

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Velosef for Injection 1 g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1g of cefradine.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
A white to off-white free-flowing powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The treatment of infections of the urinary, respiratory tracts and of the skin and soft tissues, bones and joints; also septicaemia and endocarditis. 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.

Velosef 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 post operative infection 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, Velosef should be administered immediately prior to surgery and continued during the postoperative period.

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

Sterile Velosef 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.

4.2 Posology and method of administration

Intramuscular or intravenous injection and intravenous infusion.

Adults and children over 10 years:

Treatment: The usual dose range of Velosef for injection is 2-4g daily in four equally divided doses. This may be increased up to 8g a day for severe infections, e.g. septicaemia and endocarditis. For the majority of infections, the

usual dose is 500 mg q.i.d. (four times a day) in equally spaced doses; severe or chronic infections may require larger doses. Prolonged intensive therapy is needed for complications such as prostatitis and epididymitis. Patients who are severely ill and who require high serum levels of Velosef for treating their infections should be started on intravenous therapy.

Limited experience indicates that intraperitoneal administration of Velosef may be effective after surgery in cases of peritonitis where a surgical drainage system has been established.

Surgical Prophylaxis:

The recommended dose for surgical prophylaxis is a single, pre operative 1-2g IM or IV dose. Subsequent parenteral or oral doses can be administered as appropriate.

Children under 10 years:

The usual dose is 50-100 mg/kg/day total given in four equally divided doses. More serious illnesses (e.g. typhoid fever) may require 200-300 mg/kg/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, regardless of age and weight:

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 of 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 Velosef is available in both injectable and oral form, patients may be changed from the Velosef injectable to Velosef 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 500 mg Q6H and on creatinine clearance. Further modification in the dosage schedule may be required because of the dosage selected and individual variation.

<u>Creatinine Clearance</u>	<u>Dose</u>	<u>Time Interval</u>
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.

Further modification of the dosage schedule may be necessary in children.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Renal Impairment Dosage: Use of this antibiotic in patients with renal dysfunction should be monitored intensively. A modified dosage schedule in patients with decreased renal function is necessary (See Dosage).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 penicillins. There have been instances of patients who have had reactions to both drug classes (including anaphylaxis).

Concurrent uses of probenecid delays excretion of cefradine. Active drug substances of high molecular weight are incompatible with cephalosporins in parenteral mixtures.

4.6 Pregnancy and lactation

Although animal studies have not demonstrated any teratogenicity, safety in pregnancy has not been established. Therefore this antibiotic should not be used during pregnancy or lactation unless considered essential by the physician. 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

None known.

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, nausea, vomiting, diarrhoea, abdominal pain, vaginitis, candidal overgrowth. Skin and hypersensitivity reactions include urticaria, skin rashes, joint pains, 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 pseudomembranous colitis have been reported.

Elevations of blood urea nitrogen (BUN) and serum creatinine have been reported. Transient hepatitis and cholestatic jaundice have been reported very rarely. Elevations of alanine amino-transferase (ALT), aspartate amino-transferase (AST), total bilirubin and alkaline phosphatase have been observed.

Injection:

As with other parenterally administered antibiotics, transient pain may be experienced at the injection site, but is seldom the cause for discontinuing treatment. Thrombophlebitis has been reported following intravenous injection.

Since sterile abscesses have been reported following accidental subcutaneous injection, the preparation should be administered by deep intramuscular injection.

4.9 Overdose

None known.

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.

Human Pharmacology: Following intramuscular administration of a single 0.5g dose of cefradine to normal volunteers, the average peak serum concentration was 8.41 microgram/ml with the time to peak concentration being 0.93 hours. The serum half-life averaged 1.25 hours. A single 1g intravenous dose resulted in serum concentrations of 86 microgram/ml at 5 minutes and 12 microgram/ml at 1 hour; these concentrations declined to 1 microgram/ml at 4 hours. Continuous infusion of 500 mg per hour into a 70 kg man maintained a concentration of about 21.4 microgram/ml cefradine activity; this study showed that a serum concentration of approximately 3 microgram/ml can be obtained for each milligram of cefradine administered per kg of body weight per hour of infusion.

Cefradine is excreted unchanged in the urine. The kidneys excrete 57% to 80% of an intramuscular dose in the first six hours; this results in a high urine concentration, e.g. 880 micrograms/ml of urine after a 500 mg intramuscular dose. Probenecid slows tubular secretion and almost doubles peak serum concentration.

Assays of bone obtained at surgery have shown that cefradine penetrates bone tissue.

5.3 Preclinical safety data

No further relevant data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Storage before reconstitution: Do not store above 25°C.

Storage after reconstitution: Solutions for IM or IV Injection should be used immediately (see also section 6.6 below).

6.5 Nature and contents of container

1 g Type III Ph. Eur. clear glass vial with siliconed, butyl rubber stopper and aluminium seal: single vial pack.

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

For single use only. Discard any remaining contents.

Reconstitution

For intramuscular use: Aseptically add sterile water for injections or 0.9% sodium chloride injection according to the following table:

Single dose*	Volume of diluent
Vial size	to be added
1 g	4.0ml

* The preparation contains no bactericide and is intended for single use only and not multiple dose use. Shake to effect solution and withdraw the entire contents.

For intravenous use: Cefradine for injection may be administered by direct intravenous injection or by infusion. A 3 microgram/ml serum concentration can be maintained for each milligram of cefradine per kg body weight per hour of infusion.

For direct intravenous administration:
 Suitable reconstitution solutions for intravenous injection are:
 Sterile Water for Injections;
 5% Dextrose Injection;
 0.9% Sodium Chloride Injection.

Aseptically add 10 ml of the reconstitution solution to the 1 g vial. Shake to effect solution and withdraw the entire contents. The solution may be slowly injected directly into a vein over a 3 to 5 minute period.

For continuous or intermittent intravenous infusion:
 Suitable reconstitution solutions for intravenous infusion are:
 Sterile water for Injections (50mg/ml cefradine solutions are approximately isotonic);
 5% or 10% Dextrose Injection;
 0.9% Sodium Chloride Injection;
 Sodium Lactate Injection (M/6 sodium lactate);
 Dextrose and Sodium Chloride Injection;
 Lactated Ringer's Injection; Ringer's Injection;
 5% Dextrose in lactated Ringer's Injection;
 5% Dextrose in Ringer's Injection.

Aseptically add 10 ml of the reconstitution solution to the 1 g vial and shake to effect solution. Aseptically transfer the

entire contents to the IV infusion diluent.

Reconstitution solutions may vary in colour from light to straw yellow; however, this does not affect the potency.

Protect solutions of cefradine from concentrated light or direct sunlight.

Stability

For solutions for intramuscular and direct intravenous injection, chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (25°C) and 12 hours when stored in a refrigerator at 2° - 8°C.

For solutions for intravenous infusion, using Water for Injection, Glucose 5% or Sodium Chloride 0.9%, for concentrations of 10mg/ml (1%), chemical and physical in-use stability has been demonstrated for 12 hours at room temperature (25°C) and 1 week when stored in a refrigerator at 2°-8°C and, for concentrations of 50 mg/ml (5%), chemical and physical in-use stability has been demonstrated for 10 hours at room temperature (25°C) or 48 hours at 2°-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

For prolonged infusions, replace the infusion every 10 hours with a freshly-prepared solution.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Limited
Swords
County Dublin

8 MARKETING AUTHORISATION NUMBER

PA 2/14/10

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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January 2006