
250 mg	6-12 hours after start
250 mg	36-48 hours after start
250 mg	At start of next haemodialysis if >30 hours after previous dose.

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

4.3 Contraindications

Patients with known hypersensitivity to the cephalosporin antibiotics or any component of the formulation.

Patients suffering from porphyria.

4.4 Special warnings and precautions for use

There is evidence of partial cross-allergenicity between the 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).

After treatment with 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*.

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

Renal Impairment Dosage

In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be performed since cefradine accumulates in the serum and tissues unless dosage is suitably reduced. *(See Dosage).*

4.5 Interaction with other medicinal products and other forms of interaction

Use of the Cephalosporins concomitantly with other medications potentially nephrotoxic may increase the risk of renal dysfunction. Loop diuretics may increase the nephrotoxicity of cephalosporins.

Concurrent use of probenecid delays excretion of cefradine.

4.6 Pregnancy and lactation

The anti infective should not be used during pregnancy unless considered essential by the physician. Animal studies have not demonstrated any teratogenicity. 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 this medicine may cause dizziness, patients should be cautioned about operating hazardous machinery, including automobiles.

4.8 Undesirable effects

Limited essentially to gastro-intestinal disturbances and on occasion to hypersensitivity phenomena. The latter are more likely to occur in individuals who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever or urticaria. The majority of reported side-effects have been mild and are rare, and include glossitis, heartburn, dizziness, tightness in the chest, headache, nausea, vomiting, diarrhoea, abdominal pain, vaginitis, candidal overgrowth. Skin and hypersensitivity reactions include urticaria, pruritus, skin rashes, fever, arthralgia and oedema.

As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens Johnson Syndrome, anaphylaxis and toxic epidermal necrolysis. Also, mild transient eosinophilia, leucopenia and neutropenia, positive direct Coombs tests and pseudomembraneous colitis have been reported.

Elevations of BUN and serum creatinine and reversible intestinal nephritis have been reported. Transient hepatitis and cholestatic jaundice have been reported very rarely. Elevations of ALT, AST, total bilirubin and alkaline phosphatase have been observed.

4.9 Overdose

Signs and symptoms may include nausea, vomiting, diarrhoea. Treat symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions:

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.

5.2 Pharmacokinetic properties

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, and is well absorbed.

5.3 Preclinical safety data

No further relevant data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid
Guar gum
Methylcellulose
Blood orange flavour
Cinnamon flavour
Tutti frutti flavour
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Unopened: 4 years
Shelf –life following reconstitution: 14 days if refrigerated (2-8°C)/7 days if stored below 25°C.

6.4 Special precautions for storage

Do not store above 25°C.

After reconstitution discard unused syrup after 14 days if refrigerated (2-8°C), or after 7 days if stored below 25°C.

6.5 Nature and contents of container

Amber, Type III glass bottles of 100 ml with metal screw caps or plastic child resistant closures, containing 60 g powder for reconstitution.

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

Bottles:
1. Loosen powder
2. Add 60 ml of water to prepare 100 ml syrup
3. Shake vigorously

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Ltd
Swords
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 0002/014/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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