

## NEW ZEALAND DATA SHEET

# TRISUL

**Co-trimoxazole (trimethoprim/sulfamethoxazole)**

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## Presentation

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*Tablet:* 480mg (80mg trimethoprim and 400mg sulfamethoxazole), white, biconvex tablet, 11 mm diameter, imprinted "CE 80/400" with a bisect on the same side and blank on the other side.

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## Uses

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### Actions

#### In vitro activity

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid 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.

Many common pathogenic bacteria are sensitive *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. These organisms include:

#### Gram-Negative

*Brucella* spp.  
*Citrobacter* spp.  
*Escherichia coli* (including enterotoxigenic strains)  
*Haemophilus ducreyi*  
*Haemophilus influenzae* (including ampicillin-resistant strains)  
*Klebsiella/Enterobacter* spp.  
*Legionella pneumophila*  
*Morganella morganii* (previously *Proteus morganii*)  
*Neisseria* spp.  
*Proteus* spp.  
*Providencia* spp. (including previously *Proteus rettgeri*)  
Certain *Pseudomonas* spp. except *aeruginosa*  
*Salmonella* spp. including *S. typhi* and *paratyphi*  
*Serratia marcescens*  
*Shigella* spp.  
*Vibrio cholerae*  
*Yersinia* spp.

#### Gram-Positive

*Listeria monocytogenes*  
*Nocardia* spp.

*Staphylococcus aureus*  
*Staphylococcus epidermidis* and *saprophyticus*  
*Streptococcus faecalis*  
*Streptococcus pneumoniae*  
*Streptococcus viridans*

Many strains of *Bacteroides fragilis* are sensitive. Some strains of *Campylobacter fetus* subsp. *jejuni* and *Chlamydia* are sensitive without evidence of synergy. Some varieties of non-tuberculous mycobacteria are sensitive to sulfamethoxazole but not trimethoprim. Mycoplasmas, *Ureaplasma urealyticum*, *Mycobacterium tuberculosis* and *Treponema pallidum* are insensitive.

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 sensitivity testing is achieved only with recommended media free from inhibitory substances especially thymidine and thymine.

## **Pharmacokinetics**

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 to 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, and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (interstitial) 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 humans 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 concentrations of active sulfamethoxazole in amniotic fluid, aqueous humor, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluid 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 humans 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. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

## **Indications**

TRISUL should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

The *in vitro* susceptibility of bacteria to antibiotics varies geographically and with time; the local situation should always be considered when selecting antibiotic therapy.

### **Urinary tract infections**

Treatment of acute uncomplicated urinary tract infections. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

### **Respiratory tract infections**

Treatment of otitis media. TRISUL is not indicated for prophylactic or prolonged administration in otitis media.

Treatment of acute exacerbations of chronic bronchitis.

Treatment and prevention of *Pneumocystis Jirovecii*. (See Dosage and Administration and Adverse Effects).

### **Genital tract infections**

Treatment of gonorrhoea, including oro-pharyngeal and ano-rectal infection (see Dosage and Administration).

This regimen is less effective in some parts of the world due to disease caused by resistant organisms (WHO 1991).

Treatment of chancroid. (See Dosage and Administration). This regimen may be less effective in some parts of the world due to disease caused by resistant organisms (WHO 1991).

Treatment granuloma inguinale (venereum) (see Dosage and Administration).

### **Gastrointestinal tract infections**

Clinicians should be aware that first line therapy in the management of all patients with diarrhoeal disease is the maintenance of adequate hydration.

Treatment of cholera, as an adjunct to fluid and electrolyte replacement, when the organism has been shown to be sensitive *in vitro*.

Treatment of shigellosis, this regimen may be less effective in some parts of the world due to resistant organisms.

Treatment of travellers' diarrhoea (including gastroenteritis due to enterotoxigenic E. coli).

### **Other bacterial infections caused by sensitive organisms**

There are a number of other bacterial infections caused by sensitive organisms for which treatment with TRISUL may be appropriate; the use of TRISUL in such conditions should be based on clinical experience and local *in vitro* data.

Treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis.

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## **Dosage and Administration**

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It may be preferable to take TRISUL with some food or drink to minimise the possibility of gastrointestinal disturbances.

## Acute Infections

### *Adults and Children over 12 years*

Standard dosage – 2 tablets every 12 hours.

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.

### *Use in the Elderly*

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other medications.

## Special Dosage Recommendations

Unless otherwise specified STANDARD DOSAGE applies.

Where dosage is expressed as "tablets" this refers to the adult tablet, ie. 80 mg trimethoprim and 400 mg sulfamethoxazole. If other formulations are to be used appropriate adjustment should be made.

### *Impaired renal function*

Adults and Children over 12 years: (No information is available for children under 12 years of age).

<b>Creatinine Clearance (ml/min)</b>	<b>Recommended Dosage</b>
> 30	Standard dosage
15 – 30	Half the standard dosage
< 15	Not recommended

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

### *Pneumocystis Jirovecii*

#### **Treatment**

A higher dosage is recommended, using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg 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 micrograms/ml (See Adverse Effects).

#### **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 alternate days.

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

### **Children**

The following dose schedules may be used for the duration of the period at risk (see Acute Infections):

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<sup>2</sup>/day and 750 mg sulfamethoxazole/m<sup>2</sup>/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

### **Gonorrhoea**

In uncomplicated cases 4 tablets every 12 hours for two days; *or*

5 tablets followed by a further 5 tablets eight hours later; *or*

10 tablets once daily for 3 days.

If poor patient compliance is expected a single dose of 8 tablets taken under supervision may be employed.

### **Oro-pharyngeal gonococcal infection**

2 tablets three times daily for seven days.

### **Ano-rectal gonorrhoea**

The standard dosage recommendations for gonorrhoea are applicable.

### **Chancroid**

2 tablets twice daily for 7 days; if no evidence of healing is apparent after 7 days a further 7 days' treatment can be considered, however, physicians should be aware that failure to respond may indicate that the disease is caused by a resistant organism.

### **Granuloma Inguinale**

2 tablets twice daily for up to 2 weeks.

### **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.

### **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 Jirovecii* may be appropriate.

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## Contraindications

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TRISUL should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim or co-trimoxazole.

Contraindicated in patients showing marked liver parenchymal damage.

Contraindicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

Except under careful supervision TRISUL should not be given to patients with serious haematological disorders (see Adverse Effects). Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

TRISUL should not be given to premature babies nor to full term infants in the neonatal period.

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## Warnings and Precautions

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Fatalities, although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, Lyell syndrome (toxic epidermal necrolysis, TEN), fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

TRISUL should be discontinued at the first appearance of skin rash (see Adverse Effects).

Life-threatening cutaneous reactions Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfamethoxazole (one of the active ingredients in TRISUL). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, TRISUL treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of sulfamethoxazole or TRISUL, TRISUL must not be re-started in this patient at any time.

Particular care is *always* advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, eg. impaired kidney and/or liver function and/or concomitant use of other drugs.

Special care should be exercised in treating elderly or suspected folate-deficient patients; folate supplementation should be considered.

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Regular monthly blood counts are advisable when TRISUL is given for long periods since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. These changes may be reversed by administration of folic acid (5 to 10 mg/day) without interfering with the antibacterial activity. A folate supplement should also be considered with prolonged high dosage of TRISUL (see Interactions).

In glucose-6-phosphate dehydrogenase deficient (G-6-PD) patients haemolysis may occur.

TRISUL should be given with caution to patients with severe allergy or bronchial asthma.

TRISUL should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci; eradication of these organisms from the oropharynx is less effective than with penicillin.

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

The administration of TRISUL to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia.

## ***Pregnancy and Lactation***

Trimethoprim and sulfamethoxazole cross the placenta and their safety in human pregnancy has not been established. Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Therefore, co-trimoxazole should be avoided in pregnancy, particularly in the first trimester, unless the potential benefit to the mother outweighs the potential risk to the foetus; folate supplementation should be considered if co-trimoxazole 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 co-trimoxazole 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.

Trimethoprim and sulfamethoxazole are excreted into breast milk. Administration of co-trimoxazole 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 co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

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## **Adverse Effects**

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The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

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.

The following convention has been used for the classification of adverse events in terms of frequency:- Very common  $\geq 1/10$ , common  $\geq 1/100$  and  $<1/10$ , uncommon  $\geq 1/1000$  and  $<1/100$ , rare  $\geq 1/10,000$  and  $<1/1000$ , very rare  $<1/10,000$ .

### **Infections and Infestations**

Common: Monilial overgrowth

### **Blood and lymphatic system disorders**

Very rare: Leucopenia, neutropenia, thrombocytopenia, granulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.

The majority of haematological changes are mild and reversible when treatment is stopped. Most of the changes cause no clinical symptoms although they may become severe in isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with poor folate status. Fatalities have been recorded in at-risk patients and these patients should be observed carefully.

### **Immune system disorders**

Very rare: Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus.

### **Metabolism and nutrition disorders**

Very common: Hyperkalaemia

Very rare: Hypoglycaemia, hyponatraemia, anorexia

Close supervision is recommended when co-trimoxazole is used in elderly patients or in patients taking high doses of co-trimoxazole as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

### **Psychiatric disorders**

Very rare: Depression, hallucinations

### **Nervous system disorders**

Common: Headache

Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

### **Respiratory, thoracic and mediastinal disorders**

Very rare: Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

### **Gastrointestinal disorders**

Common: Nausea, diarrhoea

Uncommon: Vomiting

Very rare: Glossitis, stomatitis, pseudomembranous colitis, pancreatitis

### **Hepatobiliary disorders**

Very rare: Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

### **Skin and subcutaneous tissue disorders**

Common: Skin rashes

Very rare: Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and Lyell's syndrome (toxic epidermal necrolysis, TEN)

Lyell's syndrome carries a high mortality.

## **Musculoskeletal and connective tissue disorders**

Very rare: Arthralgia, myalgia

## **Renal and urinary disorders**

Very rare: Impaired renal function (sometimes reported as renal failure), interstitial nephritis

## **Effects associated with P.Jirovecii management**

Very rare: Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10mg/day). Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days.

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## **Interactions**

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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.

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.

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.

Reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporine following renal transplantation.

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. Careful control of the anticoagulant therapy during treatment with TRISUL 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 is advisable.

Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Concurrent use of rifampicin and Co-trimoxazole 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 (eg. 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.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.

Co-trimoxazole may increase the free plasma levels of methotrexate.

If TRISUL is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered. (See Warnings and Precautions).

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## Overdosage

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### Symptoms and Signs

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

### Treatment

If vomiting has not occurred induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete in approximately two hours. This may not be the case in gross overdosage. Dependent on the status of renal function, administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are dialysable by haemodialysis. Peritoneal dialysis is not effective.

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## Pharmaceutical Particulars

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### *List of excipients*

Povidone, sodium starch glycollate, magnesium stearate and docusate sodium.

This medicine does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

### *Special precautions for storage*

Store below 25°C. Protect from light.

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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Bottles of 500's.

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## Further Information

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Nil.

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## Name and Address

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## **Date of Preparation**

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25 November 2011