Xifarox™

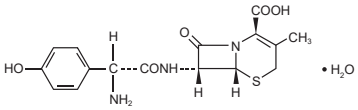
(C e f a d r o x i l)

ذیفاروکس

Capsules 500mg
Powder for Suspension 125mg/5mL & 250mg/5mL
Drops 100mg/mL

DESCRIPTION

Xifarox (Cefadroxil) is a semisynthetic, first generation cephalosporin antibiotic for oral administration. It is chemically designated as 5-Thia-1-azabicyclo [4.2.0]oct-2-ene - 2 - carboxylic acid, 7- [[amino(4-hydroxyphenyl)acetyl]amino] -3-methyl-8-oxo-, monohydrate ,[6R-[6α,7β(R*)]]. Its molecular formula is $C_{16}H_{17}N_3O_5S \cdot H_2O$ and the structural formula is:



Cefadroxil monohydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Xifarox (Cefadroxil) is available for oral administration as:

Xifarox Capsule 500mg
Each capsule contains:
Cefadroxil monohydrate equivalent to Cefadroxil USP… 500mg

Xifarox Powder for Suspension 125mg/5mL
Each reconstituted 5mL contains:
Cefadroxil monohydrate equivalent to Cefadroxil USP… 125mg

Xifarox Powder for Suspension 250mg/5mL
Each reconstituted 5mL contains:
Cefadroxil monohydrate equivalent to Cefadroxil USP… 250mg

Xifarox Drops 100mg/mL
Each reconstituted mL contains:
Cefadroxil monohydrate equivalent to Cefadroxil USP … 100mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Cefadroxil is a cephalosporin for oral administration, which inhibits bacterial wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins. The result is formation of a defective cell wall that is osmotically unstable, and bacterial cell lysis.

Microbiology

Cefadroxil has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections:

Commonly susceptible species
Gram-positive aerobes
Streptococci Group B, C and G
*Streptococcus pyogenes**
Gram-negative aerobes
*Moraxella catarrhalis**

Species for which acquired resistance may be a problem
Gram-positive aerobes
*Staphylococcus aureus (methicillin-susceptible)**
Staphylococcus epidermidis
*Streptococcus pneumoniae**
Gram-negative aerobes
Citrobacter diversus§, Escherichia coli§, Haemophilus influenza§, Klebsiella pneumoniae§, Klebsiella oxytoca§, Proteus mirabilis§*

Inherently resistant species
Gram-positive aerobes
Enterococcus spp.
Staphylococcus aureus (methicillin-resistant)
Staphylococcus epidermidis (methicillin-resistant)
Streptococcus pneumoniae (penicillin-resistant)
Gram-negative aerobes
Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

Other species
Chlamydia spp
Mykoplasma spp
Legionella spp

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications
§Species with natural intermediate susceptibility

Pharmacokinetics

Absorption
After oral administration, cefadroxil is practically completely absorbed. Simultaneous intake of food has practically no effect on absorption (AUC).

Distribution
After oral doses of 500mg (1000mg) peak plasma concentrations of about 16 (30) µg/mL are obtained after 1-1.3 hours. Between 18 and 20% of cefadroxil is bound to plasma proteins. Cephalosporins do not penetrate in the CSF and should not be used for treatment of meningitis.

Metabolism
Cefadroxil is not metabolized.

Elimination
Cefadroxil is eliminated far more slowly than comparable oral cephalosporins (half-life: about 1.4 h to 2.6 h) so that intervals between doses can be prolonged to 12-24 hours. Roughly, 90% of the substance is eliminated in unchanged form through the kidneys within 24 hours. Cefadroxil may be eliminated from the organism through hemodialysis.

Special Population

Renal impairment
Elimination is retarded, so that interval between doses must be prolonged.

THERAPEUTIC INDICATIONS

Xifarox (Cefadroxil) is indicated for the treatment of following infections caused by cefadroxil-susceptible organisms, when an oral therapy is indicated:

- Streptococcal pharyngitis and tonsillitis
- Bronchopneumonia, bacterial pneumonia
- *Urinary tract infections:* pyelonephritis, cystitis
- *Skin and soft tissue infections:* abscesses, furunculosis, impetigo, erysipelas, pyoderma, lymphadenitis
- *Other Infections:* Osteomyelitis and septic arthritis

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefadroxil and other antibacterial drugs, cefadroxil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

Adults

The dosage depends on the susceptibility of the pathogens, the severity of the disease and on the clinical status of the patient (renal and hepatic function).

Skin and Skin Structure infections: For skin and skin structure infections, the usual dosage is 1g per day in single or divided doses.

Pharyngitis and Tonsillitis: Treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis, the usual dose is 1g per day in single or two equally divided doses for 10 days.

Urinary Tract infections: For uncomplicated urinary tract infections (i.e., cystitis) the usual dosage is 1g or 2g per day in single or divided doses. For all other urinary tract infections, the usual dosage is 2g per day in divided doses.

Upper and lower respiratory tract infections: For mild infections, the usual dosage is 1g per day in two equally divided doses. For moderate to severe infections, the recommended dosage is 1g to 2g in two equally divided doses.

Children

The recommended dosage for children is 25-50mg/kg/day in two equally divided doses (every 12 hours) as indicated. For pharyngitis, tonsillitis and impetigo the recommended daily dosage may be administered as a single dose or in two equally divided doses (every 12 hours).

Daily dosage of Suspension

Child's weight (Kg)	Oral Suspension 125mg/5mL	Oral Suspension 250mg/5mL	Oral drops 100mg/mL
4	-	-	0.5 – 1 drop
5	2.5 – 5mL	-	-
10	5 – 10mL	2.5 – 5mL	-
15	7.5 – 15mL	3.75 – 7.5mL	-
20	10 – 20mL	5 – 10mL	-
25	12.5 – 25mL	6.25 – 12.5mL	-

Special Population

Patients with renal impairment

The dosage should be adjusted according to creatinine clearance rates to prevent accumulation of cefadroxil. In patients with creatinine clearance of 50 mL/min or less, the following reduced dosage schedule is recommended as a guideline for adults:

Creatinine clearence (mL/min /1.73m^2)	Serum Creatinine (mg/100mL)	Initial dose	Following dose	Dosage interval
50 - 25	1.4 - 2.5	1000mg	500mg - 1000mg	every 12 hours
25 - 10	2.5 - 5.6	1000mg	500mg - 1000mg	every 24 hours
10 - 0	> 5.6	1000mg	500mg - 1000mg	every 36 hours

Patients undergoing hemodialysis

Hemodialysis eliminates 63% of 1000mg of cephalosporin after 6 to 8 hours of hemodialysis. Elimination half-time of cephalosporin is about 3 hours during dialysis.

Patients with hemodialysis receive one additional dose of 500mg - 1000mg at the end of the hemodialysis.

Direction for Preparation of Suspension

Fill previously boiled and cooled water up to the mark on the bottle and shake well. After reconstitution, the suspension should be stored in a refrigerator (2°C-8°C) and can be used within 14 days. Shake well before use.

CONTRAINDICATIONS

Cefadroxil is contra-indicated in patients with:

- Hypersensitivity to cefadroxil, to any of the cephalosporins or to any of the excipients of the product.
- History of severe reactions to penicillins or to any other beta-lactam drugs.

ADVERSE REACTIONS

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, glossitis, pruritus, rash, allergic exanthema and urticaria.

Uncommon: Clinical pictures due to a growth of opportunistic organisms (fungi), such as vaginal mycoses, thrush.

Rare: Eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis: rare cases during prolonged used, which subside upon discontinuation of therapy, serum sickness-like reactions, cholestase and idiosyncratic hepatic failure have been reported, minor elevation of serum transaminases (ASAT, ALAT) and alkaline phosphatases, angioneurotic edema, arthralgia, interstitial nephritis and drug fever.

Very rare: Haemolytic anemia of immunologic origin, immediate allergic reaction (anaphylactic shock), headache, sleeplessness, dizziness, nervousness, pseudomembranous colitis has been reported (may range in severity from mild to life threatening), Stevens Johnson Syndrome and erythema multiforma have been reported, fatigue, direct and indirect positive Coombs' tests.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

PRECAUTIONS

Before therapy with cefadroxil is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefadroxil, cephalosporins, penicillins or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised.

If an allergic reaction to cefadroxil occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

- Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefadroxil, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotics treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- Cefadroxil does not penetrate in the CSF and is not indicated for the treatment of meningitis.
- Special caution should be exercised in patients with history of severe allergies or asthma.
- In patients with a history of non-severe hypersensitivity to penicillins, or other non-cephalosporin beta - lactam drugs, cefadroxil should be used with special caution as cross allergies occur.
- Caution is necessary in patients with renal impairment; the dosage must be adjusted according to the grade of renal impairment.
- Cefadroxil should be used with caution in patients with a history of gastro-intestinal disturbances, particularly colitis.
- The occurrence of diarrhoea may impair the resorption of other medicaments and therefore lead to an impairment of their efficacy.
- Treatment must be discontinued at once if allergic reactions occur (urticaria, exanthema, pruritus, fall of blood pressure and increased heart rate, respiratory disturbances, collapse, etc.) and suitable countermeasures should be taken (sympathomimetics, corticosteroids and/or antihistaminics).
- Particularly on prolonged use frequent checks on the blood count and regular hepatic and renal function tests are advisable. Superinfections with fungi (e.g. candida) can occur on prolonged treatment with cefadroxil.
- In case of severe and persistent diarrhoea, an antibiotic-associated pseudomembranous colitis should be considered. In that case cefadroxil must be discontinued immediately and a suitable therapy should be started.
- Severe life-threatening infections or those which require higher posology or repetitive administrations per day may benefit of parenteral cephalosporins.
- The result of the Coombs' test can be transiently positive during or after treatment with cefadroxil. This also applies to Coombs' tests carried out in newborns whose mothers received treatment with cephalosporins before delivery.
- Forced diuresis leads to a decrease of cefadroxil blood levels.
- Urinary sugar should be determined enzymatically (e.g. with test strips) during treatment with cefadroxil since reduction tests can furnish falsely elevated values.
- Cefadroxil may cause headache, dizziness, nervousness, sleeplessness and fatigue, therefore the ability to drive and use machines may be influenced.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Therefore, caution should be exercised when prescribing for the pregnant women.

Nursing Mothers

Cefadroxil is excreted in breast milk. Therefore, caution should be exercised when cefadroxil is administered to nursing mothers.

DRUG INTERACTIONS

- Cefadroxil should not be combined with bacteriostatic antibiotics (e.g. tetracycline, erythromycin, sulfonamides, chloramphenicol) since an antagonistic effect is possible.
- Treatment with cefadroxil in combination with aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics should be avoided since such combinations can potentiate nephrotoxic effects.
- Frequent checks on coagulation parameters are necessary during concomitant long term use of anticoagulants or thrombocyte aggregation inhibitors to avoid haemorrhagic complications. Concomitant use is not recommended.
- Cefadroxil binds to cholestyramine, which may lead to reduced bioavailability of cefadroxil.
- The concomitant administration of probenecid reduces the renal elimination of cefadroxil. Therefore, plasma concentrations of cefadroxil may be increased when given in combination with probenecid.
- Cefadroxil may interfere with the immunological response to the live typhoid vaccine.

OVERDOSAGE

Symptoms

Nausea, hallucinations, hyperreflexia, extrapyramidal symptoms, clouded consciousness, or even coma and renal functional impairment.

Treatment

First aid after intake of toxic doses: induce vomiting at once or gastric lavage, if necessary hemodialysis. Monitor and if necessary correct the water and electrolyte balance, monitor renal function.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Xifarox (Cefadroxil) Capsules 500mg are available in pack of 12's.
Xifarox (Cefadroxil) Powder for Suspension 125mg/5mL is available in 60mL bottle.
Xifarox (Cefadroxil) Powder for Suspension 250mg/5mL is available in 60mL bottle.
Xifarox (Cefadroxil) Drops 100mg/mL is available in 10mL bottle.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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