Urobacid® 400 mg film-coated tablets

SANDOZ

Composition
1 film-coated tablet contains: Norfloxacin, 400 mg

Properties
Norfloxacin is a fluorinated quinolone – carboxylic acid derivative. It belongs to a group of new gyrase inhibitors with an extremely broad spectrum of antibacterial action. The drug acts by inhibiting bacterial DNA gyrase, an enzyme needed for transcribing and replicating bacterial DNA. On account of this mechanism of action norfloxacin is bactericidal for a variety of grampositive and gramnegative aerobic pathogens.

Norfloxacin has shown in vitro activity against:
Enterobacteriaceae: Citrobacter sp., Citrobacter diversus, Citrobacter freundii; Edwardsiella tarda; Enterobacter sp., Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Escherichia coli; Hafnia sp.; Klebsiella sp., Klebsiella oxytoca, Klebsiella pneumoniae; Morganella morganii; Proteus sp. (indole-positive), Proteus mirabilis, Proteus vulgaris; Providencia sp., Providencia rettgeri, Providencia stuartii; Serratia sp., Serratia marcescens.
Pseudomonaceae:
Pseudomonas aeruginosa, Pseudomonas cepacia, Pseudomonas fluorescens.
Others:
Alkaligenes sp., Flavobacterium sp.
Grampositive cocci:
Enterococci; staphylococcal species, (coagulase negative) staphylococci, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus; group B, D and G streptococci, Streptococcus viridens.
Some bacteria which may be involved in acute gastroenteritis are also highly sensitive to norfloxacin. These include:
Aeromonas hydrophila, Campylobacter fetus subsp. jejuni, enterotoxin-producing E. coli, Plesiomonas shigelloides, Salmonella sp., Salmonella typhi, Shigella sp., Vibrio parahaemolyticus, Vibrio cholerae, Yersinia enterocolitica.
Norfloxacin also shows adequate activity against Bacillus cereus, Neisseria gonorrhoeae, Ureaplasma urealyticum and Haemophilus influenzae.
Most of the anaerobic agents including actinomycetal, fusobacterial, bacteroides and clostridiel species (except for Clostridium perfrigens) are resistant to norfloxacin.
In general, norfloxacin shows cross-resistances with other newer-generation gyrase inhibitors like pefloxacin, ofloxacin, ciprofloxacin and enoxacin. Pathogens resistant to older-generation gyrase inhibitors like nalidixic acid, pipemidic acid and cinoxacin are in general sensitive to norfloxacin. However, norfloxacin-resistant organisms are also resistant to older-generation gyrase inhibitors.
Cross-resistances of norfloxacin with antimicrobials of a different chemical structure are generally absent.

Pharmacokinetics
Oral norfloxacin is rapidly absorbed. About 1 hour after ingesting a 400 mg dose serum levels peak at 1.5 mg/l. The drug is eliminated from the serum at a half-life of approximately 3 – 4 hours. It diffuses readily into the tissues. Concentrations in the tonsils, the vaginal and cervical tissues, the tubes, the ovaries, the renal cortex and the gallbladder wall are only slightly below the serum levels. Biliary, hepatic and renal medullary concentrations exceed those in the serum. Urinary norfloxacin concentrations are particularly high. In normal subjects a single dose of 400 mg was shown to produce a urinary concentration of 200 mg/l and more. Urinary concentrations above 30 mg/l are sustained for at least 12 hours.
Only a minor fraction of a norfloxacin dose (about 10%) is metabolized by the liver and secreted with the bile. The main elimination pathway of the drug is renal.
At a creatinine clearance of better than or equal to 30 ml/min/1.73 squ.m. norfloxacin is eliminated as in subjects with normal kidney function. But at clearances below 30 ml/min/1.73 squ.m. BSA the excretory capacity of the kidneys is clearly reduced so that the half-life is increased to about 8 hours. In volunteers aged between 65 and 75 years whose renal function was normal for their age norfloxacin was eliminated at a slower rate on account of the age-associated reduction of renal activity. But this does apparently not affect norfloxacin absorption. The actual serum half-life in elderly patients is 4 hours.

Indications
Because of its potency and its broad spectrum of action Urobacid should not be prescribed uncritically or for trivial infections. The drug is designed for the treatment of the bacterial infections below, provided they are caused by norfloxacin-susceptible organisms:
- *Simple and complicated acute or chronic urinary tract infections* including cystitis, pyelitis, cystopyelitis, pyelonephritis, chronic prostatitis, epididymitis and urinary tract infections secondary to urologic surgery, neurogenic bladder syndrome or nephrolithiasis.
- *Acute bacterial gastroenteritis* (e.g. traveler's diarrhea).
- *Gonococcal infections* caused by penicillinase-producing or nonpenicillinase-producing strains of Neisseria gonorrhoeae.
- *Typhoid fever.*

There is evidence from studies showing that norfloxacin also has a place in the prevention of certain infections:
- *Prevention of septicemia in patients with severe neutropenia* (e.g. patients with leukemia, after bone marrow transplants or during chemotherapy). In these, norfloxacin suppresses the resident intestinal flora which may cause septicemia.
- *Prevention of bacterial gastroenteritis* (e.g. traveler's diarrhea).

Mode of application
Take film-coated tablets with abundant liquids 1 hour before or 2 hours after meals.

Dosage
The dose depends on the severity of the infection, the susceptibility of the causative agent and the patient's age, body weight and condition. Unless otherwise prescribed, the recommendations below should be followed:
Patients with urinary tract infections should take 400 mg twice a day. Treatment should be continued for 3 – 10 days depending on the clinical course. Chronic recurrent urinary tract infections may require treatment for up to 12 weeks depending on the bacteriology data.
For acute gonococcal infections a single dose of 800 mg is recommended.
Patients with infections caused by Salmonella typhi should be given 400 mg 3 times daily for 14 days.
For acute bacterial gastroenteritis the usual dose is 400 mg of Urobacid twice daily for 5 days.
To prevent bacterial gastroenteritis (traveler's diarrhea) a daily dose of 400 mg should be administered. Prophylactic treatment should be started one day before the arrival in an epidemic region and continued for 2 days after the departure from there.
To prevent septicemia a dose of 400 mg 3 times a day should be taken for as long as neutropenia is demonstrable.

Special dosage guidelines
Dosage in patients with reduced renal function
Studies in patients with a creatinine clearance below 30 ml/min/1.73 sq.m. not requiring hemodialysis showed the plasma half-life to be approximately 8 hours. As clinical trials failed to bring to light any difference in Urobacid half-life between patients with a creatinine clearance below 10 ml/min/1.73 s.squ. and those with a clearance of 10 – 30 ml/min/1.73 sq.m., the dose recommended for both patient groups is 1 film-coated tablet of 400 mg daily. At this dosage level the norfloxacin concentration in the tissues and body fluids of interest exceeds the MIC of most of the organisms susceptible to the drug.
Data on the treatment of patients with a creatinine clearance of less than 10 ml/min/1.73 sq.m. are scarce and inconclusive.
In patients with a creatinine clearance of 30 ml/min/1.73 sq.m. or less the available data are inadequate for recommending a dose for the treatment of gonorrhea.
No data are available for the treatment of patients with typhoid fever and a creatinine clearance of less than 30 ml/min/1.73 sq.m..
Dosage recommendations for elderly patients
Elderly patients with normal renal function do not need any dose adjustments.

Contraindications
The drug should not be used
- in patients hypersensitive to norfloxacin or other quinolones
- in patients with a present or past history of tendinopathies, tendinitis or tendon ruptures
- in pregnant or breast feeding women
- in children and growing adolescents.

Quinolones may stimulate the CNS causing tremor, restlessness, confusion and convulsions.
The effects of Urobacid on brain functions or the electrical activity of the brain have not been established to date. In patients with known or suspected CNS conditions, e.g. severe cerebral atherosclerosis, epilepsy or other convulsive disorders, the risks should be carefully weighed against the benefits before prescribing the drug.

Side effects
In general, Urobacid is well tolerated.
The most common side effects reported in clinical trials were gastrointestinal. These were followed by neuropsychiatric symptoms and skin manifestations.
Gastrointestinal tract
Nausea, heartburn, abdominal pain /cramps, vomiting, anorexia, dry mouth, constipation, bitter taste, bloating, lower abdominal discomfort, dyspepsia and diarrhea.
If persistent severe diarrhea occurs during or after treatment, pseudomembranous colitis should be thought of.
Nervous system/psychiatric
Headache, dizziness, insomnia, depression, anxiety, nervousness, irritability, euphoria, disorientation, hallucinations, tinnitus and hyperlactimation.
Skin
Skin rashes, photosensitivity, Stevens-Johnson syndrome, toxic dermal necrolysis, exfoliative dermatitis, erythema multiforme and pruritus are among the potential side effects.
Hypersensitivity reactions
Anaphylactic reaction, angioneurotic edema, urticaria, arthritis, myalgia, arthralgia, vasculitis, interstitial nephritis.
Liver
ALT (SGOT), AST (SGPT), alkaline phosphatase and LDH may be elevated.
Blood
Leukopenia, eosinophilia, neutropenia, thrombocytopenia and reduced PCV.
Kidneys
It is not known whether the elevated BUN and serum creatinine levels seen sporadically are drug-related.
Other adverse reactions
Rarely weakness, joint and muscle pain, joint stiffness and effusions as well as tendinitis have been reported.
Although extremely rare, rupture of the Achilles tendon has been attributed to the administration of fluorinated quinolones. Like for other drugs of this group, the dose-dependent occurrence of tendinopathies and tendon ruptures cannot altogether be excluded for norfloxacin.

Interactions
Like other organic-acid antibiotics, nitrofurantoin and norfloxacin are antagonistic in vitro.
On concomitant administration, norfloxacin elevates the serum levels of theophylline. In studies of normal subjects this phenomenon was found to show considerable intraindividual variations. But theophylline-related side effects were reported in some patients receiving norfloxacin and theophylline at the same time. Consequently, theophylline serum levels should be monitored in patients receiving both drugs and the theophylline dose she be adjusted, if necessary.
Elevated cyclosporin serum levels were reported in some patients concomitantly treated with norfloxacin and high-dose cyclosporin. This was, however, not confirmed in subsequent clinical trials. But to ensure drug safety, cyclosporin serum levels should be closely monitored in patients receiving both drugs and the dose should be adjusted, if needed.
Quinolones including Urobacid may potentiate the effects of oral warfarin anticoagulants and warfarin derivatives. If these drugs are administered together with Urobacid, the prothrombin time or other relevant clotting parameters should be closely followed.
Multivitamines, iron- or zinc-containing products, antacids and sucralfate should not be taken at the same time of day as Urobacid, but at an interval of at least 2 hours, as they may interfere with Urobacid absorption reducing its serum and urinary concentrations.
Some quinolones including Urobacid may also interfere with caffeine metabolism. This may reduce the elimination of caffeine and prolong its half-life.

Special warnings for safe use
Pregnancy should be ruled out before the drug is prescribed. As norfloxacin may cause central nervous system side effects, reactions may be slowed thus impairing the patient's capacity to drive or operate machinery, particularly on concomitant alcohol intake. Patients should be alerted to the potential occurrence of skin manifestations during norfloxacin medication and instructed to avoid sun light or UV radiation (sun lamps).
The occurrence of persistent severe diarrhea during or after treatment should prompt suspicion of pseudomembranous colitis. While rare, this condition necessitates immediate drug withdrawal and suitable treatment (e.g. with vancomycin, 250 mg 4 times a day).
As with antibiotic treatment generally, the occurrence of resistant organisms (bacteria; fungi: Candida!) should be kept in mind during prolonged treatment with Urobacid.
In patients on prolonged treatment the renal function and the blood count should be followed.

Overdosage
Data on overdosage are limited in humans. In view of the pharmacokinetics of norfloxacin, emptying of the stomach by induced vomiting and/or gastric lavage can be expected to reduce the absorption of the drug in acutely overdosed patients. Adequate fluid intake is essential and promotes renal drug elimination.

Stability
If properly stored, Urobacid film-coated tablets retain their potency up to the date of expiration shown on the pack.

Storage conditions
Store below 25 °C, protect from light and moisture.

Presentations
Single packs of 10, 14 and 20 film-coated tablets, hospital packs.

"Keep medicines out of the reach of children!"

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