1. NAME OF THE MEDICINAL PRODUCT

UNITRIM DS TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulfamethoxazole 800mg

Trimethoprim 160mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1.Therapeutic indications

Co.Trimoxazole is an antibacterial agent, effective against a wide range of gram negative and gram positive organisms. Co-Trimoxazole is indicated for treatment of respiratory tract infections, Genito urinary tract, gastro intestinal tract ,skin and other bacterial infections

4.2.Posology and method of administration

Route of administration: Oral

It may be preferable to take UNITRIM DS with some food or drink to minimize the possibility of gastrointestinal disturbances.

Standard dosage recommendations for acute infections

This dosage approximates to 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram body weight per 24 hours.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days' therapy, the patient should be reassessed.

As an alternative to Standard Dosage for acute uncomplicated lower urinary tract infections, short-term therapy of 1 to 3 days' duration has been shown to be effective.

The elderly:

See Special Warnings and Precautions for Use. Unless otherwise specified standard dosage applies.

Impaired hepatic function:

No data are available relating to dosage in patients with impaired hepatic function.

Special Dosage Recommendations

(Standard dosage applies unless otherwise specified).

Where dosage is expressed as "tablets" this refers to the adult tablet, i.e 80 mg Trimethoprim BP and 400 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Impaired renal function:

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of UNITRIM. If the concentration of total sulfamethoxazole exceeds 150 microgram/ml then treatment should be interrupted until the value falls below 120 microgram/ml.

Pneumocystis jiroveci (P. carinii) pneumonitis: Treatment: A higher dosage is recommended using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of greater than or equal to 5 microgram/ml

Prevention: Adults : The following dose schedules may be used:

160 mg trimethoprim/800 mg sulfamethoxazole daily 7 days per week.

160 mg trimethoprim/800 mg sulfamethoxazole three times per week on alternative days.

320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times per week on alternative days.

Children:

The following dose schedules may be used for the duration of the period at risk (see Standard dosage recommendations for acute infections subsection

- Standard dosage taken in two divided doses, seven days per week
- Standard dosage taken in two divided doses, three times per week on alternate days
- Standard dosage taken in two divided doses, three times per week on consecutive days
- Standard dosage taken as a single dose, three times per week on consecutive days

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Nocardiosis: There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used (one tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim).

Toxoplasmosis: There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience. For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jiroveci* pneumonitis may be appropriate.

4.3.Contraindications

UNITRIM DS should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of Unitrim DS.

Contra-indicated in patients showing marked liver parenchymal damage.

Contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

Unitrim should not be given to premature babies nor to full-term infants during the first 6 weeks of life except for the treatment/prophylaxis of PCP in infants 4 weeks of age or greater.

4.5 Interaction with other medicinal products and other forms of interaction

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular

secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.
In some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.
Reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.
Concurrent use of rifampicin and Unitrim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.
When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.
In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.
Occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co- trimoxazole be prescribed concurrently.
Co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with Unitrim is advisable.
Co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.
Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.
Co-trimoxazole may increase the free plasma levels of methotrexate.
Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.
Administration of trimethoprim/sulfamethoxazole 160mg/800mg (co- trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.
Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.
Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.

4.6 Pregnancy and lactation

There are no any adequate data from the use of Unitrim DS in pregnant women. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.
Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see 5.3 Preclinical Safety Data). Unitrim should not be

used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Unitrim is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when Unitrim is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6- phosphate dehydrogenase deficiency.

Lactation

The components of Unitrim (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Unitrim should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of Unitrim should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines

N/A

4.8 Undesirable effects

As co-trimoxazole contains trimethoprim and a sulphonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency. In addition, adverse events may vary in their incidence depending on the indication

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

ATC Code: JO1EE01

J-ANTI-INFECTIVE FOR SYSTEMIC USE
J01-ANTIBACTERIAL FOR SYSTEMIC USE
JO1E-SALFONAMIDES AND TRIMETHOPRIM
J01EE -COMBINATION OF SULFONAMIDES AND TRIMETHOPRIM INC DERIVATIVES

J01EE01 SULFAMETHOXAZOLE AND TRIMETHOPRIM

Pharmacological properties:

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives; **ATC code: J01EE01**

Mode of Action

Unitrim is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostatic. Trimethoprim binds to and reversibly inhibits bacterial dihydrofolate reductase (DHFR) and blocks the production of tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity *in vitro* between the two agents.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out- compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

Trimethoprim binds to plasmodial DHFR but less tightly than to bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Many common pathogenic bacteria are susceptible *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, *in vitro* activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

5.2 Pharmacokinetic properties

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Trimethoprim is a weak base with a pKa of 7.4. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear

fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.
Approximately 50% of trimethoprim in the plasma is protein bound. The half-life in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with young patients.
The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely..
Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in a variety of body fluids is of the order of 20 to 50% of the plasma concentration.
Approximately 66% of sulfamethoxazole in the plasma is protein bound. The half-life in man is approximately 9 to 11 hours in the presence of normal renal function.
There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25ml/minute.
The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

5.3 Preclinical safety data

Reproductive toxicology: At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats,

6. PHARMACEUTICAL PARTICULARS

6.1.List of ingredients

Starch
Methyl paraben
Micro-crystalline cellulose
Sodium starch glycolate type A
Magnesium stearate

6.2.Incompatibilities

Not applicable.

6.3.Shelf life

24 months

6.4.Special precautions for storage

Store below 25^0 C, in a dry place. Protect from light keep out of reach of children.

Legal category:
Prescription only medicine (POM)

6.5 Nature and contents of container

Al. Printed Foil, PVC Reel, Unit Carton, Literature Insert, Polythene Bag, Outer cartons label, Outer cartons, B.O.P.P. Tape

6.6 Special precautions for disposal and other handling

No special requirements.

7. REGISTRANT

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