SCHEDULING STATUS:
S4

PROPRIETARY NAMES AND DOSAGE FORMS:
CO-TRIMOXAZOLE 480 BIOTECH tablets
CO-TRIMOXAZOLE 960 BIOTECH tablets

COMPOSITION:
Each CO-TRIMOXAZOLE 480 BIOTECH Tablet contains: 80 mg Trimethoprim and 400 mg Sulphamethoxazole.
Each CO-TRIMOXAZOLE 960 BIOTECH Tablet contains: 160 mg Trimethoprim and 800 mg Sulphamethoxazole.
Inactive Ingredients: Maize starch, magnesium stearate and povidone.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.1 Antimicrobial agents other than antibiotics

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
The antimicrobial activity of the combination of trimethoprim and sulphamethoxazole results from its actions on two steps of the enzymatic pathway for the synthesis of tetrahydrofolic acid. Sulphamethoxazole inhibits the incorporation of PABA into folic acid and trimethoprim prevents the reduction of dihydrofolate to tetrahydrofolate.
Resistance may occur.
Pharmacokinetic properties
Absorption, Distribution and Excretion:
After a single oral dose of the preparation, trimethoprim is absorbed more rapidly than sulphamethoxazole. The co-administration of the medicines appears to slow the absorption of sulphamethoxazole. Peak blood concentration of trimethoprim usually occurs in 2 hours in most patients, while that of sulphamethoxazole is seen 4 hours after a single oral dose. The half-lives of trimethoprim and sulphamethoxazole are 16 and 10 hours respectively. When 400 mg of sulphamethoxazole is given with 80 mg of trimethoprim (the concentration 5:1 ratio) three times daily, the mean minimal steady state concentrations of the medicines are approximately 20 µg/ml and 1 µg/ml, respectively. Trimethoprim is rapidly distributed and concentrated in tissues, and relatively small quantities are bound to plasma protein in the presence of sulphamethoxazole.
The medicine enters the cerebrospinal fluid and sputum. High concentrations of each component of the mixture are also found in the bile. About 65 % of sulphamethoxazole is bound to plasma protein. Up to 60 % of the administered trimethoprim and from 25 % to 50 % of sulphamethoxazole are excreted in the urine in 24 hours. Two-thirds of the sulphonamide is unconjugated. Metabolites of trimethoprim are also excreted. The rates of excretion and the urine concentration of both compounds are significantly reduced in patients with uraemia.

INDICATIONS:
Urinary tract infections: The management of uncomplicated infections of the lower urinary tract and infections of the upper urinary tract.
Genital infections: Acute gonococcal urethritis in both men and women.
Respiratory tract infections: Pulmonary infections with *H. influenzae* and *Strep. pneumoniae.*

CONTRA-INDICATIONS:
Jaundice, hypersensitivity to sulphonamides or trimethoprim, impaired renal or liver function.
CO-TRIMOXAZOLE should not be given to infants within 1 to 2 months of birth.
CO-TRIMOXAZOLE should not be given to patients with porphyria.
CO-TRIMOXAZOLE should not be given to patients with megaloblastic anaemia. It should be avoided in those who may have megaloblastic bone-marrow changes or folic acid deficiency and in patients receiving anticonvulsant medicines.

WARNINGS AND SPECIAL PRECAUTIONS:
Erythema multiforme, toxic dermal necrolysis and allergic vasculitis may occur with use of CO-TRIMOXAZOLE.
Treatment with CO-TRIMOXAZOLE should be discontinued immediately if a rash appears.
CO-TRIMOXAZOLE should be used with caution in patients with allergic conditions or bronchial asthma.
Adequate fluid intake is recommended to reduce the risk of crystalluria.
Blood tests should be made frequently particularly during prolonged treatment:
the appearances of sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders.
Patients should avoid direct exposure to sunlight as it facilitates development of sensitisation dermatitis.

INTERACTIONS:
CO-TRIMOXAZOLE should be used with caution in patients receiving pyrimethamine and immunosuppressive therapy.
CO-TRIMOXAZOLE may enhance the effects of phenythoin, methotrexate and warfarin.
High doses of CO-TRIMOXAZOLE may have a hypoglycaemic effect. The antidiabetic effect of the sulphonylureas may be enhanced by concomitant administration of CO-TRIMOXAZOLE.
The action of CO-TRIMOXAZOLE may be antagonised by para-aminobenzoic acid and compounds derived from it, particularly the procaine group of local anaesthetics.
Previous or simultaneous administration of diuretics with CO-TRIMOXAZOLE may carry an increased risk of thrombocytopenia, especially in elderly patients with heart failure; death may occur.
The effects of sulphonamides may be enhanced by displacement from plasma binding sites by more highly bound acidic substances, such as phenylbutazone or sulfinpyrazone.
Concurrent use of CO-TRIMOXAZOLE with digoxin may increase the serum concentrations of digoxin.
Methenamine in combination with CO-TRIMOXAZOLE may increase the danger of crystalluria.
Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine and lamivudine.
An increased risk of nephrotoxicity has been reported with the use of CO-TRIMOXAZOLE and cyclosporine.
Severe hyperkalaemia has been noted in patients given CO-TRIMOXAZOLE together with an ACE inhibitor.

PREGNANCY AND LACTATION:
CO-TRIMOXAZOLE should not be given to pregnant women especially in early pregnancy and before delivery. Contra-indicated in nursing mothers. Sulphonamides and trimethoprim are distributed into breast milk.

DOSAGE AND DIRECTIONS FOR USE:
Adults and children over 12 years:
Two CO-TRIMOXAZOLE 480 BIOTECH tablets (or one CO-TRIMOXAZOLE 960 BIOTECH) twice daily, morning and evening after meals.
Minimum dosage for long term treatment (more than 14 days):
One CO-TRIMOXAZOLE 480 BIOTECH tablet twice daily.
Maximum dosage (for severe cases):
Three CO-TRIMOXAZOLE 480 BIOTECH tablets twice a day.
In acute infections, CO-TRIMOXAZOLE should be given for at least 5 days or until the patients have been free from symptoms for 2 days.
Dosage must be reduced in patients with renal insufficiency. CO-TRIMOXAZOLE should not be administered if creatinine clearance is less than 15 ml/minute, unless facilities for haemodialysis are available.

SIDE EFFECTS:
Blood and the lymphatic system disorders
Less frequent: CO-TRIMOXAZOLE may cause or precipitate megaloblastosis, leukopenia or thrombocytopenia.
Haematological reactions, in addition to those mentioned above, are various types of anaemia (including aplastic, haemolytic and macrocytic), coagulation disorders, methaemoglobinaemia, granulocytopenia, agranulocytosis, purpura, Henoch-Schonlein purpura, sulph-haemoglobinaemia, leucopenia and eosinophilia.
Adverse effects on the blood may be more severe in malnourished or elderly patients.
Endocrine disorders
Less frequent: Pancreatitis.
Metabolism and nutrition disorders
Less frequent: Acidosis, anorexia, goitre and hypothyroidism.
Psychiatric disorders
Less frequent: Depression, psychosis and hallucinations.
Nervous system disorders
Frequent: Headache, dizziness and fatigue.
Less frequent: Drowsiness, insomnia, nightmares, confusion, ataxia, vertigo, peripheral neuritis, aseptic meningitis.
Ear and labyrinth disorders
Frequent: Tinnitus.
Vascular disorders
Incidence not known: Polyarthritis nodosa.
Gastrointestinal disorders
Frequent: Nausea and vomiting constitute the bulk of gastrointestinal reactions. Glossitis, stomatitis and diarrhoea may occur.
Less frequent: Pseudomembranous colitis and drug fever may occur.
Hepato-biliary disorders
Less frequent: Hepatitis has been reported. Transient jaundice has been noted and appears to have the histological features of allergic cholestatic hepatitis. Most patients who have developed icterus have had a history or prior infectious hepatitis.
Skin and subcutaneous tissue disorders
Frequent: Exfoliative dermatitis, rashes and pruritus.
Less frequent: Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) may occur.
Musculoskeletal, connective tissue and bone disorders
Less frequent: Lumbar pain and arthralgia. Rhabdomyolysis has been reported mainly in AIDS patients.
Renal and urinary disorders
Less frequent: Toxic nephrosis, which may be attributed to a hypersensitivity reaction, has been reported.
Dysuria, haematuria, oliguria and anuria may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
High doses may cause diarrhoea, nausea and vomiting. It may cause a depression of haemopoiesis due to interference of the drug in the metabolism of folic acid. Injections of calcium folinate may be given to counteract this interference.
Treatment is symptomatic and supportive.

IDENTIFICATION:
CO-TRIMOXAZOLE 480 BIOTECH: White, round, flat bevelled edged tablet plain on one side and breakline on other.
CO-TRIMOXAZOLE 960 BIOTECH: White, oblong , normal convex tablet with breakline.

PRESENTATIONS:
CO-TRIMOXAZOLE 480 BIOTECH: HDPE containers, Alu-PVC blister strips, sealed aluminium bags or patient ready packs of 14, 28, 30, 56 or 100 tablets.
CO-TRIMOXAZOLE 960 BIOTECH: HDPE containers, Alu-PVC blister strips, sealed aluminium bags or patient ready packs of 14, 28, 30, 56 or 100 tablets.
All pack sizes may not necessarily be marketed.

STORAGE INSTRUCTIONS:
Store in a dry place at or below 25 °C. Protect from light. KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:
CO-TRIMOXAZOLE 480 BIOTECH: P/20.2.1/260
CO-TRIMOXAZOLE 960 BIOTECH: W/20.2.1/88

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:
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SKEDULERINGSTATUS:
S4

EIENDOMSNAAM EN DOSEERVORM:
CO-TRIMOXAZOLE 480 BIOTECH tablette
CO-TRIMOXAZOLE 960 BIOTECH tablette

SAMESTELLING:
Elke CO-TRIMOXAZOLE 480 BIOTECH tablet bevat: 80 mg trimetoprim en 400 mg sulfametoksasool.
Elke CO-TRIMOXAZOLE 960 BIOTECH tablet bevat: 160 mg trimetoprim en 800 mg sulfametoksasool.
Onaktiewe bestanddele: Magnesiumstearaat, mieliestysel en povidoon.
Suiker vry.

FARMAKOLOGIESE KLASSIFIKASIE:
A 20.2.1 Antimikrobiese middels anders as antibiotika.

FARMAKOLOGIESE WERKING:
Farmakodinamiese eienskappe
Die antimikrobiese aktiwiteit van die kombinasie van trimetoprim en sulfametoksasool is die gevolg van die optrede op twee vlakke van die ensiematiese weg vir die sintese van tetrahidrofoliensuur.
Sulfametoksasool inhibeer die inkorporering van PABS in foliensuur en trimetoprim verhoed die vermindering van dihidrofolaat na tetrahidrofolaat.
Weerstandigheid mag voorkom.
Farmakokinetiese eienskappe
Absorpsie, verspreiding en uitskeiding:
Na 'n enkele dosis van die middel word trimetoprim vinniger geabsorbeer as sulfametoksasool. Die mede-toediening van die medisyne blyk die absorpsie van sulfametoksasool te vertraag. Maksimum bloedkonsentrasies van trimetoprim vind gewoonlik binne 2 uur plaas in die meeste pasiënte, terwyl die van sulfametoksasool 4 ure na 'n enkele orale dosis gesien word. Die halfleeftye van trimetoprim en sulfametoksasool is onderskeidelik 16 en 10 uur. Wanneer 400 mg sulfametoksasool drie maal per dag met 80 mg trimetoprim (die konsentrasie 5:1 verhouding) gegee word, is die gemiddelde minimale bestendige konsentrasie van die medisyne onderskeidelik ongeveer 20 µg/ml en 1 µg/ml. Trimetoprim word vinnig versprei en gekonsentreer in weefsel, en relatief klein hoeveelhede word aan plasma proteïene gebind in die teenwoordigheid van sulfametoksasool. Die medisyne dring die serebrospinale vloeistof en speeksel in. Hoë konsentrasies van elke komponent van die mengsel word ook in die gal aangetref. Ongeveer 65 % van sulfametoksasool word aan plasma proteïene gebind. Tot 60 % van die toegediende trimetoprim en 25 % tot 50 % sulfametoksasool word binne 24 uur in die urine uitgeskei. Twee-derdes van die sulfonamied is ongekonjugeerd. Metaboliete van trimetoprim word ook uitgeskei. Die tempo van uitskeiding en die urienkonsentrasie van beide verbindings word aansienlik verminder in pasiënte met uremie.

INDIKASIES:
Urienweginfeksies: Die behandeling van ongekompliseerde infeksies van die onderste urienweg en infeksies van die boonste urienweg.
Genitale infeksies: Akute gonokokkale uretritis in beide mans en vroue.
Respiratoriese infeksies: Pulmonêre infeksies met *H. influenza* en *Strep. pneumonia*.

KONTRAINDIKASIES:
Geelsug, hipersensitiwiteit vir sulfonamiede of trimetoprim, verswakte nier- of lewerfunksie.
CO-TRIMOXAZOLE moet nie binne 1 tot 2 maande van geboorte aan babas gegee word nie.
CO-TRIMOXAZOLE moet nie aan pasiënte met porfirie gegee word nie.
CO-TRIMOXAZOLE moet nie aan pasiënte met megaloblastiese anemie gegee word nie.
Dit moet vermy word by diegene wat megaloblastiese beenmurg veranderinge of dié wat foliensuur tekorte mag hê en pasiënte wat antikonvulsante medikasie ontvang.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:
Veelvuldige eriteem multiforme, toksiese dermale nekrolise en allergiese vaskulitis kan voorkom deur gebruik te maak van CO-TRIMOXAZOLE .
Behandeling met CO-TRIMOXAZOLE moet onmiddellik gestaak word indien 'n uitslag verskyn.
CO-TRIMOXAZOLE moet met omsigtigheid gebruik word by pasiënte met allergiese toestande of brongiale asma. Voldoende vloeistofinname word aanbeveel om die risiko van kristallurie te verminder.
Bloedtoetse moet gereeld tydens langdurige behandeling gedoen word. Die verskyning van keelseer, koors, bleekheid, purpura of geelsug kan vroeë aanduidings wees van ernstige bloed afwykings.
Pasiënte moet direkte blootstelling aan sonlig vermy aangesien dit die ontwikkeling van sensitiseringsdermatitis bevorder.

INTERAKSIES:
CO-TRIMOXAZOLE moet met omsigtigheid gebruik word by pasiënte wat pirimetamien en immuunonderdrukkende behandeling ontvang.
CO-TRIMOXAZOLE mag die effekte van fenitoïen, metotreksaat en warfarien verhoog.
Hoë dosisse CO-TRIMOXAZOLE mag 'n hipoglisemiese effek hê. Die anti-diabetiese effek van die sulfonielureas mag vererger word deur die gepaardgaande toediening van CO-TRIMOXAZOLE.
Die werking van CO-TRIMOXAZOLE kan geantagoniseer word deur para-aminobenzoësuur en verbindings wat daaruit afgelei word, veral die prokaïene groep lokale verdowing.
Vorige of gelyktydige toediening van diuretika met CO-TRIMOXAZOLE kan 'n verhoogde risiko van trombositopenie dra, veral by ouer pasiënte met hartversaking; dood mag voorkom.
Die effek van sulfonamiede kan verbeter word deur verplasing vanaf plasma bindingsplekke deur meer hoogs gebonde suurstowwe, soos fenielbutasoon of sulfienpirasoon.
Gelyktydige gebruik van CO-TRIMOXAZOLE met digoksien kan die serum konsentrasies van digoksien verhoog.
Metenamien in kombinasie met CO-TRIMOXAZOLE kan die gevaar van kristallurie verhoog.
Trimetoprim is aangemeld om die nieruitskeiding te verminder en bloedkonsentrasies van zidovudien, salsitabien en lamivudien te verhoog.
'n Verhoogde risiko vir nefrotoksisiteit is aangemeld met die gebruik van CO-TRIMOXAZOLE en siklosporien.
Ernstige hiperkalemie is opgemerk by pasiënte wat CO-TRIMOXAZOLE saam met 'n ACE-inhibeerder ontvang.

SWANGERSKAP EN LAKTASIE:
CO-TRIMOXAZOLE moet nie aan swanger vroue gegee word nie, veral tydens vroeë swangerskap en voor geboorte. Die gebruik daarvan word gekontraïndikeer in moeders wat borsvoed.
Sulfonamiede en trimetoprim word deur die borsmelk oorgedra.

DOSIS EN GEBRUIKSAANWYSINGS:
Volwassenes en kinders ouer as 12 jaar: Twee CO-TRIMOXAZOLE 480 BIOTECH tablette (of een CO-TRIMOXAZOLE 960 BIOTECH tablet) twee maal per dag, oggend en aand na etes.
Minimum dosis vir langtermynbehandeling (meer as 14 dae): Een CO-TRIMOXAZOLE 480 BIOTECH tablet twee maal per dag.
Maksimum dosis (vir ernstige gevalle): Drie CO-TRIMOXAZOLE 480 BIOTECH tablette twee maal per dag.
By akute infeksies moet CO-TRIMOXAZOLE vir minstens 5 dae gegee word, of totdat die pasiënt simptoomvry is vir 2 dae.
Die dosis moet verminder word by pasiënte met nier ontoereikendheid. CO-TRIMOXAZOLE moet nie toegedien word as kreatinienopruiming minder as 15 ml/minuut is nie, tensy geriewe vir hemodialise beskikbaar is.

NEWE EFFEKTE:
Bloed- en limfstelselafwykings
Minder algemeen: CO-TRIMOXAZOLE kan megaloblastose, leukopenie of trombositopenie veroorsaak. Hematologiese reaksies, benewens die bogenoemde, is verskillende tipes anemie (insluitende aplastiese, hemolitiese en makrositiese), stollingsversteurings, metemoglobemie, granulositopenie, agranulositose, purpura, Henoch-Schönlein purpura, sulfa-hemoglobienemie, leukopenie en eosinofilie.
Nadelige effekte op die bloed kan erger wees by ondervoede of ouer pasiënte.
Endokriene afwykings
Minder algemeen: Pankreatitis.
Metabolisme en voedings afwykings
Minder algemeen: Asidose, anorexia, goiter en hipotireose.
Psigiatriese afwykings
Minder algemeen: Depressie, psigose en hallusinasies.
Senuweestelsel afwykings
Algemeen: Hoofpyn, duiseligheid en moegheid.
Minder algemeen: Lomerigheid, slaaploosheid, nagmerries, verwarring, ataksie, vertigo, perifere neuritis, aseptiese meningitis.
Oor en labirint afwykings
Algemeen: Tinnitus.
Vaskulêre versteurings
Voorkoms onbekend: Poliarteritis nodosa.
Gastroïntestinale afwykings
Algemeen: Naarheid en braking vorm die grootste deel van gastroïntestinale reaksies. Glossitis, stomatitis en diarree mag voorkom.
Minder algemeen: Pseudomembraneuse kolitis en dwelmkoors mag voorkom.
Hepatobiliêre afwykings
Minder algemeen: Hepatitis is aangemeld. Oorlopende geelsug is opgemerk en blyk die histologiese kenmerke van allergiese cholestatiese hepatitis te hê. Die meeste pasiënte wat ikterus ontwikkel het, het 'n geskiedenis of vorige aansteeklike hepatitis gehad.
Vel- en subkutane weefselafwykings
Algemeen: Eksfoliatiewe dermatitis, uitslag en jeuk.
Minder algemeen: Stevens-Johnson sindroom en toksiese epidermale nekrolise (Lyell se sindroom) kan voorkom.
Muskuloskeletale, bindweefsel- en beenafwykings
Minder algemeen: Lumbale pyn en artralgie. Rhabdomiolise is hoofsaaklik gerapporteer in VIGS-pasiënte.
Nier- en urinêre afwykings
Minder algemeen: Giftige nefrose, wat aan hipersensitiwiteitsreaksies toegeskryf kan word, is aangemeld. Disurie, hematurie, oligurie en anurie kan voorkom.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:
Hoë dosisse kan diarree, naarheid en braking veroorsaak. Dit kan depressie van hemopoiëse veroorsaak as gevolg van teenwerking van die medikasie in die metabolisme van foliensuur. Inspuitings van kalsiumfolien mag gegee word om hierdie teenwerking teen te werk.
Behandeling is simptomaties en ondersteunend van aard.

IDENTIFIKASIE:
CO-TRIMOXAZOLE 480 BIOTECH Wit, ronde, plat fasetvormige tablette, glad aan die een kant en met 'n breeklyn aan die ander kant.
CO-TRIMOXAZOLE 960 BIOTECH Wit, langwerpige tablette, normale konvekse tablet met breeklyn.

AANBIEDING:
CO-TRIMOXAZOLE 480 BIOTECH: HDPE houer, Alu-PVC stulpstroke, geseëlde aluminium sakkies of pasiënt gereed pakke van 14, 28, 30, 56 or 100 tablette.
CO-TRIMOXAZOLE 960 BIOTECH: HDPE houer, Alu-PVC stulpstroke, geseëlde aluminium sakkies of pasiënt gereed pakke van 14, 28, 30, 56 or 100 tablette.
Al die verpakkingsgroottes word nie noodwendig bemark nie.

BERGINGSAANWYSINGS:
Bewaar in 'n droë plek teen of benede 25 °C.
Beskerm teen lig.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:
CO-TRIMOXAZOLE 480 BIOTECH P/20.2.1/260
CO-TRIMOXAZOLE 960 BIOTECH W/20.2.1/88

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:
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Suid Afrika

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