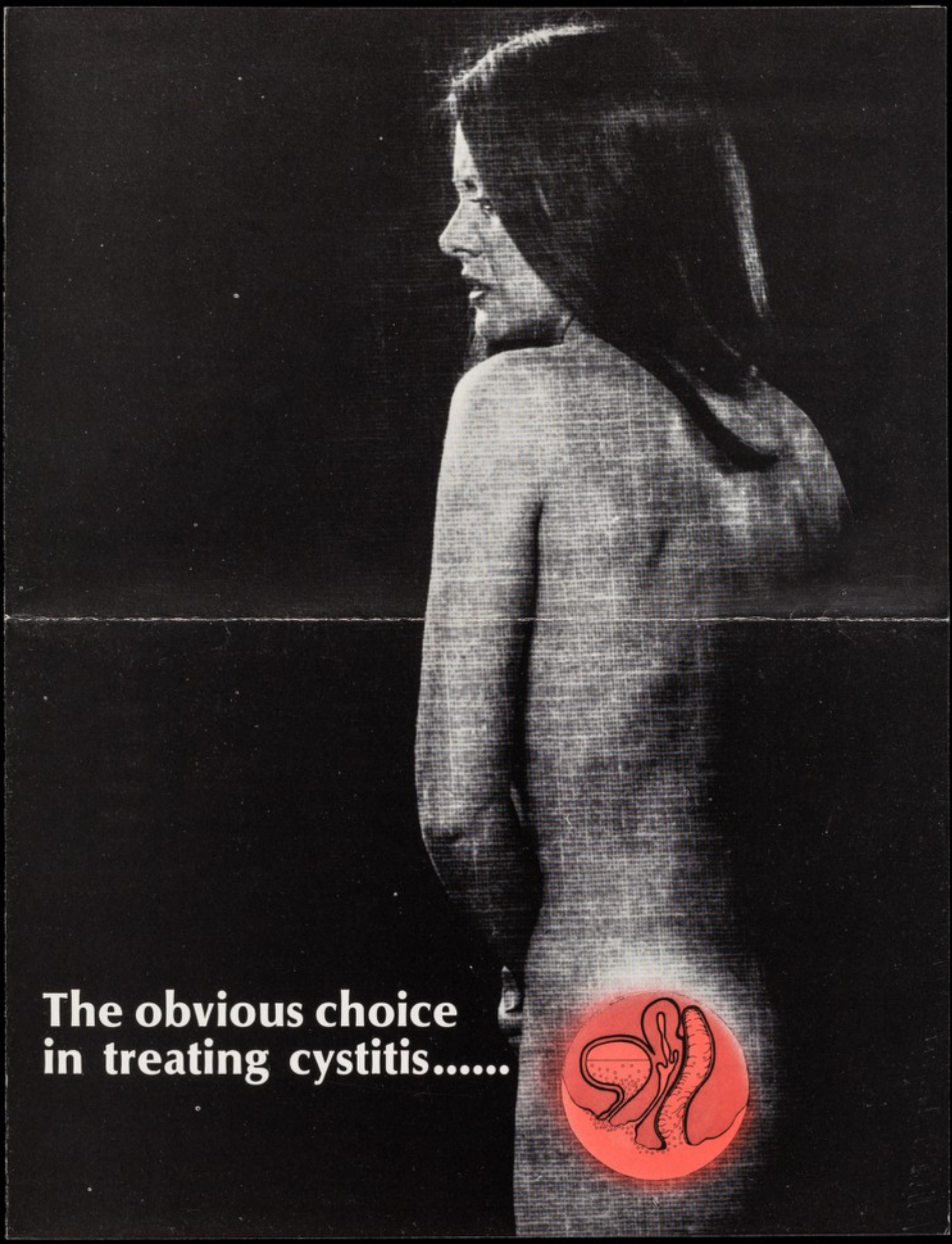
The obvious choice in treating cystitis..... : Mezenol DS the multi-tract approach in U.T.I.


The obvious choice
in treating cystitis.....

MEZENOL* DS

Reg. No. Double strength tablets K/20.2/190. Adult tablets G/20.2/97. Paediatric Suspension G/20.2/99.
Co-trimoxazole Mezenol* *Trademark.

the multi-tract approach in U.T.I.†

"It is generally accepted that nearly all bacterial colonisations of the bladder urine originate in ascending infection. Faecal organisms contaminate the perineum, vestibule and periurethral regions and thence gain admission to the urinary tract.

. . . The female is more vulnerable than the male because of the shorter urethra and because of its position relative to the source of infection. . ."[1]

MEZENOL* DS
does not significantly affect the resistance pattern of the lower bowel coliform flora. Colonisation by predominant faecal organisms is minimised.

MEZENOL* DS
is highly effective with greater spectrum of sensitivity compared to other antimicrobials

MEZENOL* DS
the logical attack against U.T.I. pathogens

Spectrum of Activity:

Drug	Sulphadimidine	Sulphafurazole	Sulphamethizole	Tetracycline	Nitrofurantoin	MEZENOL* Co-trimoxazole	MEZENOL* DS Co-trimoxazole DS	Ampicillin	Amoxycillin	Talampicillin	Nalidixic Acid	Cephalosporin
Dose (Normal renal function)	1g six-hourly	1g six-hourly	200mg six-hourly	250mg six-hourly	100mg eight-hourly	2 Tabs 12 hourly	1 Tab 12 hourly	500mg six-hourly	250mg eight-hourly	250mg eight-hourly	1g six-hourly	500mg six-hourly
E coli	■■■□	■■■□	■■■□	■■■□	■■■■	■■■■	■■■■	■■□□	■■□□	■■□□	■■■■	■■■□
Proteus mirabilis	■■■□	■■■□	■■■□	■□□□	■□□□	■■■■	■■■■	■■■□	■■■□	■■■□	■■■□	■■■□
Kl. aerog.	■■□□	■■□□	■■□□	■■■□	■■□□	■■■□	■■■□	■□□□	■□□□	■□□□	■■■□	■■■□
Strep. faec.	■□□□	■□□□	■□□□	■■□□	■■■■	■■■□	■■■□	■■■■	■■■■	■■■■	■□□□	■■□□
Staph	■■■□	■■■□	■■■□	■■■□	■■■■	■■■■	■■■■	■■□□	■■□□	■■□□	■□□□	■■■■
Ps. procyaned	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□	■□□□

Spectrum of sensitivity/resistance: ■■■■ Usually sensitive ■■■□ Occasional resistance ■■□□ Resistance common ■□□□ Resistance usual

Chart adapted from reference (1)

MEZENOL* DS

For recurrent urinary tract infection† in adults

"Standby courses of co-trimoxazole ..... should be given to the patient so that she can start treatment at the onset of symptoms ....."[1]

"For intransigent problems, prolonged courses of suppressant antimicrobials have proved useful ..... co-trimoxazole (1 tablet nightly) ..... given at night because bladder emptying occurs less frequently during the night hours." [1]

MEZENOL* DS

For urinary tract infection† in children

"Choice of Drug ..... co-trimoxazole is suitable because it is excreted in high concentration in the urine and does not significantly affect the resistance pattern of the lower bowel coliform flora..... ..... and because of
- *Good compliance*
- *Little bowel flora resistance*
- *Few side effects*
- *Good prophylactic"*[2]

THE OBVIOUS CHOICE...
MEZENOL* DS

MEZENOL* DS (Double strength) tablets containing 160 mg trimethoprim and 800 mg sulphamethoxazole

MEZENOL* Tablets containing 80 mg trimethoprim and 400 mg sulphamethoxazole

MEZENOL* Suspension containing 40 mg trimethoprim and 200 mg sulphamethoxazole per 5 ml suspension

The first double strength co-trimoxazole in Southern & Central Africa

The most economical form of co-trimoxazole—
Double in strength, lower in cost.

The most convenient form of co-trimoxazole—simpler dosage
one tablet (instead of 2) b.d., encourages greater patient compliance

Further information available on request. †due to susceptible organisms.
References: (1) Antony J. Wing, Medicine S.A. 28-31 p.43-50 (1) I.C.S. Normand & Jean Smellie, Medicine S.A. 28-31 p.51-56 Feb 1978.

MEZENOL* DS

the multi-tract approach in U.T.I.†

Registration Number:
Double Strength Tablets K/20.2/190
Adult Tablets G/20.2/97
Paediatric Suspension G/20.2/99

PHARMACOLOGICAL CLASSIFICATION: 20.2

DISTRIBUTION CATEGORY: PP

APPROVED NAME: Co-Trimoxazole

TRADE NAME:
mezenol

COMPOSITION

D-S Tablets– 160 mg trimethoprim and 800 mg sulphamethoxazole per tablet.
Adult Tablets – 80 mg trimethoprim and 400 mg sulphamethoxazole per tablet.
Suspension – 40 mg trimethoprim and 200 mg sulphamethoxazole per 5 ml suspension (preserved with 0.2% m/v methylhydroxybenzoate and 0.02% m/v propylhydroxybenzoate).

IDENTIFICATION:
D-S Tablet – white oblonged scored with CAPS and MEZENOL D-S on either face.
Adult Tablet – white scored tablet with CAPS and MZL on either face.
Suspension – pink suspension.

PHARMACOLOGICAL ACTION:

The introduction of trimethoprim in combination with sulphamethoxazole constitutes an important advance in the development of clinically effective antimicrobial agents and represents the practical application of a theoretical consideration; that is, if two drugs act on sequential steps in the pathway of an obligate enzymatic reaction in bacteria, the result of their combination will be supraadditive. Extensive biochemical studies of the mode of action of this combination of compounds clearly indicated that this is the case. The details of the mechanisms of action of this preparation were defined well before its range of clinical effectiveness was established. There is little doubt that, in this combination of tremethoprim, sulphonamide will find a broader area of therapeutic usefulness.

Antibacterial Spectrum – The antibacterial spectrum of trimethoprim is similar to that of sulphamethoxazole, although the former drug is usually 20 to 100 times more potent that the latter. The data presented here refer to the antimicrobial activity of the combination of trimethoprim and sulphamethoxazole. All strains of Strep. pneumoniae, C. diphtheriae, and N. meningitidis are sensitive to trimethoprim sulphamethoxazole. From 50 to 95% of strains of Staph. aureus, epidermidis, Strep. pyrogenes, the viridans group of streptococci, Strep. faecalis, E. coli, Pr. mirabilis, Pr. morganii, Pr. rettgeri, Enterobacter (aerobacter) species, Salmonella, Shigella, Pseud. pseudomallei, Serratia and Alcaligenes species are inhibited. Also sensitive are Klebsiella species, Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Y. enterocolitica and Nocardia asteroides. Very few strains of Pseud. aeruginosa are sensitive. Methicillin-resistant strains of Staph. aureus, although also resistant to trimethoprim or sulphamethoxazole alone, are susceptible to the combination. A synergistic interaction between the components of the preparation is apparent even when microorganisms are resistant to sulphonamide or resistant to sulphonamide and moderately resistant to trimethoprim. However, a maximal degree of synergism occurs when microorganisms are sensitive to both components. The activity of trimethoprim-sulphamethoxazole **in vitro** depends on the medium in which it is determined; for example, trace of thymidine almost completely abolish the antibacterial activity.

Mechanism of Action – 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. Sulphonamide inhibits the incorporation of PABA into folic acid, and trimethoprim prevents the reduction of dihydrofolate to tetrahydrofolate. The latter is the form of folate essential for one carbon transfer reactions, for example, the synthesis of thymidylate from deoxyuridylate. Selective toxicity for microorganisms is achieved in two ways. Mammalian cells utilize preformed folates from the diet and do not synthesize the compound. Furthermore, trimethoprim is a highly selective inhibitor of dihydrofolate reductase of lower organisms. This is vitally important, since this enzymatic function is a crucial one in all species. The synergistic interaction between sulphonamides and trimethoprim is thus predictable from their respective mechanisms. There is an optimal ratio of the concentrations of the two agents for synergism, and this is equal to the ratio of the minimal inhibitory concentrations of the drugs acting independently. The pharmacokenetic properties of the sulphonamide chosen to be in combination with trimethoprim are thus important, since relative constancy of the concentrations of the two compounds in the body is desired.

Bacterial resistance – The frequency of development of bacterial resistance to trimethoprim sulphamethoxazole is lower than it is to either of the agents alone. This is logical since a microorganism that has acquired resistance to one of the components may still be killed by the other. Resistance in gram-negative bacteria is associated with presence of R factors, which can be transferred to susceptible microorganisms by conjugation. Resistance to high concentrations of sulphonamides and to moderate concentrations of trimethoprim has been demonstrated to be transferred in this manner. Resistance to trimethoprim in Staph. aureus appears to be determined by a chromosomal gene rather than by a plasmid. The development of resistance to the combination also occurs in vivo. E. coli resistant to trimethoprim and H. influenzae resistant to trimethoprim-sulphamethoxazole have been isolated from patients treated with the combination.

Absorption, Distribution and Excretion – After a single oral dose of the combined preparation trimethoprim is absorbed more readily than sulphamethoxazole. The coadministration of the drugs appears to slow the absorption of sulphamethoxazole. Peak blood concentrations of trimethoprim usually occur by two hours in most patients, while peak concentrations of sulphamethoxazole are seen by four 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 conventional 5:1 ratio), three times daily, the mean minimal steady state concentrations of the drugs are approximately 20 and 1ug/ml respectively – the optimal ratio that is sought. Trimethoprim is rapidly distributed and concentrated in tissues, and relatively small quantities are bound to plasma protein in the presence of sulphamethoxazole. The drug enters the cerebrospinal fluid and sputum readily. High concentrations of each component of the mixture are also found in bile. About 65% of sulphamethoxazole is bound to plasma protein. Up to 60% of 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 concentrations of both compounds are significantly reduced in patients with uremia.

INDICATIONS:

Urinary Tract Infections – The sulphonamides remain very useful for the management of most patients with uncomplicated infections of the lower urinary tract. The sulphonamides should be reserved for the management of acute and chronic cystitis, chronic infections of the upper urinary tract and asymptomatic bacilluria. Since acute cystitis is most often caused by E. Coli or Pr. mirabilis, the sulphonamides are highly effective. Experience with the treatment of uncomplicated lower urinary tract infections with trimethoprim sulphamethoxazole is now sufficiently extensive to indicate that it is often highly effective, even when the infecting agent is resistant to the sulphonamides alone. The preparation has been shown to produce a better therapeutic effect than does either of its components given separately when the infecting microorganisms are of the family Entrobacteriaceae. It has also been used in the same dose in patients with chronic or recurrent upper and lower urinary tract disease. When Strep. faecalis is the causative microorganism, however, resistance often develops within two weeks of treatment. Asymptomatic bacilluria usually responds promptly to treatment with one tablet every six hours for two weeks. Limited experience with use of this combination in 120 pregnant patients with bacilluria revealed no evidence of teratogenicity.

Genital Infections – Trimethoprim sulphamethoxazole is effective in the management of acute gonococcal urethritis in both men and women. It appears to be as effective as a single dose of 4.8 million units of procaine penicillin G plus 1 g of probenecid. The drug has no effect in preventing incubating syphilis or in curing the established disease. Trimethoprim sulphamethoxazole appears to produce a beneficial effect on some but not all instances of acute and chronic prostatis and in prostatic abscess. Both short term therapy and long term therapy have been recommended.

Respiratory Tract Infections – Pulmonary infections of various types have been treated with the combination. The microorganisms involved have been H. Influenzae, and Strep. pneumoniae. It has been suggested that trimethoprim sulphamethoxazole may be an effective prophylactic agent in this kind of disease. A few cases of lung abscess pneumonia, and bronchiectasis have been treated successfully. It must be pointed out, however, the experience with therapy of bronchopulmonary infections with this preparation is still too limited to establish the parameters of effectiveness.

Miscellaneous Infections – Several reports have suggested that trimethoprim sulphamethoxazole may be effective in the therapy of brucellosis even when localised lesions such as arthritis, endocarditis or epididymo-orchitis are present.
There is some difference of opinion concerning the therapeutic value of trimethoprim sulphamethoxazole in typhoid fever. The experience of Scragg and Rubidge (1971) suggests that, in children, this drug is not as effective as chloramphenicol. In adults with this disease, trimethoprim sulphamethoxazole appears to be as effective as chloramphenicol when the dose is 2 tablets every 12 hours for 15 days.
The combination has been used in the treatment of cholera; it appears to be an effective alternative to tetracycline. Although attempts have been made to treat subacute bacterial endocarditis with trimethoprim sulphamethoxazole, this is not advisable in cases due to the viridans group of streptococci, other streptococci or Staph. aureus, since experience is much too limited as yet and highly effective agents for the therapy of this disease are available. However, there is some evidence that valvular infection due to Pseud. cepacia may respond favourably, especially when polymyxin is given simultaneously. Trimethoprim sulphamethoxazole appears to be effective in the management of carriers of S. typhi and other species of Salmonella. It has been suggested that the presence of chronic disease of the gallbladder is associated with a high incidence of failure to clear the carrier state.

CONTRA-INDICATIONS:

The use of co-trimoxazole is contra-indicated in persons with jaundice and in persons who have shown hypersensitivity to sulphamonides. It is also generally considered to be contra-indicated in patients with impaired renal or liver function. The effect of sulphonamides may be enhanced by displacement from plasma binding sites by more highly bound acidic substances. Co-trimoxazole should not be given to infants within at least two weeks of birth and to pregnant women especially in early pregnancy and prior to delivery. Repeated haematological investigations are required during prolonged therapy.

DOSAGE and DIRECTIONS for USE:

MEZENOL is administered orally in the morning and evening, after meals.
1. Adults and children over 12 years: 1 D.S. tablet twice daily or 1 to 3 ordinary tablets, twice daily.
2. Children: Average dosage is 6 mg trimethoprim and 30 mg sulphamethoxazole per kg bodymass daily.

USUAL DOSAGES:

6 weeks to 5 months: 2.5 ml paediatric suspension twice daily.
6 months to 5 years: 5 ml paediatric suspension twice daily.
6 to 12 years: 10 ml paediatric suspension twice daily.
When treating acute infections the duration of treatment should be at least five days or until symptoms have disappeared for at least two days.

SIDE EFFECTS and SPECIAL PRECAUTIONS:

There is no evidence that trimethoprim sulphamethoxazole, when given in the recommended doses, induces folate deficiency in normal persons. However, the margin between toxicity for bacteria and that for man may be relatively narrow when the cells of the patient are deficient in folate. In such cases, trimethoprim sulphamethoxazole may cause or precipitate megaloblastosis, leukopenia or thrombocytopenia. In routine use, the combination appears to exert little toxicity. About 75% of the side effects involve the skin. These are typical of those known to be produced by sulphonamides, as already described. Exfoliative dermatitis Stevens – Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome) are rare, occurring primarily in older individuals. Skin reactions have developed in from 1.6 to 8% of individuals in different series of patients. Nausea and vomiting constitute the bulk of gastrointestinal reactions; diarrhoea is rare. Glossitis and stomatitis are relatively common. Mild and 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 of prior infectious hepatitis. Central nervous system reactions consist of head-ache, depression and hallucinations, manifestations known to be produced by sulphonamides. Hematological reactions, in addition to those mentioned above, are various types of assaemia (including aplastic, hemolytic and macrocytic), coagulation disorders, granulocytopenia, agranulocytosis, purpura, Henoch-Schonlein purpura, and sulphhemoglobinemia. Previous or simultaneous administration of diuretics with trimethoprim sulphamethoxazole may carry an increased risk of thrombocytorpenia, especially in elderly patients with heart failure; death may occur. It should be remembered that trimethoprim sulphamethoxazole is a relatively new drug combination with toxic potential equal at least to that of the sulphonamide. Furthermore, the cost of a therapeutic course of this combination is considerably more than that of sulphamethoxazole alone. In all such decisions, the results of microbia sensitivity testing must of course be considered.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

High doses may cause diarrhoea, nausea and vomiting and skin rashes and other allergic reactions. 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. Blood counts should be made frequently particularly in patients undergoing prolonged treatment. Supportive measures i.e. cortisone, i.v. infusion, adrenaline, etc., can be used if anaphylaxis occurs.

CONDITIONS OF REGISTRATION OF THE MEDICINE:

None.

PRESENTATION:

D-S Tablets – containers of 10 and 100 tablets.
Adult Tablets – containers of 20, 100 and 500 tablets.
Suspension – containers of 100 ml suspension.

STORAGE CONDITIONS:

mezenol should be stored in a well-closed container, in a cool, dark, dry place, beyond the reach of children.

Further information is available on request.

CAPS

A PHARMACEUTICAL HALLMARK FOR QUALITY EFFICACY AND ECONOMY

9/79