COTRIMOXAZOLE

BACTILLE - TS

400 mg/80 mg per 5 mL Suspension

ANTIBACTERIAL

Rx

FORMULATION:
Each 5 mL (1 teaspoonful) contains:
Sulfamethoxazole .... 400 mg
Trimethoprim .... 80 mg

PRODUCT DESCRIPTION:
White to cream, lemon-vanilla flavored suspension

PHARMACODYNAMICS AND PHARMACOKINETICS:
Sulfamethoxazole and other sulfonamides interfere with the bacterial nucleic acid synthesis by blocking the conversion of p-aminobenzoic acid to the coenzyme dihydrofolic acid, a reduced form of folic acid. Their action is mainly bacteriostatic.

Trimethoprim is a dihydrofolate reductase inhibitor which blocks the production of tetrahydrofolic acid from bacterial dihydrofolic acid which is needed for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. Trimethoprim acts in the same metabolic pathway as the sulfonamides. Thus, cotrimoxazole blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to bacteria.

Sulfamethozaxole and trimethoprim act on the different parts of the folate metabolism producing a potent synergy between its components in vitro. Depending on the growth condition, trimethoprim may be bacteriostatic or bactericidal.

The antibacterial effect of cotrimoxazole is against a wide range of gram-negative and gram-positive organisms, e.g., *E. coli, Salmonella, Klebsiella* most of the *Enterobacter, Shigella, Proteus, Serratia, Streptococcus* (including group A beta-hemolytic streptococcus), some strains of *Streptococcus pneumoniae*, *Staphylococcus, Pneumococcus, Clostridium perfringens, Bacillus antracis,* and *Nocardia asteroides*.

Cotrimoxazole is particularly active against the problem organisms Haemophilus influenzae and Proteus mirabilis or vulgaris. Other sensitive organisms include *Actinomyces spp*., *Brucella, Klebsiella granulomatis, Legionella,* and *Yersinia pestis.*

Cotrimoxazole is also active against the protozoan *Pneumocystis carinii* and has some activity against *Plasmodium falciparum* and *Toxoplasma gondii*. It is not active against *Mycobacterium tuberculosis* and *Treponema pallidum*. *Pseudomonas aeruginosa* is frequently insensitive.

When cotrimoxazole is administered by mouth, plasma concentrations of trimethoprim and sulfamethoxazole are generally around the optimal ratio of 1:20, although they vary from 1:2 to 1:30 or more. The ratio of the two drugs is usually much lower in the tissues since trimethoprim, the more lipophilic drug, penetrates many tissues better than sulfamethoxazole and has a much larger volume of distribution. The ratio may vary from 1:1 to 1:5 in the urine depending on the pH.

Following oral administration, sulfamethoxazole is readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur at about 2 hours and plasma half-life is about 6-12 hours. Patients with severe renal impairment have prolonged plasma half-life. Sulfonamides like sulfamethoxazole freely diffuse throughout the body tissues and fluids such as urine, saliva, sweat, bile, cerebrospinal, peritoneal, ocular, and synovial fluids, and in pleural and other effusions. Sulfamethoxazole crosses the placenta and the fetal circulation. Low concentrations have been detected in breast milk.

After an oral dose, trimethoprim is rapidly and completely absorbed from the gastrointestinal track. Peak plasma concentrations are about 1 to 4 hours. Half-life in adults is about 8 to 10hours. Half-life is prolonged in severe renal impairment and in neonates, whose renal function is immature. It is widely distributed to various tissues and body fluids including kidney, liver, lungs, bronchial secretions, saliva, aqueous humor, prostatic tissue and fluid, and vaginal secretions. While concentrations in these tissues are said to be higher in serum concentrations, concentrations in the CSF are about 25 – 50% of those in the serum. Trimethoprim rapidly crosses the placenta and appears in breast milk. It is excreted primarily by the kidney. About 10 – 20% of trimethoprim is metabolized in the liver. Small amounts are excreted in the feces via the bile. About 40 – 60% of a dose is excreted in urine.

INDICATIONS:
For the treatment of infections of the genito-urinary tract, respiratory tract infections such as bronchitis and *Pneumocystis carinii* pneumonia and enteric infections.

DOSAGE AND ADMINISTRATION:
For Children – to be given every 12 hours,
From 6 weeks – 5 months: 120 mg (1.25 mL)
6 months – 5 years: 240 mg (2.5 mL)
6 – 12 years: 480 mg (5 mL)

- **Prophylaxis of *Pneumocystis carinii* infections**

From 6 weeks – 5 months: 120 mg (1.25 mL) twice daily on 3 consecutive days or 7 days per week
6 months – 5 years: 240 mg (2.5 mL)
6 – 12 years: 480 mg (5 mL)
Note: 480 mg of cotrimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg.

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS:
Cotrimoxazole should not be given to patients with a history of sensitivity to sulfonamide or trimethoprim. Treatment with cotrimoxazole should be discontinued immediately at the first appearance of skin rash or of any other serious adverse reaction.

Care should be exercised in patients with history of asthma or allergy. Patients with AIDS may be prone to adverse reactions. Sulfamethoxazole is also considered to be contraindicated in lupus erythematosus as it may exacerbate the condition.

Cotrimoxazole is contraindicated in patients with marked liver parenchymal damage, megaloblastic anemia or severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed. It should be used with caution in patients with lesser degrees of liver impairment.

It should be used with caution in patients with renal impairment. In patients with renal or hepatic impairment, a reduced or less frequent dosage is recommended in order to avoid accumulation of trimethoprim in the blood. For such patients, serum assays or monitoring of plasma drug concentrations are necessary.

To minimize the risk of crystalluria, an adequate fluid intake should be ensured during treatment.

To minimize the risk of undesirable reactions, the duration of treatment should be as short as possible, particularly in elderly patients since they are more susceptible to adverse effects. Alkalinization of the urine increases urinary excretion of sulfamethoxazole but decreases urinary excretion of trimethoprim.

In elderly patients or patients with previous folic acid deficiency or kidney failure, hematologic changes indicative of folic acid deficiency may occur. These are reversible by folinic acid therapy.

In patients on prolonged therapy with cotrimoxazole, regular blood counts, urinalysis and renal function tests should be done. If a significant reduction of the blood count of any formed element is noted, treatment with cotrimoxazole should be discontinued.
Cotrimoxazole should not be given to premature babies nor during the 1st week of life because of the risk of producing kernicterus. It is usually not given to children under 3 months to infants below 6 weeks.

Other than in exceptional cases, cotrimoxazole should not be given to patients with serious hematological disorders, to patients with a G6PD deficiency unless absolutely essential and only in minimal doses to prevent the possibility of hemolysis.

In patients predisposed to folate deficiency such as elderly patients and in those receiving high doses of cotrimoxazole for a prolonged period, folate supplementation may be necessary. Cotrimoxazole is contraindicated in patients with megaloblastic anemia caused by folate deficiency.

Sulfonamides may interfere with some diagnostic tests such as tests for urea, creatinine, urine glucose and urobilinogen. Trimethoprim may interfere with some diagnostic tests, including the Jaffé reaction for creatinine and those for serum-methotrexate assay where dihydrofolate reductase is used.

Cross-sensitivity is known to occur among sulfonamides. Fatal outcome, though rare, has been reported in connection with severe reactions, e.g., blood dyscrasia, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and fulminant liver necrosis.

USE IN PREGNANCY AND LACTATION:
Cotrimoxazole should be avoided during pregnancy and lactation. Throughout pregnancy, sulfonamides should be used only in the absence of a suitable alternative drug.

Although sulfonamides are excreted into the breast milk in small amounts, they are generally contraindicated in nursing mothers because of the risk of kernicterus. Care is required when using trimethoprim in breastfeeding mothers.

DRUG INTERACTIONS:
Owing to the displacement of sulfamethoxazole from plasma binding sites or to the inhibition of metabolism, it potentiates the effects of some drugs, such as oral anticoagulants, methotrexate, and phenytoin.

Possible interactions of sulfamethoxazole with other highly protein bound drugs such as NSAIDS should be considered.

Sulfonylureas, oral antidiabetic drugs, and methotrexate may increase the antibacterial activity of sulfamethoxazole. PABA and its derivatives particularly potassium aminobenzoate and the procaine group of local anesthetics may antagonize sulfamethoxazole.

The antidiabetic effect of the sulfonylurea compounds may be enhanced by sulfonamides. High doses of sulfonamides have been reported to have a hypoglycemic effect.

There were isolated reports of possible failure of hormonal contraceptives that resulted in pregnancy in females who were given sulfonamides.

Trimethoprim has been reported to increase the serum concentration and potentiate the effect of phenytoin, digoxin, procainamide, warfarin, rosiglitazone, and repaglinide. This may due to either competitive inhibition of renal excretion, decreased metabolism or both.

Trimethoprim may reduce the renal excretion and increase the blood concentrations of antiviral agents such as zidovudine, zalcitabine, and lamivudine. Rifampicin may decrease the concentration of trimethoprim. Dapsone and trimethoprim increase each other's serum concentrations.

The use of trimethoprim or cotrimoxazole and ciclosporin has been reported to increase the risk of nephrotoxicity.
Hyponatremia has occurred in patients who were given trimethoprim with diuretics. Severe hyperkalemia has been reported in patients given trimethoprim together with an ACE inhibitor.

Use of trimethoprim with bone marrow suppressing drugs may increase the likelihood of myelosuppression. There may be a risk of megaloblastic anemia if trimethoprim is given with other folate inhibitors, such as pyrimethamine or methotrexate.

There is an increased risk of thrombocytopenia in elderly patients given cotrimoxazole with diuretics.

ADVERSE REACTIONS:
The most common side effects of cotrimoxazole are those from its components. The most common adverse effects from sulfamethoxazole and trimethoprim are fever, gastrointestinal disturbances (mainly nausea and vomiting and diarrhea) and skin reactions such as pruritis, skin rash, and photosensitivity reactions. Rarely, the following skin reactions have been reported, erythema nodosum, exfoliative dermatitis, erythema multiforme, Steven-Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome).

Stomatitis and glossitis may occur. Hematological changes have been observed in some patients, particularly the elderly. The reported changes consist primarily of neutropenia and thrombocytopenia. Observed less frequently: leukopenia, aplastic and hemolytic anemia, purpura, agranulocytosis, bone marrow depression, and systemic reactions may occur. Jaundice has also rarely occurred and has usually been mild and transient, frequently occurring in patients with past history of infectious hepatitis. The effect of cotrimoxazole on human folate metabolism appears to be negligible.

Sulfamethoxazole may be associated with nephrotoxic reactions including interstitial nephritis and tubular necrosis which may result in renal failure. Hematuria, oliguria, and anuria may also occur. Myocarditis, pulmonary eosinophilia, fibrosing alveolitis, vasculitis including polyarteritis nodosa was also reported. The slow acetylators of sulfamethoxazole maybe at higher risk of adverse effects than the fast acetylators.

Other adverse effects include hypoglycemia, hypothyroidism, and neurological reactions including aseptic meningitis, ataxia, benign intracranial hypertension, convulsion, dizziness, drowsiness, peripheral neuropathies, psychosis, tinnitus, vertigo, pancreatitis and rarely cyanosis due to methemoglobinemia. Acute hemolytic anemia is a rare complication which may be associated with G6PD deficiency.

Manifestations of generalized hypersensitivity reaction to sulfonamides include syndrome resembling serum sickness, hepatic necrosis, hepatomegaly, and jaundice. Anaphylaxis has been reported very rarely.

Sulfamethoxazole may cause alteration of the gastrointestinal microflora and there's a small probability that pseudomembranous colitis may occur.

Trimethoprim is associated with disturbances in liver enzyme values and cholestatic jaundice, as well as increase levels of creatinine and blood urea nitrogen. Trimethoprim may induce hyperkalemia.

OVERDOSE AND TREATMENT:
Cotrimoxazole may cause abnormalities in hematopoiesis due to the interference of folic acid metabolism manifested by megaloblastic anemia, leucopenia, and thrombocytopenia particularly when given for a long period of time. Calcium folinate 5 to 15 mg may be given to discontinue this effect.

If someone takes dose larger than the recommended, call a doctor, emergency medical services (EMS), or the nearest poison control center immediately.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Boston Round Amber Glass Bottle in a box (75 mL)

DR-XY17489

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

"For suspected adverse drug reactions, report to the FDA: www.fda.gov.ph"

Manufactured for:
PNSV ASIA CORPORATION
4th Flr., S.V. More Group Corporate Center
#16 Scout Tuazon cor. Roces Ave., Quezon City
Metro Manila, Philippines
by: Hizon Laboratories, Inc.
Assumption Road, Sumulong Highway
Antipolo City

Date of Renewal of Authorization: 06 November 2018
Date of Revision of Package insert: 07 September 2018