SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

Chemotrim Tablet

2. Qualitative and quantitative composition

Each tablet contains Trimethoprim 80mg and Sulphamethoxazole 400mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

A light pink tablet with AFRAB inscribed on one side and a marked line on the other.

4. Clinical particulars

4.1 Therapeutic indications

Chemotrim is a broad spectrum chemotherapeutic agent widely used for the treatment of urinary tract infection, (acute and chronic) respiratory tract infections (including *pneumocystis carinii*), genital infection such as gonorrhea, gastro-intestinal tract infection, skin and soft tissues infections. Sensitivity testing of the culture media should be free of thymidine, a special antagonist to Trimethoprim

4.2 Posology and method of administration

Children over 12 years and Adult:
In mild infection: 2 tablets every 12 hours.
In severe infection: 2 tablets every 8 hours.

Method of Administration

Oral administration only

4.3 Contraindications

Chemotrim should not be given to patients with a history of hypersensitivity to

sulphonamides or trimethoprim. Chemotrim is contra-indicated in patients with severe hepatic parenchymal damage. Should not be given to patients with serious haematological disorders.

Chemotrim should not be given to neonates or premature babies.

4.4 Special warnings and precautions for use

Folate supplement should be considered when giving Chemotrim to suspected folate deficient patients and to the elderly or in prolonged high doses.

The safety of chemotrim in human pregnancy has not been established.
Sulphonamide containing products should not be administered in late pregnancy because of the risk of kernicteris.

4.5 Interaction with other medicinal products and other forms of interaction

Chemotrim has been shown to potentiate the anti-coagulant activity of warfarin. Careful control of anti-coagulant therapy during treatment with Chemotrim is advisable.
Chemotrim prolongs the half life of phenytoin and may affect thyroid function tests.

4.6 Fertility,Pregnancy and Lactation

Pregnancy

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see section 5.3). There are no adequate data from the use of sulfamethoxazole/trimethoprim in pregnant women. Some epidemiologic studies suggest that exposure to sulfamethoxazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot. However, findings are inconsistent and limitations of observational studies do not allow definite conclusions on an association between sulfamethoxazole/trimethoprim exposure and the risk of embryofoetal toxicity. If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the foetus. Because of the potential risk of teratogenicity, sulfamethoxazole/trimethoprim should only be used in pregnancy, particularly in the first trimester, when the benefit is considered to outweigh the risks. In this case, folate supplementation should be considered. Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significant 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 sulfamethoxazole/trimethoprim 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 sulfamethoxazole/trimethoprim are excreted in breast milk. Administration of sulfamethoxazole/trimethoprim should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing hyperbilirubinaemia and kernicterus.

Fertility

Data on the continuous treatment of adult males for one month with a sulfamethoxazole/trimethoprim combination indicated a disruption of spermatogenesis, potentially caused by folate deprivation of spermatogenic cells through the inhibitory action of trimethoprim on dihydrofolate reductase. Sulfamethoxazole/trimethoprim did not affect the fertility of rats.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of co-trimoxazole on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of co-trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

Chemotrim is well tolerated but the most side effects include mild nausea with or without vomiting and skin rashes, various haematological changes have been reported the majority being mild and reversible when treatment was stopped.

4.9 Overdose

Nausea, vomiting, dizziness and confusion are likely symptoms of over dosage, gastric lavage may be useful though absorption from the GIT is very rapid and complete in approximately two hours.

Acidification of the rate of elimination of trimethoprim. Calcium folinate (3-6mg/day) will counteract effect of trimethoprim in the bone marrow.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives;

ATC code: J01EE01

Mechanism of Action

Co-trimoxazole 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 bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to 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.

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

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.

Susceptability testing breakpoints

EUCAST

Enterobacteriaceae: S≤ 2 R> 4

S. maltophilia: S≤ 4 R> 4

Acinetobacter: S≤ 2 R> 4

Staphylococcus: S≤ 2 R> 4

Enterococcus: S≤ 0.032 R> 1

Streptococcus ABCG: S≤ 1 R> 2

Streptococcus pneumoniae: S≤ 1 R> 2

Hemophilus influenza: S≤ 0.5 R> 1

Moraxella catarrhalis: S≤0.5 R >1

Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant. *These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.

Trimethoprim: sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration.

Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

Commonly susceptible species:
Gram-positive aerobes: *Staphylococcus aureus* *Staphylococcus saprophyticus* *Streptococcus pyogenes*
Gram-negative aerobes: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Salmonella* spp. *Stenotrophomonas maltophilia* *Yersinia* spp.
Species for which acquired resistance may be a problem:
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium* *Nocardia* spp. *Staphylococcus epidermidis* *Streptococcus pneumoniae*
Gram-negative aerobes: *Citrobacter* spp.

Enterobacter aerogenes *Escherichia coli* *Klebsiella pneumoniae* *Klebsiella pneumonia* *Proteus mirabilis* *Proteus vulgaris* *Providencia* spp. *Serratia marcesans*
Inherently resistant organisms:
Gram-negative aerobes: *Pseudomonas aeruginosa* *Shigella* spp. *Vibrio cholera*

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound.

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 66% of sulfamethoxazole in the plasma is protein bound. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim 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 elderly patients 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.

The half-life of sulfamethoxazole 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 25 ml /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.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

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.

In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of Co-Trimoxazole should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Elderly patients

In elderly patients, a slight reduction in renal clearance of sulfamethoxazole but not trimethoprim has been observed.

Paediatric population

See special dosage regimen (see section 4.2).

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, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. Pharmaceutical particulars
6.1 List of excipients

Corn starch
Povidon PVP K-30
Tartrazine orange
Magnesium stearate
Talcum powder
Microstalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 ° C.

6.5 Nature and contents of container

Blister pack of 10 x 10 tablets and Hospital pack of 1000’s tablets

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. APPLICANT/MANUFACTURER

Afrab Chem Limited
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