

DATA SHEET

Ranbaxy-Cefaclor

Cefaclor (Ph. Eur.) 250 mg capsules

Cefaclor (Ph. Eur.) 500 mg capsules

Cefaclor (Ph. Eur.) 125 mg/5 ml oral suspension

Cefaclor (Ph. Eur.) 250 mg/5 ml oral suspension

Cefaclor (Ph. Eur.) 375 mg Modified Release Tablets

Presentation

Capsule 250 mg: Purple/white size 2 gelatine capsule imprinted with "CEFACLOR 250" on both the cap and body of the capsule.

Capsule 500 mg: Purple/grey size OEL gelatine capsule imprinted with "CEFACLOR 500" on both the cap and body of the capsule.

Oral suspension 125 mg/5 ml: White to off-white granular powder, which upon reconstitution with water forms a red strawberry, flavoured suspension with a sweet taste.

Oral suspension 250 mg/5 ml: White to off-white granular powder, which upon reconstitution with water forms a red strawberry, flavoured suspension with a sweet taste.

Sustained release tablets: Capsule shaped, biconvex, unscored, blue film-coated tablet, imprinted with "Cefaclor CD 375mg" in black.

Uses

Actions

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms to cefaclor, clinical efficacy for infections other than those included in the Indications section is unknown.

Aerobes, Gram-positive: Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains; *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); *Streptococcus pneumoniae*; *Corynebacterium* spp.

Aerobes, Gram-negative: *Moraxella (Branhamella) catarrhalis*; *Haemophilus influenzae*, including beta-lactamase-producing ampicillin-resistant strains; *Escherichia coli*; *Proteus mirabilis*; *Klebsiella* spp.; *Citrobacter diversus*; *Neisseria gonorrhoeae* (penicillinase-producing and non-penicillinase-producing strains).

Anaerobes: *Propionibacteria acnes* and *Bacteroides* spp. (excluding *Bacteroides fragilis*); *Peptococcus* spp.; *Peptostreptococcus* spp.

Susceptibility testing

Dilution or diffusion techniques either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Resistance

Most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*] and *Enterococcus faecium* [formerly *Streptococcus faecium*]) are resistant to cefaclor and other cephalosporins. Cefaclor is not active against most strains of *Enterobacter* spp, *Serratia* spp, *Morganella morganii*, *Proteus vulgaris*, and *Providencia rettgeri*. It has no activity against *Pseudomonas* spp or *Acinetobacter* spp. When tested by *in vitro* methods staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

Onset and duration of action

As with antibiotic therapy in general, administration of cefaclor should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained. A minimum of ten days of treatment is recommended in infections caused by group A beta-haemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis.

Pharmacokinetics

Cefaclor is well absorbed after oral administration, whether taken with food or while fasting; however, when it is taken with food, the peak concentration achieved is 50-75 % of that observed when the medicine is administered to fasting subjects and generally appears from 45 to 60 minutes later. The presence of food in the gastrointestinal tract does not alter the total amount of cefaclor absorbed. Following doses of 250 mg, 500 mg, and 1 g, to fasting subjects average peak serum levels of approximately 7, 13, and 23 µg/ml, respectively, were obtained at 30 to 60 minutes. The reduced peak serum levels resulting from the administration of cefaclor with food should be considered with reference to the sensitivity of the infecting organism, severity of illness, the dose being administered and the variability in the peak plasma levels which occur with cefaclor.

About 25 % of cefaclor is bound to plasma proteins. Cefaclor is widely distributed in the body with bactericidal concentrations achieved in middle ear fluid, sinus drainage and bronchial secretions. The volume of distribution is 0.35 litre/kg. The medicine crosses the placenta and is excreted in very low concentrations in breast milk.

Biotransformation

There is no evidence of metabolism of cefaclor in humans.

Elimination

The plasma half-life in healthy subjects is independent of dosage form and averages 40 to 60 minutes. Cefaclor is rapidly eliminated by the kidneys with approximately 60 to 85% of a dose excreted unchanged in the urine within 8 hours and the greater part within 2 hours of dosing. During this 8 hour period, peak urine concentrations following the 250 mg, 500 mg and 1 g doses were approximately 600, 900 and 1900 mg/l, respectively. Renal clearance rates far exceed the rate of glomerular filtration suggesting renal secretion of cefaclor. This is consistent with the finding that the concomitant administration of probenecid significantly prolongs the half-life of cefaclor.

Elderly patients

In elderly subjects aged over 65 years with normal serum creatinine values, a higher peak plasma concentration and area under the curve are effects resulting from mildly diminished renal function and are not expected to have clinical significance. Therefore, dosage changes are not necessary in elderly subjects with normal renal function.

Impaired renal function

The serum half-life in normal subjects is 0.6 to 0.9 hour. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the biologic half-life of the intact molecule is 2.3 to 2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Haemodialysis shortens the half-life by 25% to 30%.

Indications

Cefaclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated micro-organisms:

Lower respiratory infections, including pneumonia caused by *S. pneumoniae*, *H. influenzae* (including both ampicillin-sensitive and ampicillin-resistant strains), and *S. pyogenes* (Group A beta-haemolytic streptococci), *M. catarrhalis*, acute bronchitis, and acute exacerbations of chronic bronchitis.

Upper respiratory infections, including pharyngitis and tonsillitis caused by *S. pyogenes* (Group A beta-haemolytic streptococci) and *M. catarrhalis*.

Note: Penicillin is the usual medicine of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Amoxicillin has been recommended by The American Heart Association as the standard regimen for the prophylaxis of bacterial endocarditis for dental, oral, and upper respiratory tract procedures, with Penicillin V a rational and acceptable alternative in the prophylaxis against α -haemolytic streptococcal bacteraemia in this setting. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever or bacterial endocarditis are not available at present.

Otitis media caused by *S. pneumoniae*, *H. influenzae* (including both ampicillin-sensitive and ampicillin-resistant strains) staphylococci, and *S. pyogenes* (Group A beta-haemolytic streptococci), and *M. catarrhalis*.

Skin and soft-tissue infections caused by *Staphylococcus aureus* (including β -lactamase producing strains), *S. pyogenes* (Group A beta-haemolytic streptococci) and *Staphylococcus epidermidis* (including β -lactamase producing strains).

Urinary tract infections, including pyelonephritis and cystitis caused by *E. coli*, *P. mirabilis*, *Klebsiella* sp., and coagulase-negative staphylococci.

Note: Cefaclor has been found to be effective in both acute and chronic urinary tract infectious; sinusitis; gonococcal urethritis.

Skin and skin structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A beta-haemolytic streptococci).

Sinusitis.

Gonococcal urethritis, but appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefaclor.

Therapy may be started while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly.

Dosage and Administration

Cefaclor is administered orally.

Cefaclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (refer to Warnings and precautions).

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dosage of cefaclor should be administered for at least 10 days.

Adults - Capsules

The usual adult dosage is 250 mg every 8 to 12 hours.

For bronchitis and pneumonia, the dosage is 250 mg administered 3 times daily. A dosage of 250 mg administered 3 times daily for 10 days is recommended for sinusitis.

For more severe infections, such as pneumonia, or those caused by less susceptible organisms doses may be doubled.

For mild to moderate infections of the urinary tract, skin and soft tissues, and upper respiratory tract, a dosage of 250 mg administered 2 times daily may be sufficient. Doses of 4 g/day have been administered safely to normal subjects for 28 days, but the total daily dosage should not exceed this amount.

For the treatment of acute gonococcal urethritis in males and females, a single dose of 3 g combined with probenecid, 1 g, is given.

Children – Powder for Suspension

The usual recommended daily dosage for children with mild to moderate infections is 20 mg/kg/day in divided doses every 8 to 12 hours. For bronchitis and pneumonia, the dosage is 20 mg/kg/day in divided doses administered 3 times daily. If cefaclor is administered as Ranbaxy-cefaclor 125 mg/5 ml granules for oral suspension, the doses equivalent to 20 mg/kg/day are: 2.5 ml three times daily for a child weighing 9 kg; 5 ml three times daily for a child weighing 18 kg.

In more serious infections, otitis media and infections caused by less susceptible organisms, the recommended dosage is 40 mg/kg/day in divided doses every 8 to 12 hours, with a maximum dosage of 1 g/day. If cefaclor is administered as Ranbaxy cefaclor 125 mg/5 ml granules for oral suspension, the doses equivalent to 40 mg/kg/day are: 5 ml three times daily for a child weighing 9 kg; 10 ml three times daily for a child weighing 18 kg.

Twice daily treatment option

For the treatment of otitis media and pharyngitis, the total daily dosage may be divided and administered every 12 hours.

Adults – Modified Release Tablets

The tablets should not be cut, crushed or chewed.

The usual dose is 375 mg twice daily.

For pneumonia, and acute bacterial sinusitis, the recommended dosage is 750 mg twice daily. For acute bacterial sinusitis the tablets should be taken for 10 days.

For infections involving *S.pyrogenes* (group A Streptococci), a therapeutic dosage of Ranbaxy-Cefaclor CD tablets should be administered for at least 10 days.

Contraindications

Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings and Precautions

Before initiating therapy with Ranbaxy-cefaclor, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefaclor, cephalosporins, penicillins, or other medicines. Cefaclor should not ordinarily be given to those allergic to cephalosporins or to penicillins, especially where an allergic or urticarial reaction has occurred. If an allergic reaction to cefaclor occurs, the medicine should be discontinued and, if necessary, the patient should be treated with appropriate agents, eg. pressor amines, antihistamines, or corticosteroids. Antibiotics, including cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to medicines.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including cefaclor. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Cl. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis, e.g. opiates and diphenoxylate with atropine, may prolong and/or worsen the condition and should not be used.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In haematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the medicine.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under

such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

Cefaclor should be used with caution in patients with hepatic disease, as documented clinical experience in this group of patients is lacking.

Antibiotics, including cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Pregnancy and lactation

Use in pregnancy

(Category B1). This category includes medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

The oral administration of high dose cefaclor (500 mg/kg) in pregnant rats and mice has resulted in a slight increase of minor skeletal malformation. Reproduction studies performed in mice and rats using doses up to 12 times the human dose and in ferrets at 3 times the maximum human dose, have revealed no evidence of impaired fertility or harm to the foetus attributed to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

The effect of cefaclor on labour and delivery is unknown.

Use in lactation

Small amounts of cefaclor have been detected in breast milk following administration of single 500 mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at 2, 3, 4 and 5 hours, respectively.

Trace amounts were detected at 1 hour.

Residual cefaclor may be present in breast milk at levels corresponding to approximately 0.7% of the maternal dose. Cephalosporins are considered to be compatible with breastfeeding although there are theoretical risks of alterations to infant bowel flora and allergic sensitisation.

Use in neonates

Safety and efficacy of cefaclor for use in infants less than one month of age have not been established.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect.

Other

Preclinical safety data.

Studies have not been performed to determine the carcinogenic or mutagenic potential of cefaclor in animals. Reproduction studies have revealed no evidence of impaired fertility.

Adverse Effects

Gastrointestinal: Symptoms occur in about 2.5 % of patients and include diarrhoea (1 in 70). Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

Nausea and vomiting have been reported rarely.

As with some penicillin and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity

Reactions have been reported in about 1.5 % of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Angioedema has been reported rarely.

Cases of serum-sickness-like reactions have been reported with the use of cefaclor. These are characterised by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, serum-sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor.

Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5 %) in one focused trial to 2 in 8346 (0.024 %) in overall clinical trials (with an incidence in children in clinical trials of 0.055 %) to 1 in 38000 (0.003 %) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. Occasionally these reactions have resulted in hospitalisation, usually of short duration (median hospitalisation = 2 to 3 days, based on post-marketing surveillance studies). In those requiring hospitalisation, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children.

Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.

More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Other: Effects considered related to therapy-included eosinophilia (1 in 50 patients). Genital pruritus or vaginitis (less than 1 in 100 patients), and rarely, thrombocytopenia or reversible interstitial nephritis.

Causal Relationship Uncertain:

CNS: Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations and somnolence have been reported.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with medicine therapy occur, the medicine should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Haematopoietic: As has also been reported with other β -lactam antibiotics, transient lymphocytosis, leukopenia, and rarely, haemolytic anaemia and reversible neutropenia of possible clinical significance. There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and coumadin concomitantly.

Other

Transitory abnormalities in clinical laboratory test results have been reported, but their clinical significance is uncertain. These include slight elevations in AST, ALT or alkaline phosphatase values (1 in 40); transient fluctuations in leucocyte count, predominantly lymphocytosis in infants and young children; and slight elevations in serum urea or serum creatinine (less than 1 in 500) or abnormalities of urinalysis such as haematuria, pyuria (less than 1 in 200).

Interactions

Medicine interactions

There have been rare reports of increased anticoagulant effect when cefaclor and oral anticoagulants were administered concomitantly (refer to Adverse effects). As with other beta-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

Interactions with laboratory tests

A false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or tableted reagents containing buffered copper (II) sulphate, but not with enzyme-based reagents.

Overdosage

Clinical Features: The toxic symptoms following an overdose of cefaclor may include nausea, vomiting, epigastric distress, and diarrhoea. The severity of the epigastric distress and the diarrhoea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction or the effects of other intoxication.

Management: In managing overdosage consider the possibility of multiple agent overdoses, medicine interaction, and unusual kinetics in your patient. Unless 5 times the normal dose of cefaclor has been ingested, gastrointestinal decontamination will not be necessary. Protect the patients airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patients vital signs, blood gases, serum electrolytes, etc.

Absorption of medicines from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying.

Repeated doses of charcoal over time may hasten elimination of some medicines that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefaclor.

Pharmaceutical Precautions

Capsules: Store below 25 °C protected from light and moisture. Shelf life: 3 years.

Oral suspensions: store below 25 °C in well closed containers protected from light and moisture. Shelf life: 2 years. Once reconstituted the suspension should be stored between 2 and 8 °C and used within 14 days.

Directions for preparing the 125 mg/5 ml oral suspension: Add 70 ml of water to the dry powder and shake to disperse. To help with dispersion, the water may be added in two portions shaking between each addition.

Directions for preparing the 250 mg/5 ml oral suspension: Add 53 ml of water to the dry powder and shake to disperse. To help with dispersion, the water may be added in two portions shaking between each addition.

Modified Release Tablets: Store below 25 °C protected from light and moisture. Shelf life: 2 years.

Medicine Classification

Prescription Medicine

Package Quantities

Ranbaxy-Cefaclor 250 mg and 500 mg capsules: 100 capsules packed in HDPE bottles.

Ranbaxy-Cefaclor oral suspension 125 mg/5 ml: bottles of powder for 100 ml suspension.

Ranbaxy-Cefaclor oral suspension 250 mg/5 ml: bottles of powder for 75 ml suspension

Ranbaxy-Cefaclor SR Modified Release 375 mg tablets: 14 tablets packed in blisters

Further Information

Cefaclor is 3-chloro-7-d-(2-phenylglycinamido)-3-cephem-4-carboxylic acid and is available commercially as the monohydrate. The formula and molecular weight of the monohydrate form is $C_{15}H_{14}ClN_3O_4S \cdot H_2O$ and 385.8 respectively.

Ranbaxy-Cefaclor capsules contain cefaclor as cefaclor monohydrate, maize starch, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate. **Capsule shell:** gelatine, Ponceau 4R, Carmoisine, Brilliant blue, titanium dioxide, methyl paraben and propyl paraben.

Ranbaxy-Cefaclor oral suspensions contain cefaclor as cefaclor monohydrate, xanthan gum, sodium benzoate, sucrose, colloidal silicon dioxide, FD & C Red No 40 (allura red AC), strawberry flavour, sodium citrate, citric acid and simethicone.

Ranbaxy-Cefaclor SR Modified Release 375 mg tablets contain cefaclor as cefaclor monohydrate, hypromellose (methocel K4MCR premium and methocel E5 premium), hydroxypropyl cellulose, lactose, colloidal anhydrous silica, magnesium stearate and purified talc. The film coating materials are hypromellose (2910 5cP E464), titanium dioxide (E171), polyethylene glycol 400, indigo carmine CI73015 and purified water. The printing ink contains purified water, iron oxide black, propylene glycol, hypromellose (2910 6cP) and isopropyl alcohol.

Name and Address

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand

Phone: (09) 835 0660

Fax: (09) 835 0665

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