Trimox - Trimox Forte

Trimethoprim
Sulfamethoxazole

Urufarma

LI-0000-00

Formula:
Trimox:
Each coated tablet contains:
Trimethoprim.....80 mg
Sulfamethoxazole .....400 mg
Excipients.....q.s.
Trimox Forte:
Each coated tablet contains:
Trimethoprim.....160 mg
Sulfamethoxazole .....800 mg
Excipients.....q.s.

Mode of action:
Sulfamethoxazole inhibits dihydrofolic acid synthesis by competition with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolate by reversible inhibition of dihydrofolate reductase. Thus, the association blocks two consecutive steps of essential DNA and protein biosynthesis in many bacteria.
The result of consecutive blocking is a greatly enhanced action of each compound by the other, and together they show a degree of antimicrobial synergy.

Activity:
The trimethoprim-sulfamethoxazole combination acts as an *in vitro* bactericide against a broad spectrum of gram positive and gram-negative organisms including *Streptococcus*, *Staphylococcus*, *Pneumococcus*, *Neisseria*, *Escherichia coli*, *Klebsiella*, *Proteus spp*. *Haemophilus, Sallmonella, Shigella, Vibrio cholerae,* and *Bordetella.* This medicine is highly active against *Haemophilus influenzae*, *E. coli,* and *Proteus spp*, which makes it particularly suitable for the treatment of chronic bronchitis and urinary tract infections.
The action is given by the sequential block of two bacterial enzyme systems at the same metabolic step. This synergy accounts for the high degree of bactericidal activity. *In vitro* studies have shown that bacterial resistance develops more slowly with the combination than with trimethoprim or sulfamethoxazole taken separately.

Pharmacokinetics:
Trimethoprim and sulphamethoxazole are rapidly absorbed after oral administration. Peak blood levels of the individual components occur one to four hours after oral administration. The half-lives of trimethoprim and sulfamethoxazole, 16 and 10 hours respectively, have the same relative proportion, whether they are administered individually or together. Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after administration of the medicine.
Blood levels of free trimethoprim and sulfamethoxazole are dose dependent. Upon repeated administration, the fixed ratio of blood levels of trimethoprim to sulfamethoxazole is 1:20.
Trimethoprim is found in the blood in free form, as metabolites or bound to proteins; sulfamethoxazole can be found in free form, conjugated, and bound to proteins. Free forms are considered to be the therapeutically active forms. About 44% of trimethoprim and 70% of sulfamethoxazole in blood are bound to proteins. Presence of sulfamethoxazole in plasma decreases protein binding of trimethoprim negligibly. Trimethoprim does not affect protein binding of sulfamethoxazole.
Excretion of trimethoprim and sulfamethoxazole occurs mainly through the kidneys by glomerular filtration and tubular secretion. Urine concentrations of trimethoprim and sulfamethoxazole are considerably greater than blood concentrations. When administered together, neither trimethoprim nor sulfamethoxazole affect each other's excretion levels.

Indications:
The combination of trimethoprim and sulfamethoxazole is indicated for the treatment of the following infections: treatment and prevention of pneumonia by *Pneumocystis jiroveci (P. carinii),* prevention of toxoplasmosis, nocarditis, and melioidosis.
This medicine may also be useful for other infections: middle ear infections, lung infections in patients with chronic bronchitis, urinary tract infections (bladder, kidneys), infectious diarrhoea, treatment of toxoplasmosis, genital and/or perianal lesions (granuloma inguinale or donovanosis), and brucellosis.

Contraindications:
Allergy to sulphonamides, trimethoprim, or cotrimoxazole.
Do not give this medicine to premature infants and newborns under 6 weeks of age. If you have or think you have acute porphyria (a blood disease in which haemoglobin is not properly produced). In combination with dofetilide (a medicine used to control irregular or rapid heartbeat). When administering **Trimox** or **Trimox Forte**, take the usual precautions as when prescribing any medicine to women of childbearing age.

Warnings:
Rare cases of serious, sometimes fatal reactions have been reported with trimethoprim and sulphonamides including fulminant hepatic necrosis (severe liver damage), agranulocytosis (decrease in the number of a certain type of white blood cells), aplastic anaemia (failure of the bone marrow to produce different types of cells), other blood disorders, and hypersensitivity of the respiratory tract.
Life-threatening skin eruptions (Stevens Johnson syndrome, epidermal necrolysis) and acute febrile neutrophilic dermatosis or Sweet's syndrome) have been described with trimethoprim and sulphonamide, initially appearing as reddish circular spots or blotches, often with a central blister. Treatment should be discontinued immediately upon the first appearance of a rash that may indicate the onset of serious adverse reactions. These markers may include: sore throat, fever, joint pain, cough, difficulty breathing, paleness, purple spots on the skin, jaundice, or severe blood disorders. Life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin. The period of greatest risk of serious skin reactions is during the first few weeks of treatment.
If you have developed Stevens Johnson syndrome, toxic epidermal necrolysis, or acute febrile neutrophilic dermatosis with the use of this medicine, you should not use it again at any time.
Hypersensitivity reactions with eosinophilia (increase in a certain type of white blood cells) and systemic symptoms associated with the use of trimethoprim and sulphonamide have been reported in rare cases.
Like most antibiotics, it can very rarely cause pseudomembranous colitis (inflammation of the large intestine causing diarrhoea and abdominal pain) resulting from colonisation by *Clostridium difficile*.

Precautions:
Talk to your doctor before taking **Trimox** or **Trimox Forte** in case of old age, because you may be at a higher risk of experiencing severe side effects, especially if you have liver or kidney problems, or if you are taking other medicines.
The trimethoprim and sulfamethoxazole combination should be administered with caution to patients with impaired renal or hepatic function. Adequate fluid intake and urinary excretion must be maintained to prevent crystalluria or stone formation. In cases of renal disease, a reduced or more spaced dosage is indicated to avoid drug accumulation. In such patients, it is advisable to measure the plasma concentration of the drug.
Consult your doctor if you have severe blood disorders, regular blood counts are necessary whenever long-term therapy is used. **Trimox** y **Trimox Forte** should not be used in the treatment of pharyngitis caused by Group A beta-haemolytic streptococcus (*S. pyogenes*). Special care should be taken when treating patients predisposed to folate deficiency or those with allergy or severe bronchial asthma. Haemolysis may occur in individuals with glucose 6-phosphate dehydrogenase deficiency. This reaction of often dose related.
If you are at risk of hyperkalaemia (high potassium levels) and hyponatraemia (low sodium levels) or have a diet rich in potassium, consult your doctor as they may consider the need for blood potassium and sodium monitoring. Administration of trimethoprim alters the metabolism of phenylalanine, if you suffer from phenylketonuria (a metabolic disease affecting the enzyme phenylalanine) and follow an appropriate restrictive diet this is not a problem, however, talk to your doctor before starting treatment.
Pregnancy, breastfeeding, and fertility: Tell your doctor if you are pregnant, breastfeeding, or think you might be pregnant, so that they can assess the risk/benefit of starting treatment.
Trimethoprim and sulphamethoxazole are excreted in breast milk and cross the placenta, and their safety in pregnant women has not been established. Therefore, they should be avoided during pregnancy. If trimethoprim/sulfamethoxazole is used during pregnancy, high-dose folate supplementation (up to 4-5 mg/day) may be considered. Administration of trimethoprim/sulfamethoxazole should be avoided in late pregnancy and in nursing mothers, when mothers or infants have, or are at particular risk of developing hyperbilirubinaemia, as there may be a potential risk of kernicterus (severe neurological complication due to increased bilirubin in the blood) in the newborn. This potential risk is particularly important in children at increased risk of hyperbilirubinaemia, such as premature infants or those with glucose-6-phosphate dehydrogenase deficiency.
Effects on driving and using machines: **Trimox** and **Trimox Forte** have little to no effect on driving and using machines.

Adverse reactions
The most common adverse effects are hyperkalaemia (high potassium levels).
Other common adverse effects are candidiasis (candida fungal overgrowth), headache, nausea, diarrhoea, and skin rashes.
Uncommon effects include vomiting.
Rare adverse effects are hypersensitivity reactions with eosinophilia (increase of a certain type of white blood cells) and systemic symptoms. Very rare adverse effects are: leukopenia (decrease in the number of white blood cells), neutropenia (decrease in the number of a certain type of white blood cells), thrombocytopenia (decrease in the number of platelets), agranulocytosis (decrease in the number of a certain type of white blood cells), megaloblastic anaemia (decrease in the number of red blood cells and increase in their size), aplastic anaemia (failure of the marrow to produce different types of cells), haemolytic anaemia (characterised by an insufficient number of red blood cells), methaemoglobinaemia (inability of haemoglobin to carry oxygen), eosinophilia (abnormally high number of a certain type of white blood cell), purpura (reddish spots on the skin), haemolysis (rupture of red blood cells) in certain susceptible patients deficient in glucose 6-phosphate dehydrogenase. Serum sickness (allergy-like hypersensitivity reaction), anaphylaxis (severe allergic reaction), allergic myocarditis (allergic reaction affecting the heart), angioedema (fluid retention in the skin and mucous membranes), fever, allergic vasculitis similar to Schoenlein-Henoch purpura (inflammation mainly affecting small veins), periarteritis nodosa (vascular disease), systemic lupus erythematosus (immune-type disease). Hypoglycaemia (low blood glucose), hyponatraemia (low blood sodium), anorexia (metabolic disorder). Depression, hallucinations, aseptic meningitis, convulsions, peripheral neuritis (damage and impairment of peripheral nerves), ataxia (loss of coordination), vertigo, tinnitus (ringing in the ear), dizziness, cough, difficulty breathing, pulmonary infiltrates, glossitis (inflammation of the tongue), stomatitis (lesions in the mouth), pseudomembranous colitis (inflammation of the colon), pancreatitis (inflammation of the pancreas), hepatobiliary disorders (impaired liver function), photosensitivity (skin reaction due to interaction with light), exfoliative dermatitis (severe inflammation of the entire skin surface), fixed drug eruption (allergic reaction), erythema multiforme (allergic reaction affecting the skin), arthralgia (joint pain), myalgia (muscle pain), impaired kidney function, uveitis (inflammation of the eye). Life-threatening skin rashes (Stevens Johnson syndrome, toxic epidermal necrolysis) may occur. Some very rare adverse effects are: possibly related to the treatment of *Pneumocystis jiroveci* (*R. carinii*) pneumonitis; severe hypersensitivity reactions, rash, fever, neutropenia (decrease in the number of a certain type of white blood cells), thrombocytopenia (decrease in the number of platelets), increased liver enzymes, hyperkalaemia (elevated potassium level), hyponatraemia (decrease in blood sodium) and rhabdomyolysis (muscle destruction or swelling with severe muscle pain and weakness).

Overdose:
Symptoms of overdose include vomiting, mental disturbances, petechiae, purpura, and jaundice. In severe cases haematuria, crystalluria, and anuria may occur.
Treatment is symptomatic and may include gastric lavage and forced diuresis. Alkalinisation of the urine may aid in the elimination of sulphamethoxazole.
Hypersensitivity reactions may require treatment with steroids. Calcium folinate, 3 to 6 mg intramuscularly for 5 to 7 days, may help counteract the effects of trimethoprim on haemopoiesis.

Posology:
The usual dose for adults and children over the age of 12 is: 160 mg of trimethoprim and 800 mg of sulfamethoxazole every 12 hours (1 tablet of Trimox Forte or 2 tablets of Trimox).
Talk to your doctor if you do not see improvements after 7 days of treatment, so that you get checked again.
For treatment of urinary tract infections and infectious diarrhoea, the usual alternative dose is:
2 tablets of Trimox or 1 tablet of Trimox Forte (160/800 mg of trimethoprim and sulfamethoxazole) every 12 hours for 3 days.
In adults and children over 12 years of age the recommended dose according to the creatinine clearance (ml/min) is:

Creatinine clearance (ml/min)	Recommended dose
>30	Usual dose
15-30	Half the usual dose
<15	Not recommended

Your doctor may have your blood tested every 2 to 3 days to measure the amount of medicine in your blood.
Pneumocystis jiroveci pneumonia (P carinii)
Treatment:
Adults and children: 20 mg/kg/day of trimethoprim and 100 mg/kg/day of sulfamethoxazole, split into 2 or more doses, for two weeks.
Prophylaxis (prevention):
Adults:
The following dosage regimes can be used:
- 2 tablets of Trimox or 1 tablet of Trimox Forte (160 mg of trimethoprim/800 mg of sulfamethoxazole) once a day, 7 days a week.
- 2 tablets of Trimox or 1 tablet of Trimox Forte (160 mg of trimethoprim/800 mg of sulfamethoxazole) three times a week, every other day.
- 2 tablets of Trimox or 1 tablet of Trimox Forte (160 mg of trimethoprim/800 mg of sulfamethoxazole), twice a day, three times a week, every other day.

Toxoplasmosis
Primary prophylaxis (primary prevention):
Adults and children over the age of 12:
- 1 tablet of Trimox (80 mg of Trimethoprim/400 mg of sulfamethoxazole) once a day.
- 2 tablets of Trimox o 1 tablet of Trimox Forte (160 mg of trimethoprim/ 800 mg of sulfamethoxazole) 3 times a week.
- 2 tablets of Trimox or 1 tablet of Trimox Forte (160 mg of trimethoprim/ 800 mg of sulfamethoxazole) once a day.

Treatment:
Adults: 5 mg/kg of trimethoprim and 25 mg/kg of sulfamethoxazole every 12 hours for 6 weeks.
Granuloma Inguinale (Donovanosis)
160 mg of trimethoprim and 800 mg of sulfamethoxazole (2 tablets of Trimox or 1 tablet of Trimox Forte) twice a day for at least 3 weeks or until all lesions have disappeared completely.
Nocardiosis
10 to 15 mg/kg/day of trimethoprim and 50 to 75 mg/kg/day of sulfamethoxazole, split into 2 or more doses, for 3 to 6 months. Treatment should be more prolonged in immunosuppressed patients. All patients with central nervous system involvement should be treated for at least one year.
Brucellosis
Adults and children over the age of 8:
160 mg of trimethoprim/800 mg of sulfamethoxazole (2 tablets of Trimox or 1 tablet of Trimox Forte) every 12 hours for 6 weeks.
Melioidosis
8 mg/kg/day of trimethoprim and 40 mg/kg/day of sulfamethoxazole (not more than 320 mg of trimethoprim/1600 mg of sulfamethoxazole) every 12 hours for 3-6 months.

Presentations:
Trimox: Packs containing 20 coated tablets.
Trimox Forte: Packs containing 10 coated tablets.

Keep at room temperature (15 - 30°C).

In case of poisoning, seek medical assistance immediately.

Keep out of the reach of children.

URUFARMA S.A.
Monte Caseros 3260 - Montevideo - Uruguay
Phone: (+598) 2487 2424
E-mail: depto_medico@urufarma.com.uy
Website: www.urufarma.com.uy