PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

Ceftriaxone 250 Unimed (Injection)

Ceftriaxone 1 g Unimed (Injection)

COMPOSITION:

Ceftriaxone 250 Unimed

Each vial contains:

Ceftriaxone sodium (Sterile)

equivalent to ceftriaxone 250 mg

Ceftriaxone 1 g Unimed

Each vial contains:

Ceftriaxone sodium (Sterile)

equivalent to ceftriaxone 1 g

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1. Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Ceftriaxone is a broad-spectrum cephalosporin with a long plasma elimination half-life of approximately 8 hours in normal adults.

Antimicrobial Profile

(In vitro sensitivity does not necessarily imply *in vivo* efficacy).

The *in vitro* spectrum of activity of ceftriaxone encompasses:

(a) Gram-positive organisms:

Streptococcus pneumoniae, *Streptococcus* Group A (including *Streptococcus pyogenes), Streptococcus* Group B (including *Streptococcus agalactiae), Streptococcus viridans, Streptococcus bovis* (Group D), *Staphylococcus aureus* (methicillin sensitive), *Peptostreptococcus* sp. and *Clostridium* sp.

Note: Methicillin-resistant *Staphylococcus* spp. are resistant to ceftriaxone. *Enterococcus faecalis, Enterococcus faecium* and *Listeria monocytogenes* are resistant.

(b) Gram-negative organisms:

Haemophilus influenzae (including ampicillin-resistant strains), *Haemophilus parainfluenzae, Neisseria meningitidis, Neisseria gonorrhoeae* (including penicillin-resistant strains), *Escherichia coli, Klebsiella* species**, *Enterobacter* species*, *Serratia marcescens*, *Citrobacter* species, *Proteus mirabilis*, Indole-positive *Proteus* (including *Morganella morganii*), *Salmonella* species, *Shigella* species, *Yersinia pestis* and *Treponema pallidum* (in animal experiments).

*Some isolates of these species are resistant to ceftriaxone, due to the production of the chromosomally encoded ß-lactamases.

**Some isolates of these species are resistant due to production of extended spectrum plasmid mediated ß-lactamase.

(c) Organisms which are only partially sensitive to ceftriaxone *in vitro*. *Staphylococcus epidermidis, Pseudomonas aeruginosa, Acinetobacter* sp. and *Bacteroides* sp. Ceftriaxone is stable in relation to the majority of beta-lactamases.

The following organisms are resistant:

Ureaplasma urealyticum, Mycoplasma sp., Mycobacterium sp., fungi.

It is essential to note that recommended media (free from inhibitory substances especially thymidine and thymine) and methods must be used for satisfactory sensitivity testing.

Pharmacokinetics

The maximum plasma concentration after a single IM dose of 1.0 g is about 81 mg/l and is reached in 2-3 hours after the dose. The area under the plasma concentration-time curve after IM administration is equivalent to that after IV administration of an equivalent dose, indicating 100% bioavailability of intramuscularly administered ceftriaxone.

On intravenous administration, ceftriaxone diffuses into the tissue fluid, where, if it is given in the recommended dosage range, bactericidal concentrations lasting 24 hours may be maintained. Ceftriaxone is reversibly bound to albumin, and the binding decreases with the increase in concentration e.g. from 95% binding at plasma concentrations of < 100 mg/l to 85% binding at 300 mg/l. Owing to the lower albumin content, the proportion of free ceftriaxone in interstitial fluid is correspondingly higher than in plasma.

The volume of distribution of ceftriaxone is 7-12 l. After a dose of 1-2 g, concentrations above the minimal inhibitory concentrations of most pathogens responsible for infection are detected for more than 24 hours in the following tissues or body fluids: lung, heart, biliary tract/liver, tonsil, middle ear and nasal mucosa, bone; and cerebral, pleural, prostatic and synovial fluids.

In healthy, young adult volunteers the total plasma clearance is 10-22 ml/min. The renal clearance is 5-12 ml/min. 50-60% of ceftriaxone is excreted unchanged in the urine, while 40 - 50% is excreted unchanged in the bile. The elimination half life in adults is about eight hours.

The substance is largely inactivated in the faeces due to metabolism by intestinal flora.

The mean plasma elimination half life is 8 hours in healthy, young adult volunteers. In neonates, urinary recovery accounts for about 70% of the dose. In infants aged less than eight

days and in elderly persons aged over 75 years, the average elimination half life is usually 2-3 times that in the young adult group.

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered and the elimination half life is only slightly increased. If kidney function alone is impaired, biliary elimination of ceftriaxone is increased; if liver function alone is impaired, renal elimination is increased.

In meningitis patients, administration of 50 mg per kg bodymass leads within 2-24 hours to cerebro spinal fluid concentrations several times as high as the minimum *in vitro* inhibitory concentrations required for the most common causative organisms of meningitis.

INDICATIONS:

Infections caused by pathogens sensitive to ceftriaxone such as

-sepsis

-meningitis in neonates and infants

-perioperative prophylaxis of infections

-renal and urinary tract infections

-respiratory tract infections, particularly pneumonia, and ear, nose and throat infections.

-infections of the bones, joints, soft tissue, skin and of wounds.

-abdominal infections (peritonitis, infections of the biliary tract).

-uncomplicated gonorrhoea

CONTRA-INDICATIONS:

Allergy to cephalosporins. In patients hypersensitive to penicillin, the possibility of allergic cross reactions should be borne in mind. (see **Warnings**)

Hyperbilirubinnemic neonates, especially prematures, should not be treated with **Ceftriaxone 250 and 1 g Unimed**. *In vitro* studies have shown that ceftriaxone can displace bilirubin from its binding to serum albumin and bilirubin encephalopathy can possibly develop in the patients.

Ceftriaxone 250 and 1 g Unimed should not be administered concurrently with calcium-containing solutions or products in newborns because of the risk of precipitation of ceftriaxone-calcium salt (see **Warnings**).

WARNINGS:

Before therapy with **Ceftriaxone 250 and 1 g Unimed** is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other medicines. About 10% of penicillin-sensitive patients may also be allergic to cephalosporins although the true incidence is uncertain. Great care should be taken if **Ceftriaxone 250 and 1 g Unimed** is to be given to such patients.

Ceftriaxone 250 and 1 g Unimed must not be mixed or administered simultaneously with calcium-containing solutions or products, even via different infusion lines. Calcium-containing solutions or products must not be administered within 48 hours of last administration of Ceftriaxone 250 and 1 g Unimed.

Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration of ceftriaxone and calcium-containing solutions differed (see Contra-indications and Side-effects).

Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute Ceftriaxone 250 and 1 g Unimed. Particulate formation can result.

Interaction with calcium-containing products:

There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, **Ceftriaxone 250 and 1 g Unimed** and calcium-containing solutions, including calcium-containing infusions such as parenteral

nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone (**Ceftriaxone 250 and 1 g Unimed**) and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see **Contra-indications** and **Dosage and directions for use**).

No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

INTERACTIONS:

Interactions of **Ceftriaxone 250 and 1 g Unimed** with calcium-containing products: (See **Warnings**)

No impairment of renal function has been observed after concurrent administration of large doses of **Ceftriaxone 250 and 1 g Unimed** and potent diuretics (e.g. furosemide). There is no evidence that **Ceftriaxone 250 and 1 g Unimed** increases renal toxicity of aminoglycosides. No effects similar to that of disulfiram has been demonstrated after administration of alcohol with **Ceftriaxone 250 and 1 g Unimed**. **Ceftriaxone 250 and 1 g Unimed** does not contain an N-methyl-thiotetrazole moiety associated with possible ethanol intolerance and bleeding problems. In an *in vitro* study antagonistic effects have been observed with the combination of chloramphenicol and **Ceftriaxone 250 and 1 g Unimed**. There may be antagonism between **Ceftriaxone 250 and 1 g Unimed** and bacteriostatic antibacterial agents. **Ceftriaxone 250 and 1 g Unimed** may interfere with the Jaffe method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function. In patients treated with ceftriaxone the Coombs' test may become false positive. **Ceftriaxone 250 and 1 g Unimed** may result in false positive tests for galactosemia.

Likewise, nonenzymatic methods for the glucose determination in urine may give false positive results. For this reason urine glucose determination during therapy with **Ceftriaxone 250 and 1 g Unimed** should be done enzymatically.

PREGNANCY AND LACTATION:

Safety in human pregnancy has not been established. As ceftriaxone is excreted in the breast milk at low concentrations, caution is advised in nursing mothers.

DOSAGE AND DIRECTIONS FOR USE:

Standard dosage

Adults and children over twelve: 1-2g ceftriaxone once daily (every 24 hours).

In severe infections and in cases in which the pathogens are only moderately sensitive to ceftriaxone, the daily dosage may be increased to 4 g administered daily.

Infants and young children may receive from 20-80 mg per kg body-mass daily; depending on the severity of the infection, usually 12-24 hourly.

In cases of premature babies, the daily dosage should not exceed 50 mg per kg body mass on account of the immaturity of the infant's enzyme systems.

Elderly patients: The dosages recommended for adults require no modification in the case of geriatric patients.

Duration of therapy: The duration of therapy varies according to the course of the disease. Administration of ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Special dosage instructions: Meningitis: In bacterial meningitis in infants and children, treatment begins with doses of 100 mg per kg (not to exceed 4 g) once daily. As soon as the causative organism has been identified and its sensitivity determined, the dosage can be reduced accordingly.

Gonorrhoea: For the treatment of gonorrhoea (penicillinase-producing and non-penicillinase-producing strains), a single IM dose of 250 mg ceftriaxone is recommended.

Perioperative prophylaxis**:** A single dose of 1-2 g ceftriaxone administered 30-90 minutes prior to surgery. In colorectal surgery, concurrent (but separate) administration of ceftriaxone with a 5-nitroimidazole, e.g. ornidazole, has proven effective.

Impaired renal and hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of ceftriaxone provided that the hepatic function is intact.

In case of severe renal failure (creatinine clearance < 10 ml/min) the ceftriaxone dosage should not exceed 2 g daily. In patients with liver damage, there is no need for the dosage to be reduced provided renal function is intact.

In cases of concomitant severe renal and hepatic dysfunction, the plasma concentrations of ceftriaxone should be determined at regular intervals. In patients undergoing dialysis no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced.

Intramuscular Injection

For IM injection, **Ceftriaxone 250 Unimed** should be dissolved in 2 ml and **Ceftriaxone 1 g Unimed** in 3,5 ml of water for injection. **Ceftriaxone 250 and 1 g Unimed** dissolved in a 1% lidocaine solution can reduce pain at the site of injection. If 1% lidocaine is used, **Ceftriaxone 250 Unimed** should be dissolved in 0,9 ml and **Ceftriaxone 1 g Unimed** in 3,6 ml of 1% lidocaine solution. **Ceftriaxone 250 and 1 g Unimed** must be injected well within the body of a relatively large muscle. It is recommended that not more than 1g be injected on either side. Reconstitution with 1% lidocaine (without adrenaline) has no effect on the absorption or the elimination of Ceftriaxone. The lidocaine solution must never be administered intravenously.

Intravenous Injection

For IV injection, **Ceftriaxone 250 Unimed** is dissolved in 5 ml water for injection and **Ceftriaxone 1 g Unimed** dissolved in 10 ml water for injection. The intravenous administration should be given over two to four minutes.

Intravenous infusion

The infusion should be given over a period of at least 30 minutes. For IV infusion, 2 g of **Ceftriaxone 250 and 1 g Unimed** is dissolved in approximately 40 ml of sterile water for injection. **Ceftriaxone 250 and 1 g Unimed** solutions should not be mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, owing to possible incompatibility.

Incompatibilities:

Do not use diluents containing calcium, such as Ringer's solution or Hartman's solution to reconstitute **Ceftriaxone 250 and 1 g Unimed**. Particulate formation can result. **Ceftriaxone 250 and 1 g Unimed** and calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age even via different infusion lines at different sites (see **Contra-indications** and **Warnings**).

Ceftriaxone is incompatible with amsacrine, vancomycin and fluconazole and aminoglycosides.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side effects

Blood and the lymphatic system disorders

Frequent: Eosinophilia.

Less frequent: Haematoma or bleeding.

Rare: Thrombocytopenia, neutropenia, leukopenia, granulocytopenia and haemolytic anaemia.

Isolated cases of agranulocytosis (<500/mm^3) have been reported, most of them following total doses of 20 g or more.

Immune system disorders

Rare: Anaphylactic or anaphylactoid reactions. Anaphylactic shock.

Nervous system disorders

Frequent: Headache.

Less frequent: Dizziness.

Gastro-intestinal disorders

Frequent: Loose stools/diarrhoea, nausea, vomiting, stomatitis, glossitis.

Less frequent: Pseudomembranous colitis.

Hepato-biliary disorders

Less frequent: Increase in liver enzymes; hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders

Less frequent: Allergic dermatitis, pruritus, urticaria, oedema.

Rare: Exanthema, erythema multiforme.

Renal and urinary disorders

Rare: Oliguria, increase in serum creatinine. Nephrotoxicity has been reported. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

Reproductive system and breast disorders

Less frequent: Mycosis of the genital tract.

General disorders and administration site conditions

Less frequent: Inflammatory reactions in the vein wall may occur after IV administration. Fever and shivering.

Special precautions

Anaphylactic shock requires immediate counter measures.

Acute renal tubular necrosis has followed excessive dosage and has also been associated with the use of **Ceftriaxone 250 and 1 g Unimed** in older patients or those with pre-existing renal impairment, or with the concomitant administration of nephrotoxic agents such as aminoglycosides.

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

Pseudomembranous colitis has been reported with **Ceftriaxone 250 and 1 g Unimed**. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea

subsequent to the administration of **Ceftriaxone 250 and 1 g Unimed**. Superinfections with non-susceptible micro-organisms may occur.

Inflammatory reactions in the vein wall may occur after IV administration. These may be minimised by slow (2-4 minutes) injection of **Ceftriaxone 250 and 1 g Unimed**. Intramuscular injection without lidocaine solution is painful. Shadows which have been mistaken for gallstones have been detected by sonograms of the gallbladder, usually following higher than the standard recommended dose. These shadows are, however, precipitates of calcium ceftriaxone which disappear on completion or discontinuation of ceftriaxone therapy.

In less frequent cases, these findings have been associated with symptoms. In symptomatic cases, conservative non-surgical management is recommended. Discontinuation of **Ceftriaxone 250 and 1 g Unimed** treatment in symptomatic cases should be at the discretion of the clinician. During prolonged treatment the blood profile should be checked at regular intervals. Renal and haemotological status should be monitored especially during prolonged and high dose therapy. There is a potential risk associated with concomitant use of **Ceftriaxone 250 and 1 g Unimed** with calcium-containing solutions or products. (See **Warnings**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the case of overdosage, plasma concentration would not be reduced by haemodialysis or peritoneal dialysis. Treatment is supportive and symptomatic.

IDENTIFICATION:

Ceftriaxone 250 Unimed*:*

White to yellowish orange, crystalline powder in 5 ml clear glass USP type I, moulded vials with blue flip-off seals.

Ceftriaxone 1 g Unimed*:*

White to yellowish orange, crystalline powder in 15 ml clear glass USP type I, moulded vials with blue flip-off seals.

On constitution a pale yellow to reddish orange clear solution is obtained.

PRESENTATION:

Ceftriaxone 250 Unimed: Cartons containing 1 clear glass USP Type I vial.

Ceftriaxone 1 g Unimed: Cartons containing 1 clear glass USP Type I vial.

STORAGE INSTRUCTIONS:

Store at or below 25°C, protected from light and moisture. Do not freeze.

Reconstituted solution to be stored in original vials.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

Ceftriaxone 250 Unimed: 34/20.1.1/0318

Ceftriaxone 1 g Unimed: 34/20.1.1/0319

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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