PROPOSED AMENDED PROFESSIONAL INFORMATION (Clean copy)

SCHEDULING STATUS

S4

PROPRIETARY NAMES (and dosage forms)

MEDAZINE 1 g INJECTION (Powder for injection)

MEDAZINE 2 g INJECTION (Powder for injection)

COMPOSITION

MEDAZINE 1 g INJECTION

Each vial contains cefoxitin sodium equivalent to cefoxitin 1 g.

MEDAZINE 2 g INJECTION

Each vial contains cefoxitin sodium equivalent to cefoxitin 2 g.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Cefoxitin sodium is a second generation cephalosporin. It is a bactericidal broad spectrum semi-synthetic β-lactam antibiotic for parenteral administration.

This class of β-lactam antibiotics, the cephamycins, is characterised by a 7-alpha-methoxy-β-lactam. The methoxy group is responsible for the property of resistance to degradation by bacterial β-lactamases (penicillinases and cephalosporinases).

Microbiology:

Cefoxitin has a broad spectrum of antibacterial activity against Gram-negative and Gram-positive pathogens, both aerobic and anaerobic. Cefoxitin is bactericidal and inhibits bacterial cell wall synthesis. Cefoxitin is not active against *Pseudomonas spp.,* most strains of enterococci and many strains of *Enterobacter cloacae*, methicillin-resistant staphylococci and *Listeria monocytogenes.*

Pharmacokinetics:

Cefoxitin, administered parenterally, produces high serum and urine concentrations. It is excreted

almost completely unchanged as active Cefoxitin by the kidneys, and has a mean terminal serum half-life of approximately one hour. Cefoxitin passes rapidly into body fluids such as bile, pleural and ascitic fluids, bronchial and urogenital tissue and bone.

Probenecid slows tubular excretion and increases and prolongs blood levels.

Even in the presence of inflammation, Cefoxitin sodium penetrates the blood brain barrier poorly.

In the cerebrospinal fluid, clinically effective levels have not been shown.

INDICATIONS

Treatment:

MEDAZINE INJECTION is indicated for the treatment of the infections due to susceptible organisms.

Prophylaxis:

MEDAZINE INJECTION is indicated for the prevention of certain post-operative infections in patients undergoing surgical procedures that are classified as contaminated, potentially contaminated, or where the occurrence of post-operative infection could be especially serious.

CONTRA-INDICATIONS

Hypersensitivity to cefoxitin or cephalosporins, pencillins or any other betalactam class of antibiotics, or any of the other ingredients of the product.

Porphyria.

WARNINGS

Should be used with caution in:

- Persons with a history of gastrointestinal disease especially colitis.
- Children younger than 2 years, as safety and efficacy have not been established in this age group.

The diagnosis of pseudomembranous colitis caused by *Clostridium difficile* must be considered in patients who develop diarrhoea with the use of **MEDAZINE INJECTION**. This may be life-threatening and appropriate measures should be taken, including discontinuation of **MEDAZINE INJECTION**.

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and the other β-lactam antibiotics, penicillins and cephalosporins.

INTERACTIONS

Probenecid slows tubular excretion of cefoxitin and increases serum levels thereof.

Enhanced nephrotoxicity with a loop diuretic (e.g. furosemide) may occur.

Aminoglycosides (e.g. gentamicin) and other potentially nephrotoxic medicines should be used with caution with **MEDAZINE INJECTION**.

Possible antagonism between **MEDAZINE INJECTION** and bacteriostatic antibacterial agents may also occur.

MEDAZINE INJECTION may antagonise piperacillin and other β-lactam antibiotics.

PREGNANCY AND LACTATION

The safety of **MEDAZINE INJECTION** in pregnancy and lactation has not been established.

Cefoxitin is excreted in breast milk.

DOSAGE AND DIRECTIONS FOR USE

MEDAZINE INJECTION may be administered intravenously or intramuscularly.

The dose depends on the susceptibility of the infecting organism, the severity of the infection and the age, weight and renal function of the patient.

Treatment Dosage

Adults

The usual adult dosage is 1 g or 2 g of **MEDAZINE INJECTION** every 8 hours with a maximum of 3 g every 6 hours in very severe infections.

Dosage in Renal Insufficiency

In adults with renal insufficiency, an initial loading dose of 1 - 2 g may be given. After a loading dose, the recommendations for maintenance dosage may be used as a guide.

In the patients undergoing haemodialysis, the loading dose of 1 - 2 g should be given after each haemodialysis, and the maintenance dose should be given as indicated in the table below.

MAINTENANCE DOSAGE OF MEDAZINE INJECTION IN ADULTS WITH REDUCED RENAL FUNCTION		
CREATININE CLEARANCE (ml/min)	DOSE	FREQUENCY
50 – 30	1 – 2 g	Every 8 – 12h
29 – 10	1 – 2 g	Every 12 – 24h

9 – 5	0,5 – 1 g	Every 12 – 24h
< 5	0,5 – 1 g	Every 24 – 48h

Uncomplicated Gonorrhoea

For single dose therapy of uncomplicated gonorrhoea, including that caused by penicillinase-producing strains, the recommended dose is 2 g of **MEDAZINE INJECTION** intramuscularly given with 1 g of probenecid by mouth (at the same time or up to 1 hour before).

Children (2 years or older): 20 - 40 mg/kg every 6 hours or every 8 hours.

In severe infections the total daily dosage may be increased to a maximum of 200 mg/kg but not to exceed 12 g per day.

The use in children under 2 years of age is not recommended.

In children with renal insufficiency the dose frequency should be reduced as indicated for adults.

MEDAZINE INJECTION is not indicated for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

In children with renal insufficiency the dosage frequency should be reduced as indicated for adults.

Prophylaxis Dosage

For prophylactic use in surgery the following dosage is recommended:

Adults

The first dose of 2 g is administered intravenously ½ to 1 hour pre-operatively. The second and third doses should be given as 2 g intravenously or intramuscularly at 6 hour intervals.

2 years of age and over Children

In case of infants and children, 30 - 40 mg/kg doses may be given at times designated above.

Prophylactic therapy should not extend beyond 24 hours.

Administration

Intravenous Administration

Reconstitute **MEDAZINE 1 g INJECTION** with 10 ml of Sterile Water for injection. Reconstitute **MEDAZINE 2 g INJECTION** with 10 to 20 ml of Sterile Water for injection. Shake to dissolve and then withdraw entire contents of vial into syringe.

For direct intravenous injection, **MEDAZINE INJECTION** may be slowly injected into the vein over a period of 3 to 5 minutes or may be given through the tubing when the patient is receiving parenteral solutions.

An intermittent intravenous infusion of **MEDAZINE INJECTION** may be employed when large amounts of fluid are to be given. However, during infusion of the solution containing **MEDAZINE INJECTION**, it may be advisable temporarily to discontinue administration of any other infusion solution at the same site (by using an appropriate I.V. infusion set).

Intramuscular Administration

Reconstitute **MEDAZINE 1 g INJECTION** with 2 ml of Sterile Water for Injection, or 0,5 % or 1 % lidocaine hydrochloride (without epinephrine, adrenaline) solution. Reconstitute **MEDAZINE 2 g INJECTION** with 4 ml of Sterile Water for Injection, or 0,5 % or 1 % lidocaine hydrochloride (without epinephrine, adrenaline) solution.

MEDAZINE INJECTION is given by deep injection into a large muscle mass. Avoid injection into a blood vessel.

Compatibility and Stability

MEDAZINE INJECTION is compatible with the following solutions:

0,9 % Sodium Chloride

5 % or 10 % Dextrose

5 % Dextrose and 0,9 % Sodium Chloride

5 % Dextrose Injection with 0,2 % or 0,45 % Sodium chloride

5 % Dextrose in Lactated Ringer's

5 % or 10 % Invert Sugar in Water

5 % Sodium Bicarbonate Injection

Sodium Lactate Solution

Mannitol 10 %

*Reconstituted **MEDAZINE INJECTION** diluted in the above diluents is stable for 24 hours under refrigeration (2 - 8 °C) and at room temperature (25 °C).

MEDAZINE INJECTION has been shown to be chemically and visually compatible with aminoglycosides such as amikacin, gentamycin, kanamycin and tobramycin when admixed in 200 ml of 0,9 % sodium chloride or 5 % dextrose in water.

***MEDAZINE INJECTION**, as constituted with:

Sterile Water for Injection

0.5 % and 1 % lidocaine HCl

maintains satisfactory potency for 24 hours under refrigeration (2 - 8°C) and at room temperature (25 °C).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Immune system disorders:

Less frequent: Hypersensitive reactions, anaphylaxis, eosonophilia.

Ear and labyrinth disorders:

Less frequent: Hearing loss.

General disorders and administrative site conditions:

Less frequent:

Thrombophlebitis has occurred with intravenous administration. Pain, induration and tenderness after intramuscular injections have been reported.

Skin and subcutaneous tissue disorders:

Less frequent:

Maculopapular rash (including exfoliative dermatitis), urticaria, pruritus, fever, toxic epidermal necrolysis, erythma multiforme, Stevens Johnsons Syndrome.

Cardiac disorders:

The following side-effect has been reported and its frequency is unknown:

Hypotension

Gastrointestinal disorders:

Frequent:

Nausea, vomiting and diarrhoea have been reported.

Less frequent:

Symptoms of pseudomembranous colitis can appear during or after **MEDAZINE INJECTION** treatment.

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

Blood and the lymphatic system disorders:

Frequent:

Transient leukopaenia, neutropaenia, thrombocytopaenia

Less frequent:

Haemolytic anaemia, hypoprothrombinaemia.

The following side-effects have been reported and their frequencies are unknown:

Agranulocytosis, Granulocytopaenia, aplastic anaemia, bone marrow depression, pancytopenia.

Investigations:

The following side-effect has been reported and its frequency is unknown:

Some individuals, particularly those with uraemia, may develop positive direct Coombs tests during therapy with **MEDAZINE INJECTION**.

Hepato-biliary disorders:

The following side-effects have been reported and their frequencies are unknown:

Transient elevations in AST, ALT, serum LDH, and serum alkaline phosphatase and jaundice have been reported.

Renal and urinary disorders:

Less frequent: Renal dysfunction.

The following side-effect has been reported and its frequency is unknown:

Elevations in serum creatinine and/or blood urea levels have been observed. Toxic nephropathy and acute renal failure have been reported.

Special Precautions:

Severe reactions (including anaphylaxis) have been reported with β-lactam antibiotics.

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous colitis may develop. It is important to consider its diagnosis in patients who develop diarrhoea in association with the use of **MEDAZINE INJECTION**. Such colitis may range in severity from mild to life threatening. Treatment should be discontinued if symptoms suggestive of pseudomembranous colitis arise. Mild cases of pseudomembranous colitis may respond to discontinuance of the medicine. When the colitis does not improve after the medicine of choice for antibiotic associated pseudomembranous colitis produced by *C.difficile*.

MEDAZINE INJECTION should be given with caution to patients with renal impairment.

The total daily dosage should be reduced when **MEDAZINE INJECTION** is administered to patients with renal insufficiency (See **"DOSAGE AND DIRECTIONS FOR USE"**) because high and prolonged serum antibiotic concentrations can occur from usual doses.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Treatment is symptomatic and supportive.

IDENTIFICATION

A white to yellow powder. After reconstitution, a colourless to light amber solution is produced.

PRESENTATION

MEDAZINE 1 g INJECTION:

20 ml type-I clear transparent glass moulded vial fitted with 20 mm grey bromo butyl rubber stopper and sealed with 20 mm black colour aluminium flip off seal.

Pack sizes: 1's: Each printed carton contains one vial.

10's: Each printed carton contains ten vials.

MEDAZINE 2 g INJECTION:

20 ml type-I moulded clear transparent glass vial fitted with 20 mm grey bromo butyl rubber stopper and sealed with 20 mm dark pink colour aluminium flip off seal.

Pack sizes: 1's: Each printed carton contains one vial.

10's: Each printed carton contains ten vials.

STORAGE INSTRUCTIONS

MEDAZINE INJECTION in the dry state should be stored below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

MEZADIN 1 g INJECTION 44/20.1.1/0312

MEZADIN 2 g INJECTION 44/20.1.1/0313

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

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