PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

ADCO CEFAZOLIN 500 mg powder for solution for injection

ADCO CEFAZOLIN 1 g powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO CEFAZOLIN 500 mg: Each vial contains cefazolin sodium equivalent to 500 mg cefazolin.

ADCO CEFAZOLIN 1 g: Each vial contains cefazolin sodium equivalent to 1 g cefazolin.

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White or almost white sterile cefazolin powder for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO CEFAZOLIN is indicated in the treatment of the following infections due to susceptible micro-organisms:

Respiratory tract infections due to Group A beta–haemolytic streptococci, *S. pneumoniae*, *Klebsiella* species, *H. influenzae*, and *S. aureus* (including penicillinase-producing strains).

Genito-urinary tract infections due to susceptible *Enterobacteriaceae*, e.g. *E. coli*, *P. mirabilis*, *Klebsiella* species and some strains of *Enterobacter* and enterococci.

Skin and skin structure infections due to *S. aureus* (including penicillinase-producing strains) and group A beta-haemolytic streptococci and other susceptible strains of streptococci.

Bone and joint infections due to *S. aureus*.

Septicaemia due to *S. pneumoniae*, *S. aureus* (penicillin-sensitive and penicillin-resistant), *P. mirabilis*, *E. coli* and *Klebsiella* species.

Endocarditis due to *S. aureus* (penicillin-sensitive and penicillin-resistant) and Group A beta-haemolytic streptococci, although cefazolin is not first line therapy for *S. aureus* endocarditis or septicaemia.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to ADCO CEFAZOLIN. If the tests show that the causative organism is resistant to ADCO CEFAZOLIN, other appropriate therapy should be instituted.

Peri-operative prophylaxis

The prophylactic administration of ADCO CEFAZOLIN pre-operatively, intra-operatively and postoperatively may reduce the incidence of postoperative infections in patients undergoing abdominal hysterectomy. The prophylactic administration of ADCO CEFAZOLIN should usually be discontinued within a 24-hour period after the surgical procedure.

4.2 Posology and method of administration

Posology

Usual adult dosage

The usual adult dosages are given in the table below.

Usual adult dosage		
Type of infection	**Dose**	**Frequency**
Pneumococcal pneumonia	500 mg to 1 g	Every 6 to 12 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	Every 8 hours
Acute uncomplicated genito-urinary tract infections	1 g	Every 12 hours
Moderate to severe infections	500 mg to 1 g	Every 6 to 8 hours
Severe, life-threatening infections (e.g. endocarditis, septicaemia)	1 g to 1,5 g	Every 6 hours

Although the normal adult dosage is 500 mg to 1 g every 6 - 12 hours, the recommended maximum daily dose is 6 g. In severe, life-threatening infections a maximum of 12 g per day has been used.

Special populations

Dosage adjustment for patients with reduced renal function

ADCO CEFAZOLIN may be used in patients with impaired renal function according to the following guidelines:

Creatinine clearance of > 55 mL/min OR serum creatinine < 130 micromoles/L	Normal daily doses
Creatinine clearance of 35 – 54 mL/min OR serum creatinine 139 – 260 micromoles/L	Normal daily doses at intervals of at least 8 hours
Creatinine clearance of 11 – 34 mL/min OR serum creatinine 269 – 390 micromoles/L	Half the normal daily doses at intervals of at least 12 hours
Creatinine clearance of < 10 mL/min OR serum creatinine > 399 micromoles/L	Half the normal daily doses at intervals between 18 – 24 hours

All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. For information about peritoneal dialysis (see section 5.2).

Peri-operative prophylactic use

To prevent postoperative infection in contaminated or potentially contaminated abdominal hysterectomy, the recommended doses are as follows:

a. 1 g IV administered half an hour to 1 hour prior to the start of surgery.

b. For lengthy operative procedures (e.g. 2 hours or longer), 1 g IV or IM during surgery (doses and dosing intervals modified according to the duration of the operative procedure).

c. 1 g IV or IM every 6 to 8 hours for a maximum of 24 hours postoperatively has been used. However, in certain cases, postoperative dosing up to 5 days has been used.

It is important that the above recommendations are adhered to. Throughout the surgical procedure, cefazolin levels in serum and tissue need to be high enough to provide adequate bactericidal protection against infectious organisms. Following the procedure, this antibiotic cover must be maintained as recommended in order to prevent infection.

Paediatric dosage

In children a total daily dosage of 25 mg/kg to 50 mg/kg of body mass, divided into three or four equal doses, is effective for most mild to moderately severe infections. For severe infections, total daily dosage may be increased to 100 mg/kg of body mass.

In children with severe renal impairment (creatinine clearance of 20 to 5 mL/min), 10 % of the normal daily dose given every 24 hours should be sufficient. In children with moderate renal impairment (creatinine clearance of 40 to 20 mL/min), 25 % of the normal daily dosage given in divided doses every 12 hours should be sufficient. In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min), 60 % of the normal daily dosage given in

divided doses every 12 hours should be sufficient. All dosage recommendations apply after an initial loading dose is administered.

Paediatric dosage guide

(500 mg vial with 2 mL diluent or 1 g vial with 4 mL diluent)

Mass	**25 mg/kg/day divided into 3 doses**		**25 mg/kg/day divided into 4 doses**	
kg	**Approximate single dose (every 8 hours)**	**Volume needed with dilution of 225 mg/mL**	**Approximate single dose (every 6 hours)**	**Volume needed with dilution of 225 mg/mL**
4,5	40 mg	0,17 mL	30 mg	0,12 mL
9,0	75 mg	0,33 mL	55 mg	0,25 mL
13,5	115 mg	0,50 mL	85 mg	0,37 mL
18,0	150 mg	0,66 mL	115 mg	0,50 mL
22,5	190 mg	0,83 mL	140 mg	0,61 mL
Mass	**50 mg/kg/day divided into 3 doses**		**50 mg/kg/day divided into 4 doses**	
kg	**Approximate single dose (every 8 hours)**	**Volume needed with dilution of 225 mg/mL**	**Approximate single dose (every 6 hours)**	**Volume needed with dilution of 225 mg/mL**
4,5	75 mg	0,35 mL	55 mg	0,25 mL
9,5	150 mg	0,7 mL	110 mg	0,5 mL
13,5	225 mg	1 mL	170 mg	0,75 mL
18,0	300 mg	1,35 mL	225 mg	1 mL

22,5	375 mg	1,7 mL	285 mg	1,25 mL

Method of administration

ADCO CEFAZOLIN may be administered intramuscularly or intravenously after reconstitution (shake reconstituted solution well until clear). The total daily dosages are the same for both routes of administration.

Intramuscular administration

ADCO CEFAZOLIN should be injected deep into a large muscular mass.

Intravenous administration

ADCO CEFAZOLIN may be administered by direct intravenous bolus injection or by continuous or intermittent infusion.

Intermittent intravenous infusion

ADCO CEFAZOLIN may be administered along with primary intravenous fluid management programmes in a volume control set or in a separate, secondary IV bottle.

Intravenous injection *(Administer solution directly into a vein or through tubing):* Dilute reconstituted ADCO CEFAZOLIN 500 mg or 1 g in a minimum of 10 ml of sterile water for injection and inject solution slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

For instructions on reconstitution of the product before administration, see section 6.6.

4.3 Contraindications

ADCO CEFAZOLIN is contra-indicated in patients with a known allergy to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

BEFORE ADCO CEFAZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE ADMINISTERED WITH CAUTION TO PENICILLIN-SENSITIVE PATIENTS.
SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY OCCUR. ADCO CEFAZOLIN SHOULD BE DISCONTINUED AND THE PATIENT TREATED WITH ADRENALINE, CORTICOSTEROIDS AND ANTIHISTAMINES.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

There is some clinical and laboratory evidence of partial cross-allergenicity between the penicillins and the cephalosporins. About 10 % of patients who are penicillin-sensitive may also be allergic to cephalosporins, but the actual incidence is uncertain. Patients have been reported to have had severe hypersensitivity reactions, including anaphylaxis, to both medicines. Any patient who has shown some form of allergy particularly to medicines should

receive antibiotics cautiously and no exception should be made in this regard to ADCO CEFAZOLIN.

If an allergic reaction to ADCO CEFAZOLIN occurs, the medicine should be discontinued and the patient treated with the appropriate therapy.

Pseudomembranous colitis, due to *Clostridium difficile* superinfection, has been reported with many broad-spectrum antibiotics particularly cephalosporins, therefore it is important to consider its diagnosis in patients who develop diarrhoea in association with their use. Such enterocolitis may be life-threatening and appropriate measures should be taken, including discontinuation of the antibiotics. In individuals with a history of gastrointestinal disease, particularly colitis, broad spectrum antibiotics should be prescribed with caution.

Prolonged use of ADCO CEFAZOLIN may result in the overgrowth of non-susceptible organisms and possible superinfection. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

When ADCO CEFAZOLIN is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see section 4.2).

Safety and effectiveness for use in premature infants and infants under one month of age have not been established. See section 4.2 for recommended dosage in children over one month. As experience in premature infants and neonates is limited, the use of ADCO CEFAZOLIN in these patients should only be undertaken with caution.

The intrathecal administration of ADCO CEFAZOLIN is not an approved route of administration for this antibiotic; in fact, there have been reports of severe central nervous system (CNS) toxicity including seizures when ADCO CEFAZOLIN was administered in this manner.

ADCO CEFAZOLIN contains sodium

ADCO CEFAZOLIN 500 mg contains approximately 25,3 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1,27 % of the recommended maximum daily dietary intake of sodium for an adult.

ADCO CEFAZOLIN 1 g contains approximately 50,6 mg sodium, equivalent to 2,53 % of the recommended maximum daily dietary intake of sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Used concurrently, probenecid decreases renal tubular secretion of cefazolin, resulting in increased and more prolonged serum levels of cefazolin.

The efficacy of oestrogen-containing contraceptives may be decreased by the concomitant administration of ADCO CEFAZOLIN.

Concomitant administration of cephalosporins and aminoglycoside antibiotics has been associated with increased nephrotoxicity.

Medicine/laboratory test interactions

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets, but not with glucose oxidase urine sugar analysis tests, e.g. Tes-Tape.

Positive direct and indirect Coombs tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

4.6 Fertility, pregnancy, and lactation

Use in pregnancy

Safety of this product for use during pregnancy has not been established.

ADCO CEFAZOLIN has been found to readily cross the placental barrier into the cord blood and amniotic fluid.

Nursing mothers

Cefazolin is present in very low concentrations in the milk of nursing mothers.

4.7 Effects on ability to drive and use machines

ADCO CEFAZOLIN is presumed to be safe or unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated summary of adverse reactions

The following side effects have been reported and may occur with ADCO CEFAZOLIN:

System Organ Class	Frequency	Adverse Event
	Frequent	Eosinophilia

Blood and the lymphatic system disorders	Less frequent	Neutropenia, leucopenia, agranulocytosis, thrombocytosis, thrombocytopenia
	Frequency not known	Thrombocythaemia, positive direct and indirect Coombs tests have occurred Possible bleeding disorders due to hypoprothrombinaemia and/or platelet dysfunction
Immune system disorders	Less frequent	Drug fever, skin rash, urticaria, reactions resembling serum sickness, vulvar pruritus, eosinophilia, bronchospasms and anaphylaxis, hypersensitivity
	Frequency not known	Angioedema
Nervous system disorders	Less frequent	Confusion, stupor and headache may occur. In high doses, convulsions may occur
Cardiac disorders	Frequency not known	Kounis syndrome
Gastrointestinal disorders	Frequent	Nausea and vomiting have been reported. Diarrhoea and oral candidiasis (oral thrush) have been reported

	Less frequent	Symptoms of pseudomembranous colitis (diarrhoea) may appear either during or after antibiotic treatment
	Frequency not known	Anorexia
Hepato-biliary disorders	Frequency not known	Transient increases in transaminase liver enzymes and alkaline phosphate levels have been observed Hepatitis and cholestatic jaundice have been reported
Skin and subcutaneous tissue disorders	Less frequent	Stevens-Johnson syndrome
	Frequency not known	Linear IgA disease
Renal and urinary disorders:	Frequency not known	Increased levels of urea may occur, and are not always associated with clinical evidence of renal impairment Nephrotoxicity i.e. acute tubular necrosis, as well as interstitial nephritis and other renal disorders have been reported The combined use of potassium and loop diuretics or aminoglycosides has

		been associated with an increased incidence of renal function impairment
Reproductive system and breast disorders	Frequent	Vaginal candidiasis
	Less frequent	Genital pruritus, genital moniliasis and vaginitis
General disorders and administrative site conditions	Less frequent	Pain on intramuscular injection, sometimes with induration, has occurred. Thrombophlebitis at the site of injection has been noted
	Frequency not known	Other reactions included genital and anal pruritus

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For reporting side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

The administration of large doses of parenteral cephalosporins may cause dizziness, paraesthesias, headache, confusion and stupor. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is most likely to occur. Laboratory abnormalities that may occur after an overdose include elevations in creatinine, urea, liver enzymes and bilirubin, a positive Coombs test, thrombocytosis or thrombocytopenia, eosinophilia, leucopenia and prolongation of the prothrombin time.

Treatment is symptomatic and supportive.

If convulsions occur, the cephalosporin therapy should be stopped; anticonvulsant therapy may be administered if clinically indicated.

In cases of severe overdosage, particularly in patients with renal failure, combined haemodialysis and haemoperfusion may be considered if the response to more conservative therapy fails. However, no data supporting such therapy is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Other Beta-lactam antibacterials, first-generation cephalosporins, ATC code: J01DB04

Cefazolin sodium is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-[[(5-methyl-1, 3, 4-thiadiazol-2-yl)-thio] methyl]-7-[2-(1H-tetrazol-1-yl)

acetamido]-3-cephem-4-carboxylic acid. The molecular formula is $C_{14}H_{14}N_8O_4S_3$ (sodium salt). The molecular mass is 476,5. The pH of the reconstituted solution is between 4,0 and 6,0.

Cefazolin exerts its pharmacological action by the bactericidal inhibition of bacterial cell wall transpeptidase. The plasma half-life of cefazolin is approximately 1,8 hours, although this increases in patients with renal impairment. About 85 % of the drug in the circulation is bound to plasma proteins. Diffusion into bone and into ascitic, pleural and synovial fluid occurs readily. Cefazolin crosses the placenta and into foetal circulation. There is little diffusion into cerebrospinal fluid and breast milk.

When cefazolin is administered to patients with unobstructed biliary tracts, high concentrations, well above serum levels, occur in the gall bladder tissue and bile. In the presence of obstruction, however, the concentration of cefazolin is considerably lower in bile than in serum.

Microbiology

ADCO CEFAZOLIN is active against the following organisms *in vitro*.

In vitro sensitivity does not necessarily imply *in vivo* activity.

- *Staphylococcus aureus* (both penicillinase- and non-penicillinase-producing strains)
- *Staphylococcus epidermidis*
- *Streptococci*, including Group A beta-haemolytic streptococci. Many strains of enterococci are resistant
- *Streptococcus pneumoniae*
- *Escherichia coli*

- *Proteus mirabilis*
- *Klebsiella* species
- *Enterobacter aerogenes*
- *Haemophilus influenzae.*

Almost uniformly resistant to cefazolin: *Serratia*, *Pseudomonas* and *Acinetobacter calcoaceticus*.

Uniformly resistant to cefazolin: methicillin-resistant staphylococci.

Resistant to cefazolin: most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter cloacae*, *Morganella morganii* and *Providencia rettgeri.*

The minimum inhibitory concentrations of cefazolin for susceptible gram-positive cocci range from about 0,1 to 1 mcg/mL; for the majority of susceptible gram-negative bacteria, concentrations of greater than 1 mcg/mL are required.

5.2 Pharmacokinetic properties

Cefazolin is excreted unchanged in the urine, mainly by glomerular filtration and some renal tubular secretion. Probenecid delays excretion of cefazolin. Cefazolin is removed to some extent by haemodialysis.

Following intramuscular doses of 500 mg or 1 g, peak plasma concentrations of over 30 mcg/mL, or over 60 mcg/mL respectively, are obtained after 1 to 2 hours. Within 24 hours, 80 % of an intramuscular dose is excreted renally. Peak urine concentrations of 1 mg and 4 mg per millilitre have been reported after intramuscular doses of 500 mg and 1 g respectively.

Intravenous administration may be a constant or intermittent infusion or a bolus dose. In normal volunteers, a constant intravenous infusion of cefazolin in doses of 3,5 mg/kg for 1 hour, followed by 1,5 mg/kg for the next two hours, may produce a steady serum level of approximately 28 mcg/mL during the third hour. In normal patients, the peak serum concentration following a single 1 g bolus intravenous injection is approximately 188 mcg/mL. After 1 hour following administration, the serum levels decline to approximately 70 mcg/mL, at 2 hours to 45 mcg/mL, and at 4 hours to 16 mcg/mL.

In patients undergoing peritoneal dialysis (2 litres/hour), mean serum levels of cefazolin were approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialysing solution containing 50 mg/litre and 150 mg/litre respectively. Mean peak levels were 29 mcg/mL (range 13 – 44 mcg/mL) with 50 mg/litre (3 patients) and 72 mcg/mL (range 26 – 142 mcg/mL) with 150 mg/litre (6 patients). At the end of dialysis, 1 g of cefazolin was inserted and left in the peritoneal cavity. The final 1 g resulted in mean peak of 63 mcg/mL within 2 hours.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in sections 6.4 and 6.6.

6.3 Shelf life

Before reconstitution:

36 months

After reconstitution:

If storage of the reconstituted or the diluted solution is necessary, it may be stored for a maximum period of 36 hours, below 25 °C or for 96 hours if stored at 2 – 8 °C. This is provided that reconstitution or dilution is carried out under validated aseptic conditions.

6.4 Special precautions for storage

Store the dried powder at or below 25 °C. Do not remove vials from outer carton until required for use.

The product does not contain an antimicrobial preservative. Prior to administration, parenteral drug products should be inspected visually for particulate matter and discolouration whenever solution and container permit. Reconstituted solutions should be used within three hours, and any unused portions must be discarded (see section 6.3).

DO NOT FREEZE DILUTED ADCO CEFAZOLIN SOLUTIONS.

Chemical and physical compatibility have been demonstrated with the following solutions:

Water for injection

0,9 % Sodium chloride injection

5 % Glucose injection

10 % Glucose injection

5 % Glucose and 0,9 % sodium chloride injection

5 % Glucose and 0,45 % sodium chloride injection

Ringer Lactate injection

6.5 Nature and contents of container

ADCO CEFAZOLIN 500 mg powder for solution for injection is a 10 ml colourless glass vial sealed with a grey rubber stopper and an aluminium cap. It contains white or almost white sterile cefazolin powder for injection. The reconstituted solution is clear and colourless.

ADCO CEFAZOLIN 1 g powder for solution for injection is a 10 ml colourless glass vial sealed with a grey rubber stopper and an aluminium cap. It contains white or almost white sterile cefazolin powder for injection. The reconstituted solution is clear and colourless.

ADCO CEFAZOLIN 500 mg and 1 g powder for solution for injection is supplied in cartons containing 10 units (vials).

Not all strengths and/or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution of the product before administration

Intramuscular administration

500 mg vial: Reconstitute with sterile water for injection, bacteriostatic water for injection or 0,9 % sodium chloride injection. Shake well until dissolved.

The 500 mg vial should have 2 ml of the diluent added to it. This results in a 2,2 mL solution for injection with a cefazolin concentration of approximately 225 mg/mL.

1 g vial: The 1 g vial should be reconstituted only with sterile water for injection or bacteriostatic water for injection.

The 1 g vial should have 2,5 ml of the diluent added to it. This results in a 3 mL solution for injection with a cefazolin concentration of approximately 330 mg/mL. Shake well until dissolved.

Reconstituted solution: Ensure that the reconstituted solution is clear. If the solution is turbid, do not use.

Intermittent intravenous infusion

Reconstituted ADCO CEFAZOLIN 500 mg or 1 g may be diluted in 50 ml to 100 ml of one of the following intravenous solutions:

0,9 % Sodium chloride injection

5 % or 10 % Glucose injection

5 % Glucose and 0,9 % sodium chloride injection (may also be used with 5 % glucose and 0,45 % or 0,2 % sodium chloride injection)

Ringer Lactate injection

Water for Injection.

Intravenous injection

Dilute reconstituted ADCO CEFAZOLIN 500 mg or 1 g in a minimum of 10 ml of sterile water for injection and inject solution slowly over a period of 3 to 5 minutes. Do not inject in less than 3 minutes.

The reconstituted solution must be used within 3 hours. Discard any unused portion.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

ADCO CEFAZOLIN 500 mg: 36/20.1.1/0259

ADCO CEFAZOLIN 1 g: 36/20.1.1/0260

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

05 September 2003

10 DATE OF REVISION OF THE TEXT

28 March 2025