Primera

COTRIMOXAZOLE PRIMECOTRIX

Rx

240 mg/5 mL SUSPENSION
A N T I B A C T E R I A L

FORMULATION:
Each 5 mL (1 teaspoonful) contains:
Sulfamethoxazole, USP…….200 mg
Trimethoprim ……..…40 mg

DESCRIPTION:
Cotrimoxazole (Primecotrix) is a synthetic antibacterial combination product containing 200 mg sulfamethoxazole and 40 mg trimethoprim per 5 mL for oral administration. Cotrimoxazole (Primecotrix) is a white to off-white suspension with orange/butterscotch flavor with sweet fruit/candy taste.

PHARMACODYNAMICS:
Cotrimoxazole (Primecotrix) contains Sulfamethoxazole and Trimethoprim which sequentially inhibits two bacterial enzymes that result in successive stage in the biosynthesis of the folinic acid in the microorganisms. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Sulfamethoxazole inhibits the bacterial synthesis of dihydrofolic acid by competing with PABA (Para Amino Benzoic Acid). This result is more in bactericidal activity in vitro at concentrations at which the individual substances are only bacteriostatic. Sulfamethoxazole and Trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acid and proteins essential to many bacteria.

PHARMACOKINETICS:
Absorption:
Trimethoprim and Sulfamethoxazole are completely and rapidly absorbed after oral administration. Following a single dose of 800 mg of Sulfamethoxazole and 160 mg of Trimethoprim, peak plasma concentrations of 40-80 µg/mL of Sulfamethoxazole and 1.5-30 µg/mL of Trimethoprim are reached within 1-4 hours. Following 12-hour interval of repeated above dosage administration, minimum plasma concentration is achieved in 2-3 days at steady state range between 32 µg/mL and 63 µg/mL Sulfamethoxazole and 1.3 µg/mL—2.8 µg/mL Trimethoprim.

Bioavailabilty:
The absolute oral bioavailability of absorption of Sulfamethoxazole and Trimethoprim is complete for reaching 100% of both drugs.

Distribution:
The volume of distribution is approximately 0.2 L/kg for Sulfamethoxazole and 1.6 L/kg for trimethoprim, while the plasma protein binding reaches 66.2% of Sulfamethoxazole and 37% for Trimethoprim. Superior penetration by Trimethoprim, relative to Sulfamethoxazole has been reported in saliva, normal and inflamed lung tissues, bile fluid, vaginal fluid, seminal fluid and non-inflamed prostatic tissue whereas penetration into aqueous humor and cerebrospinal fluid is similar on both compounds.

Metabolism:
Trimethoprim dose is metabolized by 20%. The cytochrome P450 isoenzymes involved in the oxidative metabolism of Trimethoprim have not been identified. The principal Trimethoprim metabolites are 1- and 3-oxides and the 3- and 4- hydroxy derivatives; some metabolites are microbiologically active. Approximately 80% of Sulfamethoxazole is metabolized by the liver, predominantly to the N-4 acetyl derivative and to a lesser extent by glucuronide conjugation. Sulfamethoxazole also undergoes oxidative metabolism. The first step of the oxidative pathway, which leads to the formation of the hydroxylamine derivative is catalyzed by CYP2C9

Elimination:
The elimination half-life of Sulfamethoxazole is 11 hours and for Trimethoprim is 10 hours. The metabolites of Sulfamethoxazole and Trimethoprim are eliminated clearly by the kidneys through glomerular filtration and tubular secretion by giving the urine concentrations of both active substances higher than the blood concentrations. One quarter Sulfamethoxazole and 2/3 of Trimethoprim are excreted unchanged into the urine. The total plasma clearance of Trimethoprim equal 1.9 mL/min/kg. The total plasma clearance of Sulfamethoxazole is equal to 0.32 mL/min/kg. Small quantity of Sulfamethoxazole and Trimethoprim are eliminated via feces. Both of their metabolites are eliminated entirely by the kidneys through glomerular filtration and tubular secretion, giving urine concentrations of both active substances considerably higher than the concentration in the blood.

INDICATIONS:
For acute and chronic disorders of upper and lower respiratory tract infections.

DOSAGE AND ADMINISTRATION:
6 weeks to 5 months :½ tsp. (2.5 mL)
5 months to 5 years :1 tsp. (5 mL)
6 years to 12 years :2 tsp. (10 mL)
To be taken every 12 hours or as prescribed by the physician.

CONTRAINDICATION:
• Cotrimoxazole (Primecotrix) is contraindicated in patients with marked liver parenchymal damage.
• Cotrimoxazole (Primecotrix) is also contraindicated in patients with severe renal insufficiency when repeated determination of plasma concentration cannot be monitored.
• Cotrimoxazole (Primecotrix) should not be given to patients with history of hypersensitivity to its active ingredient or any excipients.
• Cotrimoxazole (Primecotrix) is contraindicated to pregnancy.
• Cotrimoxazole (Primecotrix) should not be given to newborn until first 6 weeks of life.

WARNINGS AND PRECAUTIONS :
• Cotrimoxazole (Primecotrix) should be used with caution during administration in patients with a history of severe allergy and bronchial asthma.
• Cotrimoxazole (Primecotrix) should not be given to patients with G6PD due to the possibility of hemolysis. Therefore, Cotrimoxazole (Primecotrix) should only be used in the judgment of physician. The potential benefits may warrant the use of drug in G6PD patients despite the potential risk.
• Idiosyncratic reactions to sulfonamides are prone to patients who are slow acetylators.
• Patients with porphyria or thyroid dysfunction should be cautious with all drugs containing sulfonamides.
• In patients with Folic acid deficiency or Kidney failure, hematological changes are indicative of folic acid deficiency. These are reversible by folinic acid therapy.
• Patients taking trimethoprim and methotrexate may lead to pancytopenia.
• Cotrimoxazole (Primecotrix) should not be given to patients with serious hematological disorders. If Cotrimoxazole (Primecotrix) is given for prolonged period, regular blood count is required. If a significant reduction in count of any formed blood element occurred, Cotrimoxazole (Primecotrix) should be discontinued.

PREGNANCY AND LACTATION:
Pregnancy:
Cotrimoxazole (Primecotrix) crosses the placental barrier and may thus interfere with the folic acid metabolism. Cotrimoxazole (Primecotrix) should be used during pregnancy only if recommended by the physician and should be given 5 mg of folic acid daily.The potential benefit justifies the potential risk of the fetus. Cotrimoxazole (Primecotrix) should be avoided during the last stage of pregnancy because of the possible risk of kernicterus on neonates. Base on the study report to pregnant women, literature reviews and spontaneous reports of malformations, Cotrimoxazole (Primecotrix) appears to present no significant risk of teratogenicity in humans.

Lactation:
Trimethoprim and Sulfamethoxazole may be ingested by breast fed infant, possible risk for the infant should be weighed against the expected therapeutic benefit of the mother. Both Trimethoprim and Sulfamethoxazole pass into the breast milk.

DRUG INTERACTIONS:
Cotrimoxazole (Primecotrix) must not be given in combination with dofetilide. Trimetophrim may inhibit renal excretion of dofetilide.
Patients receiving amantadine or memantine may increase risk of neurological adverse effect such as delirium and myoclonus.
Cotrimoxazole (Primecotrix) and dapsone may cause methemoglobinemia. Patients receiving both cotrimoxazole (Primecotrix) and dapsone should be monitored. Alternative therapy should be considered if possible.
Patients receiving repaglinide, pioglitazone, rosiglitazone and sulfonylurea derivative such as glibenclamide, gliclazide, chlorpropamide and tolbutamide should be monitored regularly for hypoglycemia. Concomitant use of Cotrimoxazole (Primecotrix) together with digoxin may increase digoxin blood level. Serum digoxin level should be monitored.
Cotrimoxazole (Primecotrix) with co-administration of clozapine should be avoided. Clozapine is a drug known to have a substantial potential for causing agranulocytosis.
Elderly patients concurrently receiving thiazide diuretics have occasional reports that there is an increase incidence of thrombocytopenia. Platelets should be monitored regularly in patients receiving diuretics.
Cases of pancytopenia have been reported in patients taking the combination of trimethoprim and methotrexate.
Co-administration of Cotrimoxazole (Primecotrix) may reduce the efficacy of tricyclic antidepressants.
Patients receiving Cotrimoxazole (Primecotrix) and zidovudine should be monitored for hematological toxicity. Zidovudine is known to induce hematological abnormalities.
Caution should be used when Cotrimoxazole (Primecotrix) is administered with other agents that increase serum potassium level, such as Angiotensin Converting Enzyme Inhibitor (ACEi) and the Angiotensin Renin Blockers (ARBs), due to the potassium sparing effect of Cotrimoxazole (Primecotrix). Frequent monitoring of serum potassium is recommended specially in patients with potassium disorder, renal insufficiency in patients receiving high dose of Cotrimoxazole (Primecotrix).

ADVERSE DRUG REACTION:

The most common side effects of Cotrimoxazole (Primecotrix) are skin rashes and gastrointestinal disturbances.
The following standard categories for frequency are used below:
Very common ≥1/10; Common ≥1/100 and <1/10; Uncommon ≥1/1,000 and <1/100; Rare ≥1/10,000 and <1/1,000 and very rare <1/10,000.

Adverse Events Reported in the General Patient Population Treated with Cotrimoxazole		
Blood and Lymphatic system disorders	**very rare <1/10,000**	Agranulocytosis Anemia(megaloblastic, hemolytic, autoimmune aplastic) Pancytopenia Methemoglobinemia
	Rare ≥1/10,000 and <1/1,000	The changes most commonly seen have been: Granulocytopenia Leucopenia Thrombocytopenia Most of the hematological changes observed have been mild, asymptomatic and reversible on withdrawal therapy.
Gastrointestinal disorders	**very rare <1/10,000**	Acute Pancreatitis have been reported; several patients had serious illness including AIDS patients Pseudomembranous enterocolitis
	Rare ≥1/10,000 and <1/1,000	Diarrhea Glossitis Stomatitis
	Common ≥1/100 and <1/10	Nausea (with or without vomiting)
Hepatobiliary disorders	**very rare <1/10,000**	Elevated Bilirubin Hepatitis Cholestasis Elevated transaminases Liver necrosis Vanishing bile duct syndrome
Immune system disorders	**very rare <1/10,000**	Hypersensitivity reactions have been reported. Allergic reactions may occur in patients who are hypersensitive to the excipients: e.g. fever, angioneurotic edema, anaphylactoid reaction and serum sickness. Pulmonary infiltrates occur in eosinophilic or allergic alveolitis have been reported. They manifest themselves through symptoms such as cough or shortness of breath. Cases of periarthritis nodosa and allergic myocarditis have been reported. Should such symptoms appear or unexpectedly worsen, the patient should be re-evaluated and discontinuation of Cotrimoxazole should be considered.
Infections and infestations	**very rare <1/10,000**	Candidiasis
Metabolism and Nutrition disorders	**very rare <1/10,000**	High dose of Trimethoprim, as used in patients with *Pneumocystis carinii* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even at the recommended doses Trimethoprim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, renal insufficiency or who are receiving drugs which induce hyperkalemia. Close monitoring of serum potassium is warranted in this patients. Hyponatremia have been reported. Hypoglycemia have been reported on nondiabetic patients.
Musculoskeletal, connective tissues and bone disorders	**very rare <1/10,000**	Arthralgia Myalgia Isolated cases of rhabdomyolysis have been reported
Nervous System disorders	**very rare <1/10,000**	Aseptic meningitis Ataxia Convulsions Neuropathy (paresthesia and peripheral neuritis) Tinnitus Uveitis Vertigo
Psychiatric disorders	**very rare <1/10,000**	Single case of hallucinations

Renal & Urinary disorders	**very rare <1/10,000**	Cotrimoxazole may increase diuresis, particularly on patients with edema of cardiac origin. Crystalluria Elevated serum creatinine Elevated Blood Urea Nitrogen (BUN) Impaired renal function
Skin and Subcutaneous tissue disorders	**very rare <1/10,000**	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Erythema Multiforme Henoch-Schoenlein Purpura Stevens-Johnson Syndrome Toxic Epidermal Necrolysis (Lyell's Syndrome) *Sulfonamides containing drugs may linked to photosensitivity*
	Common ≥1/100 and <1/10	Multiple skin reactions have been described; these are generally mild and quickly reversible after withdrawal of medication.

These differences concern the following System Organ Classes:		
Blood and lymphatic disorders	**Very common ≥1/10**	Leucopenia Granulocytopenia Thrombocytopenia
Gastrointestinal disorders	**Very common ≥1/10**	Anorexia Nausea (with or without vomiting)
General disorders and administration site conditions	**Very common ≥1/10**	Fever usually in conjunction with maculopapular eruptions
Hepatobiliary disorders	**Very common ≥1/10**	Elevated transaminases
Skin and Subcutaneous tissue disorders	**Very common ≥1/10**	Maculopapular rash usually with pruritus
Metabolism and nutrition disorders	**Very common ≥1/10**	Hyperkalemia
	Uncommon ≥1/1,000 and <1/100	Hypoglycemia Hyponatremia

Safety of Cotrimoxazole in HIV infected Patients:
The HIV patient population is similar to the general patient population in terms of the spectrum of adverse events that may occur. However, some adverse events may occur with a higher frequency and a difference in the clinical feature.

OVERDOSAGE AND TREATMENT:
Overdosage:
Cotrimoxazole (Primecotrix) acute over dosage symptoms may include such as nausea, vomiting, diarrhea, vertigo, dizziness, mental and visual disturbances, crystalluria, anuria, and hematuria may occur in severe cases of over dosage.
Cotrimoxazole (Primecotrix) chronic over dosage symptoms may include such as bone marrow depression, manifested as thrombocytopenia or leucopenia. Blood dyscrasias due to folinic acid deficiency may occur.

Treatment:
Cotrimoxazole (Primecotrix) overdosage treatment may depend on the symptoms. The following treatment measure may be considered. Promotion of renal excretion by alkalinization of urine by forced diuresis in which it increases sulfamethoxazole elimination. Prevention of further absorption. Hemodialysis. Electrolyte and blood count monitoring. Peritoneal dialysis is not applicable nor effective for treatment. If jaundice or blood dyscrasia occurs, calcium folinate therapy should be instituted for these complications. 3-6mg IM for 5-7 days should be given to counteract the effect of trimethoprim on hematopoiesis.

STORAGE CONDITION:
Protect from light
Keep bottle tightly closed
Shake well before using
Store at temperatures not exceeding 30°C

AVAILABILITY:
Amber Glass Bottle x 60 mL (Box of 1's)

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

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

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