SOUTH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PURBAC INJECTION 5 ml

COMPOSITION

Each 5 ml of PURBAC INJECTION 5 ml contains:

Sulphamethoxazole 400 mg

Trimethoprim 80 mg

Excipients:

Benzyl alcohol, ethyl alcohol, nitrogen, propylene glycol, water for injection

Alcohol:

Ethyl alcohol 10 % *v/v*

Sugar free

CATEGORY AND CLASS

A 20.2 Anti-microbial agents other than antibiotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The introduction of trimethoprim in combination with sulphamethoxazole represents the

practical application of a theoretical consideration, that is, if two medicines act on sequential steps in the pathway of an obligate enzymatic reaction in bacteria, the result of their combination will be supra-additive.

Pharmacokinetic properties

Mechanism of action:

Sulphamethoxazole inhibits the incorporation of PABA into folic acid and trimethoprim is a highly selective inhibitor of dihydrofolate reductase. Therefore by using trimethoprim and sulphamethoxazole in combination, the maximum synergistic effect is achieved and the risk of bacterial resistance developing is reduced to a minimum.

Antibacterial spectrum

All strains of *Strep. pneumoniae*, *C. diphtheria*, and *N. meningitidis* are sensitive to co-trimoxazole. From 50 to 95 % of strains of *Staph. aureus, Epidermidis, Strep. pyogenes*, the *Viridans* group of *Streptococci, Strep faecalis, E. coli, Pr. mirabilis, Pr. morganii, 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 asteroids*. 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 micro-organisms are resistant to sulphonamide or resistant to trimethoprim. However a maximal degree of synergism occurs when micro-organisms are sensitive to both components.

Bacterial resistance

The frequency of development of bacterial resistance to co-trimoxazole is lower than it is to either of the components alone. Resistance in gram-negative bacteria is associated with the presence of R- factors, which can be transferred to susceptible micro-organisms 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. influenza* resistant to co-trimoxazole have been isolated from patients treated with the combination.

Absorption, distribution and excretion

The co-administration of the medicine appears to slow the absorption of sulphamethoxazole. 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 medicine are approximately 20 and 1 µg/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 medicine 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 sulphonamide are excreted in the urine in 24 hours. The rates of excretion and the urine concentrations of both compounds are significantly reduced in patients with uremia.

INDICATIONS

PURBAC INJECTION 5 ml is indicated for infections, caused by sensitive micro-organisms, requiring parenteral treatment.

CONTRAINDICATIONS

The use of PURBAC INJECTION 5 ml is contraindicated in persons with jaundice, porphyria and in persons who have shown hypersensitivity to sulphonamides.

It is also generally considered to be contraindicated in patients with impaired renal or liver functions.

The effects of sulphonamides may be enhanced by displacement from plasma binding sites by more highly bound acidic substances.

PURBAC INJECTION 5 ml should not be given to infants within at least 2 weeks of birth and to pregnant women.

Repeated haematological investigations are required during prolonged therapy.

WARNINGS AND SPECIAL PRECAUTIONS

In all decisions, the results of microbial sensitivity testing must be considered.

PURBAC INJECTION 5 ml must not be injected intramuscularly or subcutaneously.

INTERACTIONS

The effects of sulphonamides may be enhanced by displacement from plasma binding sites by more highly bound acidic substances.

Prior or simultaneous administration of diuretics with PURBAC INJECTION 5 ml may carry an increased risk of thrombocytopenia, especially in elderly patients with heart failure. Death may occur. It should be remembered that PURBAC INJECTION 5 ml has the toxic potential equal at least to that of the sulphonamides.

HUMAN REPRODUCTION

PURBAC INJECTION 5 ml should not be given to infants within at least 2 weeks of birth and to pregnant women.

DOSAGE AND DIRECTIONS FOR USE

TO BE GIVEN BY INTRAVENOUS INFUSION ONLY.

DILUTE BEFORE USE.

Adults and children over 12 years:

Standard dosage: 10 ml twice daily, morning and evening.

Minimum dosage: For long term treatment (more than 14 days): 5 ml twice daily, morning and evening.

Maximum dosage: For particularly severe cases: 15 ml twice daily, morning and evening.

Dosage for children up to 12 years:

6 weeks to 5 months: 1,25 ml twice daily, morning and evening.

6 months to 5 years: 2,5 ml twice daily, morning and evening.

6 years to 12 years: 5,0 ml twice daily, morning and evening.

Typhoid fever:

Adult dosage: 5 ml twice daily, morning and evening for 15 days.

The recommended dosage is approximately 6 mg trimethoprim and 30 mg sulphamethoxazole per kg body mass per day, divided into two equal doses, morning and evening. In acute infections, PURBAC INJECTION 5 ml should be given for at least 5 days or until patient has been symptom free for 2 days. As soon as oral treatment becomes possible, the intravenous administration must be discontinued.

PURBAC INJECTION 5 ml must not be injected intravenously in the undiluted state, but must be added to infusions such as Dextrose 5 %, Dextrose 10 %, Inverted sugar 10 %, Laevulose 5 % ,Ringer-lactate solution, Sodium Chloride 0,9 % solution and Sodium Chloride 0,45 % + Dextrose 2,5 % solution in the ratio of 1 to 30 ml of infusion.

PURBAC INJECTION 5 ml must not be injected intramuscularly or subcutaneously.

Infusion solutions must be used within 6 hours of preparation and must be administered slowly over a period of approximately one and a half hours.

SIDE EFFECTS

The margin between therapeutic and toxic blood levels, in man, is relatively narrow, especially in patients deficient in folates. In such cases, PURBAC INJECTION 5 ml may cause or precipitate megaloblastosis, leucopoenia or thrombocytopenia, erythema multiforme, toxic dermal necrolysis and allergic vasculitis. 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. Exfoliative dermatitis, Stevens-Johnson syndrome, and toxic dermal necrolysis (Lyell's syndrome) occur primarily in older individuals. Nausea and vomiting and diarrhoea constitute the bulk of gastrointestinal reactions .Glossitis and stomatitis occur. Transient jaundice has been noted and appears to have the histological features of allergic cholestatic hepatitis. Most patients who have

developed icterus have a history of prior infectious hepatitis. Central nervous system reactions consist of headache, depression and hallucinations. Haematological reactions, in addition to those mentioned above, include various types of anaemia (including aplastic, haemolytic and macrocytic), coagulation disorders, granulocytopoenia, agranulocytosis, purpura, Henoch-Schonlein purpura, and sulph-globinaemia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

See “SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS”. High doses may cause diarrhoea, nausea and vomiting, skin rashes and other allergic reactions. It may cause a depression of haemopoiesis due to interference of the medicine in the metabolism of folic acid.

Treatment

Injections of calcium folinate may be given to counteract this interference. Blood counts should be performed more frequently, particularly in patients undergoing prolonged treatment. Supportive measures i.e. cortisone, intravenous infusion, adrenaline etc. can be used if anaphylaxis occurs.

IDENTIFICATION

A colourless or slightly yellow solution.

PRESENTATION

1 x 5 ml clear glass ampoule. 10 ampoules are packed in an outer cardboard carton together with a leaflet.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not refrigerate.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

L/20.2/336

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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