# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP is an antibacterial combination product, containing 16 mg Trimethoprim BP and 80 mg Sulfamethoxazole BP per mL in a 40 percent propylene glycol vehicle.

**Excipient(s) with known effect**

- Sodium metabisulfite
- Ethanol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection

The solution is clear and has a pH of approximately 10.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Parenteral administration of sulfamethoxazole/trimethoprim is indicated where oral dosage is not desirable or practical, e.g. pre- and post-operative infections associated with surgery, trauma or gynaecology; septicaemia and other infections due to sensitive organisms such as typhoid and paratyphoid.

### 4.2 Dose and method of administration

**Dose**

***Dosage for Adults and Children over 12 years***

Standard Dose: 10 mL diluted and infused twice daily.

For severe infections: 15 mL diluted and infused twice daily.

***Paediatric Population***

Dosage for Children to 12 years

The recommended dosage is approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg bodyweight per day, divided into two equal doses, morning and evening. As a guide,

the following doses of DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP may be used:

| | |
|---|---|
| 2 months to 5 months: | 1.25 mL diluted and infused twice daily. |
| 6 months to 5 years: | 2.5 mL diluted and infused twice daily. |
| 6 years to 12 years: | 5 mL diluted and infused twice daily. |

The recommended dosage for patients with documented *Pneumocystis jirovecii* pneumonia is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days.

**Dose Adjustments**

***Renal Impairment***

In patients with impaired renal function, the dosage and/or frequency of administration of sulfamethoxazole/trimethoprim needs to be modified.

The following dosage regimens have been published for the administration of sulfamethoxazole/trimethoprim tablets to patients with reduced kidney function. In view of the close similarity of plasma levels of trimethoprim and sulfamethoxazole when sulfamethoxazole/trimethoprim is given orally and intravenously, there is no reason to suppose that these regimens cannot be followed with DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP.

**Criteria of Kidney Function**

| **(non-protein nitrogen is unsuitable)** | | **Recommended Dosage Regimens** |
|---|---|---|
| **Creatinine Clearance mL/min** | **Serum Creatinine micromol/L [a]** | **One Standard Dose for Adults 160 mg TMP + 800 mg SMX** |
| Above 25 | Men < 260<br>Women < 170 | Dosage as for patients with normal kidney function, i.e. 1 standard dose every 12 hours for up to 14 days; thereafter half standard dose every 12 hours; no necessity of control analyses of drugs in plasma. |
| 25 to 15 | Men 260 to 600<br>Women 170 to 400 | One standard dose every 12 hours for 3 days; thereafter one standard dose every 24 hours for as long as allowed by control analyses [b]. |
| Below 15 | Men > 600<br>Women > 400 | Until further experience is gained, the combination should be given only if patients can undergo haemodialysis when necessary [c]; under this condition one standard dose may be administered every 24 hours as long as allowed by control analyses [b]. |

TMP = Trimethoprim
SMX = Sulfamethoxazole

a) Serum creatinine levels can be used as the basis of dosing only in cases of stable chronic renal impairment, but not acute or subacute kidney failure.

b) The concentration of total SMX should be measured in plasma samples obtained 12 hours after every third day of treatment. Treatment must be interrupted if at any time the determined plasma level of total SMX exceeds 150 micrograms/mL. As soon as the value of total SMX drops again below 120 micrograms/mL (e.g. in patients undergoing haemodialysis), treatment can be continued as recommended.

c) Both trimethoprim and sulfamethoxazole are readily dialysable, leading to a significantly shortened half-life for each drug during dialysis. It is suggested that patients undergoing haemodialysis receive a dose just before and at the end of the procedure.

**Duration of Treatment**

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP should be used ONLY during such periods as the patient is unable to accept oral therapy. In general, administration is unlikely to be required for more than a few days, and it is recommended that it be restricted to no more than three successive days.

**Method of Administration**

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP must be diluted prior to administration. Sulfamethoxazole/trimethoprim should be administered intravenously only in the form of an infusion solution, and may not be injected undiluted either intravenously or direct into the infusion tube.

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP may be mixed only with the following infusion solutions:

5% Glucose Injection

4% Glucose/0.18% Sodium Chloride Injection

0.9% Sodium Chloride

10% Glucose Injection

2.5% Glucose/0.45% Sodium Chloride Injection

0.45% Sodium Chloride Injection

10% Dextran 40 in 5% Glucose

6% Dextran 70 in 0.9% Sodium Chloride Injection

Hartmann's Injection

No other agent should be added to or mixed with the infusion.

It is important to adhere to the following minimum dilution scheme, which is based on a proportion of 1 mL DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP to 25-30 mL infusion fluid. Add one ampoule (5 mL) to 125 mL infusion solution; two ampoules (10 mL) to 250 mL infusion solution; or three ampoules (15 mL) to 500 mL infusion solution or an equivalent dilution.

The prepared infusion should be shaken well to ensure thorough mixing. Should visible turbidity or crystallisation appear in the solution during its preparation or infusion, it must be discarded and replaced by a freshly prepared solution.

It is recommended that infusion of sulfamethoxazole/trimethoprim be commenced within half an hour of preparation and the duration of infusion should not exceed 1.5 hours. However, this should be balanced against the fluid requirements of the patient.

To reduce microbiological hazards the prepared diluted solution should in any case be used as soon as practicable after preparation and within 24 hours. Do not refrigerate prepared solution.

## 4.3 Contraindications

Sulfamethoxazole/trimethoprim is contraindicated in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides and in patients showing marked hepatic damage, blood dyscrasias or with severe renal insufficiency, where repeated measurements of the plasma concentrations cannot be performed. It should not be given to patients with known hypersensitivity to trimethoprim or sulfonamides or with documented megaloblastic anaemia secondary to folate deficiency.

Premature babies and newborn babies during the first eight weeks of life should not be given sulfamethoxazole/trimethoprim, as sulfamethoxazole may interfere with the serum albumin-binding of bilirubin to produce kernicterus.

Treatment of streptococcal pharyngitis.

Concomitant administration with dofetilide (see section 4.5).

## 4.4 Special warnings and precautions for use

**Hypersensitivity and allergic reactions**

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low; such sensitivity appears to occur more frequently in asthmatic than in non-asthmatic individuals.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment. Pulmonary infiltrates reported in the context of eosinophilic or allergic alveolitis may manifest through symptoms such as cough or shortness of breath. Should such symptoms appear or unexpectedly worsen, the patient should be re-evaluated and discontinuation of sulfamethoxazole/trimethoprim therapy considered.

**Serious adverse reactions**

**FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANAEMIA, OTHER BLOOD DYSCRASIAS AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT.**

Acute respiratory failure including acute eosinophilic pneumonia has been reported in healthy adolescents with sulfamethoxazole/trimethoprim treatment.

**Sulfamethoxazole/trimethoprim should be discontinued if a skin rash appears. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.**

**Thrombocytopenia**

Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole/trimethoprim.

**Streptococcal infections and rheumatic fever**

The sulfonamides should not be used for the treatment of group A beta-haemolytic streptococcal infections (see section 4.3). In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

**Use in treatment of *Pneumocystis jirovecii* pneumonia in Human Immunodeficiency Virus (HIV) – positive patients**

Because of their unique immune dysfunction, HIV-positive patients may not tolerate or respond to sulfamethoxazole/trimethoprim in the same manner as non- HIV-positive patients. The incidence of side effects, particularly rash, fever, neutropenia, thrombocytopenia, raised liver enzymes and leucopenia necessitating cessation of therapy, with sulfamethoxazole/trimethoprim therapy in HIV-positive patients who are being treated for *Pneumocystis jirovecii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole/trimethoprim in non-HIV-positive patients. Such adverse effects have occurred in up to 80% of HIV-positive patients receiving the drug, usually during the second week of therapy. The exact mechanism(s) of this increased risk of sulfamethoxazole/trimethoprim toxicity has not been determined, but may be immunologically based. These adverse effects usually recur following rechallenge with the drug, although cautious desensitisation has been performed successfully in some patients in whom continued sulfamethoxazole/trimethoprim therapy was considered necessary. Some evidence indicates that sulfamethoxazole/trimethoprim may be better tolerated in HIV infected children than adults. Adverse effects are usually less severe in patients receiving the drug for prophylaxis of *Pneumocystis jirovecii* pneumonia compared with those receiving sulfamethoxazole/trimethoprim for treatment of the disease.

**Adjunctive treatment with leucovorin for *Pneumocystis jirovecii* pneumonia**

Treatment failure and excess mortality were observed when sulfamethoxazole/trimethoprim was used concomitantly with leucovorin for the treatment of HIV positive patients with *Pneumocystis jirovecii* pneumonia in a randomized placebo-controlled trial. Co-administration of sulfamethoxazole/trimethoprim and leucovorin during treatment of *Pneumocystis jirovecii* pneumonia should be avoided.

**Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking certain antibiotics. When SCAR is suspected, Sulfamethoxazole 400 mg and Trimethoprim 80 mg concentrate injection should be discontinued immediately and an alternative treatment should be considered.

**Use in glucose-6-phosphate dehydrogenase deficiency**

In individuals with glucose-6-phosphate dehydrogenase deficiency, haemolysis may occur. This is frequently dose-related.

**Clostridiodes difficile associated diarrhoea (CDAD)**

*Clostridiodes difficile* associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including sulfamethoxazole and trimethoprim, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy).

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement, antibiotic treatment of *C. difficile*, and surgical evaluation should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

**Hypoglycaemia**

Cases of hypoglycaemia in non-diabetic patients treated with sulfamethoxazole/trimethoprim have been reported, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of sulfamethoxazole/trimethoprim are particularly at risk.

**Electrolyte abnormalities**

Close monitoring of serum potassium and renal function is warranted in patients receiving high-dose sulfamethoxazole/trimethoprim, as used in patients with *Pneumocystis jirovecii* pneumonia, or in patients receiving standard-dose sulfamethoxazole/trimethoprim with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving drugs which induce hyperkalaemia (see section 4.5). Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole/trimethoprim, particularly for the treatment of *P. jirovecii* pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.

Patients who are “slow acetylators” may be more prone to idiosyncratic reactions to sulfonamides.

**Laboratory tests**

Complete blood counts should be done frequently in patients receiving sulfamethoxazole/trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole/trimethoprim should be discontinued.

**Folate deficiency**

Because of the possible interference with folate metabolism, regular blood counts are advisable in patients on long-term therapy, in those who are pre-disposed to folate deficiency (i.e. the elderly, chronic alcoholics and those with rheumatoid arthritis), in malabsorption syndromes, malnutrition states or during the treatment of epilepsy with anticonvulsant drugs such as phenytoin, primidone and barbiturates. Folic acid may be administered during sulfamethoxazole/trimethoprim therapy and will not interfere with the drugs' antibacterial effect. Megaloblastic anaemia and occasionally neutropenia and thrombocytopenia may be reversed by administration of calcium leucovorin (folinic acid). If signs of bone marrow suppression occur in patients receiving sulfamethoxazole/trimethoprim, leucovorin may be administered.

**Phenylalanine metabolism**

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

**Porphyria and hypothyroidism**

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

**Use in renal impairment**

In renal impairment, a reduced or less frequent dosage is recommended in order to avoid accumulation of trimethoprim in the blood. Non-ionic diffusion is the main factor in the renal handling of trimethoprim, and as renal failure advances, trimethoprim excretion decreases. For such patients, serum assays are necessary.

Patients with severe renal impairment who are receiving sulfamethoxazole/trimethoprim should be closely monitored for symptoms and signs of toxicity such as nausea, vomiting and hyperkalaemia. Sulfamethoxazole/trimethoprim should be given with caution to patients with impaired renal function and to those with underlying disorders such as: possible folate deficiency; hypoglycaemia; electrolyte abnormalities (hyperkalaemia).

Urinalysis with careful microscopic examination and renal function tests should be performed frequently, particularly for those patients with impaired renal function. Adequate fluid intake and urinary output must be maintained in order to prevent crystalluria and stone formation. In patients with renal impairment, a reduced or less frequent dosage is recommended to avoid accumulation of trimethoprim in the blood.

**Use in the elderly**

The use of sulfamethoxazole/trimethoprim in elderly patients carries an increased risk of severe adverse reactions. In rare instances fatalities have occurred. The risk of severe adverse reactions is particularly greater when complicating conditions exist, e.g. impaired kidney and/or liver function, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, or generalised bone marrow suppression (see section 4.8) or a specific decrease in platelets (with or without purpura), and hyperkalaemia are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant sulfamethoxazole/trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Haematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimise risks of undesired reactions (see section 4.2). The trimethoprim component of DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP treatment is recommended to help lower potassium serum levels.

In view of the increased risk of severe adverse reactions in the elderly, consideration should be given to whether sulfamethoxazole/trimethoprim is the antibacterial of choice in this age group.

**Paediatric population**

See sections 4.2 and 4.3.

**Effects on laboratory tests**

Two laboratory procedures, namely the *Lactobacillus casei* serum folate assay and the *L. leishmanii* serum vitamin $B_{12}$ assay are affected by sulfamethoxazole/trimethoprim.

Sulfamethoxazole/trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay.

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% of the range of normal values.

**Other**

As with other sulfonamide preparations, critical appraisal of benefit versus risk should be made in patients with liver damage, renal damage, urinary obstruction, blood dyscrasias, allergies or bronchial asthma.

The possibility of superinfection with a non-sensitive organism should be borne in mind.

## 4.5 Interaction with other medicines and other forms of interaction

**Methotrexate:** Sulfonamides such as sulfamethoxazole may displace methotrexate from protein binding sites and can compete with the renal transport of methotrexate, thereby increasing free methotrexate levels. Cases of pancytopenia have been reported in patients taking the combination of sulfamethoxazole/trimethoprim and methotrexate.

**Para-aminobenzoic acid (PABA) or its derivatives:** may antagonise the antibacterial effects of sulfamethoxazole.

**Warfarin/anticoagulants:** Anticoagulant activity may be increased by concurrent treatment with sulfamethoxazole/trimethoprim. It has been reported that sulfamethoxazole/trimethoprim

may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). This interaction should be kept in mind when sulfamethoxazole/trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

**Phenytoin:** Increased effects and side effects of phenytoin (folate deficiencies) could occur when sulfamethoxazole/trimethoprim is given concurrently. Sulfamethoxazole/trimethoprim may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). Oral sulfamethoxazole/trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

**Sulfonylureas:** Concomitant use may result in potentiation of hypoglycaemia in occasional patients.

**Diuretics:** An increased incidence of thrombocytopenia is reported when this combination is used in the elderly.

**Ciclosporin:** Deterioration in renal function in patients with renal transplants. There have been reports of marked but reversible nephrotoxicity with co-administration of sulfamethoxazole/trimethoprim and ciclosporin in renal transplant recipients.

**Pyrimethamine:** Occasional reports suggest that patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25 mg weekly may develop megaloblastic anaemia should sulfamethoxazole/trimethoprim be prescribed concurrently.

**Digoxin:** Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients. Serum digoxin levels should be monitored.

**Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, prednisolone:** Due to the potassium sparing effects of sulfamethoxazole/trimethoprim, caution should be used when other agents that increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics and prednisolone, are co-administered (see section 4.4). In the literature, two cases of hyperkalaemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin converting enzyme inhibitor.

**Tricyclic antidepressants:** The efficacy of tricyclic antidepressants can decrease when co-administered with sulfamethoxazole/trimethoprim.

**Increased sulfamethoxazole blood levels:** may occur in patients who are also receiving urinary acidifiers, oral anticoagulants, phenylbutazone, oxyphenbutazone and indomethacin.

**Cross sensitisation:** may exist between sulfamethoxazole/trimethoprim and some antithyroid agents, diuretics (acetazolamide and the thiazides) and oral hypoglycaemic drugs. Trimethoprim is an inhibitor of CYP2C8 as well as an OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2. Sulfamethoxazole/trimethoprim potentiates the effect of oral hypoglycaemics that are metabolised by CYP2C8 (e.g. pioglitazone, repaglinide, and

rosiglitazone) or CYP2C9 (e.g. glipizide and glyburide) or eliminated renally via OCT2 (e.g. metformin). Additional monitoring of blood glucose may be warranted.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions with other OCT2 substrates, memantine and metformin, have also been reported.

**Dofetilide:** Concurrent administration is contraindicated (see section 4.3). Elevated plasma concentrations of dofetilide have been reported following concurrent administration of trimethoprim and dofetilide. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including *torsade de pointes*.

**Others:** 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.

## 4.6 Fertility, pregnancy and lactation

### Fertility

No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole, doses roughly two times the recommended human daily dose on a body surface area basis.

### Pregnancy - Category C[1]

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 fetus.

Sulfonamides may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfonamides should therefore be avoided as far as possible during the last month of pregnancy. Trimethoprim may interfere with folic acid metabolism and animal experiments have shown that administration of very high doses of trimethoprim during organ development may give rise to birth defects typical of folic acid antagonism. If a trimethoprim-sulfonamide combination is given during pregnancy, folic acid supplementation may be required. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see section 4.4).

Human data:

While there are no large prospective, well-controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole/trimethoprim with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular abnormalities, urinary tract

[1] *Category C = Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.*

defects, oral clefts, and club foot. These studies, however, were limited by the small number of exposed cases and the lack of adjustment for multiple statistical comparisons and confounders. These studies are further limited by recall, selection, and information biases, and by limited generalisability of their findings. Lastly, outcome measures varied between studies, limiting cross-study comparisons.

Alternatively, other epidemiologic studies did not detect statistically significant associations between sulfamethoxazole/trimethoprim exposure and specific malformations. A retrospective study reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester.

In a separate survey, no congenital abnormalities were found in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

**Lactation**

Levels of sulfamethoxazole/trimethoprim in breast milk are approximately 2-5% of the recommended daily dose for infants over 2 months of age. Although the quantity of sulfamethoxazole/trimethoprim ingested by a breast-fed infant is small, caution should be exercised when DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP is administered to a nursing woman, especially when breastfeeding jaundiced, ill, stressed, or premature infants because of the potential risk of bilirubin displacement and kernicterus, and it is recommended that the age of the infant be considered and the possible risks be balanced against the expected therapeutic effect.

## 4.7 Effects on ability to drive and use machinery

The effects of this medicine on a person’s ability to drive and use machines were not assessed as part of its registration.

## 4.8 Undesirable effects

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria).

**Fatalities, associated with the administration of sulfonamides although rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias, and hypersensitivity of the respiratory tract (see section 4.4). Sulfamethoxazole/trimethoprim should be discontinued if a skin rash appears. Clinical signs such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions.**

Adverse reactions have been reported in approximately 5 to 7% of patients treated in the published literature. In general, the adverse reactions correspond to those of a sulfonamide of moderately low toxicity.

**Gastrointestinal disorders:** Nausea and vomiting are the most frequent gastrointestinal reactions to sulfamethoxazole/trimethoprim, but glossitis, stomatitis, abdominal pain, pancreatitis, pseudomembranous colitis and diarrhoea have also been reported.

**Blood and lymphatic system disorders:** Haematological changes have been observed in some patients, particularly the elderly. The majority of these changes were mild, asymptomatic and proved reversible on withdrawal of the drug. The reported changes consist primarily of neutropenia and thrombocytopenia. Leucopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia, hypoprothrombinaemia, aplastic and haemolytic anaemia, purpura, agranulocytosis and bone marrow depression have been observed less frequently. Haematological toxicity may occur with increased frequency in folate depleted patients including geriatric, malnourished, alcoholic, pregnant or debilitated patients; in patients receiving anti-folates (e.g. phenytoin or methotrexate) or diuretics; in patients with haemolysis or impaired renal function; and in patients receiving sulfamethoxazole/trimethoprim in high dosages and/or for prolonged periods (e.g. longer than 6 months). In geriatric patients receiving some diuretics (principally thiazides) and sulfamethoxazole/trimethoprim concomitantly, an increased incidence of thrombocytopenia with purpura has been reported. The risk of leucopenia, neutropenia and thrombocytopenia also appear to be increased in HIV-positive patients.

**Immune system disorders:** Several cases of Stevens-Johnson syndrome (erythema multiforme bullosa) and Lyell's syndrome (toxic epidermal necrolysis) have been reported. Together with exfoliative dermatitis, serum sickness and allergic myocarditis, these are the most severe allergic reactions reported with sulfonamides alone, or in combination with trimethoprim. Other reported allergic and anaphylactoid reactions include angioedema, serum sickness-like syndrome, generalised allergic reactions, generalised skin eruptions, anaphylaxis, erythema multiforme, drug fever, chills, Schönlein-Henoch purpura, pruritus, urticaria, periorbital oedema, corneal ring infiltrates, conjunctival and scleral redness and oedema, and photosensitivity. In addition, periarteritis nodosa and a positive lupus erythematous phenomenon, and systemic lupus erythromatosus have been reported.

Mild to moderate rashes, when they occur, usually appear within 7 to 14 days after initiation of sulfamethoxazole/trimethoprim. Rashes are generally erythematous, maculopapular, morbilliform, and/or pruritic. Generalised pustular dermatosis and fixed drug eruption have also been reported. HIV-positive patients appear to be at particular risk of developing rash (usually diffuse, erythematous and maculopapular) during sulfamethoxazole/trimethoprim therapy.

**Hepatobiliary disorders:** Hepatitis, hepatic changes (as indicated by abnormal elevations in alkaline phosphatase and serum transaminase levels) including cholestatic jaundice and hepatic necrosis have been reported rarely and may be fatal. Jaundice rarely occurs and has usually been mild and transient, frequently occurring in patients with a past history of infectious hepatitis. Elevation of bilirubin levels has also been reported.

**Renal and urinary disorders:** Dysuria, oliguria, anuria, haematuria, urgency and functional kidney changes (as indicated by abnormal elevations in serum urea, serum creatinine and urine protein concentrations) have been reported occasionally. Renal failure, interstitial nephritis and nephrotoxicity in association with ciclosporin have been reported. Crystalluria and stone formation have occurred in patients receiving sulfamethoxazole/trimethoprim.

**Metabolism and nutrition disorders:** Anorexia.

High doses of trimethoprim as used in patients with *Pneumocystis jirovecii* pneumonia induces progressive but reversible increase of serum potassium concentration in a substantial number of patients. Even treatment with recommended doses may cause hyperkalaemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalaemia are given concomitantly. Cases of hyponatraemia have also been reported (see section 4.4).

**Nervous system disorders:** Aseptic meningitis, seizures, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Tremor and other neurologic manifestations (e.g. ataxia, ankle clonus, apathy) developed during sulfamethoxazole/trimethoprim therapy in several HIV-positive patients; although such manifestations have also been associated with the underlying disease process, they resolved in these patients within 2 to3 days after discontinuing the drug.

**Psychiatric disorders:** Adverse nervous system effects of sulfamethoxazole/trimethoprim include, insomnia, apathy, nervousness, mental depression, and hallucinations.

**Endocrine disorders:** The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycaemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycaemia has occurred rarely in patients receiving sulfonamides.

**Musculoskeletal and connective tissue disorders:** Arthralgia, myalgia, muscle weakness. Cases of rhabdomyolysis have been reported with sulfamethoxazole/trimethoprim, mainly in AIDS patients.

**Respiratory, thoracic and mediastinal disorders:** Cough, shortness of breath, pulmonary infiltrates, acute eosinophilic pneumonia, and acute respiratory failure. Epistaxis has been reported rarely.

**General disorders and administration site conditions:** Weakness, fatigue, pain, local irritation, inflammation, and thrombophlebitis may occasionally occur with intravenous sulfamethoxazole/trimethoprim, especially if extravasation of the drug occurs.

**Skin and subcutaneous tissue disorders:** Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis have been reported with certain antibiotics. Alopecia has been reported rarely.

**Vascular disorders:** hypotension.

**Eye disorders:** Vision problems have been reported rarely.

**Post-marketing experience**

The following adverse reactions have been identified during post-approval use of sulfamethoxazole/trimethoprim. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenia purpura
- Idiopathic thrombocytopenic purpura

- QT prolongation resulting in ventricular tachycardia and *torsade de pointes*.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## 4.9 Overdose

**Acute**

***Symptoms***

Signs and symptoms of overdosage with include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness, and unconsciousness. Pyrexia, haematuria, and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage. Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion, and bone marrow depression.

***Treatment***

Stop therapy. Treatment of overdose is supportive and symptomatic care. Force fluids orally or parenterally if renal function is normal. In extreme overdosage in patients with impaired renal function, consider haemodialysis which is moderately effective in removing sulfamethoxazole and trimethoprim. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is ineffective.

No known antidote for sulfonamide poisoning exists, however, calcium folinate (the equivalent of 3 mg to 6 mg folinic acid intramuscularly for 5 to 7 days) is an effective antidote for adverse effects in the haemopoietic system caused by trimethoprim.

**Chronic**

Use of sulfamethoxazole/trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Mechanism of action**

Sulfamethoxazole/trimethoprim interferes with the bacterial synthesis of tetrahydrofolic acid, an essential stage in the production of thymidine, purines and subsequently nucleic acids. Sulfamethoxazole inhibits the formation of dihydrofolic acid from p-aminobenzoic acid;

trimethoprim inhibits the action of the enzyme dihydrofolate reductase, thus preventing the synthesis of tetrahydrofolic acid from dihydrofolic acid. Thus the combination of trimethoprim and sulfamethoxazole blocks two consecutive steps within the bacterial metabolic pathway of the biosynthesis of nucleic acids and proteins.

Sulfamethoxazole/trimethoprim usually shows *in vitro* activity against the following gram-negative and gram-positive organisms, e.g. *E. coli, Neisseria, Salmonella, Klebsiella-Enterobacter, Shigella, Vibrio cholerae, Bordetella pertussis, Streptococcus, Staphylococcus, Pneumococcus, Haemophilus influenzae* and *Proteus.*

Sulfamethoxazole/trimethoprim is also active against the protozoan *Pneumocystis jirovecii.* However, *Mycobacterium tuberculosis, Treponema pallidum, Mycoplasma* and *Pseudomonas aeruginosa* are frequently resistant to sulfamethoxazole/trimethoprim.

## 5.2 Pharmacokinetic properties

### Absorption

Concentrations of at least 0.5 microgram/mL trimethoprim and 20 microgram/mL sulfamethoxazole are reached within 30 minutes after the start of an infusion and are maintained for at least 12 hours. Mean peak steady state serum concentrations of approximately 9 and 105 microgram/mL of trimethoprim and sulfamethoxazole, respectively, are reached after intravenous (IV) infusion of 160 mg trimethoprim and 800 mg sulfamethoxazole every 8 hours in adults with normal renal function. Steady state trough concentrations reached with this intravenous (IV) dose are approximately 6 microgram/mL of trimethoprim and 70 microgram/mL of sulfamethoxazole. The administration of a trimethoprim/sulfamethoxazole ratio of 1:5 achieves trimethoprim/sulfamethoxazole concentrations in the blood of about 1:20.

### Distribution

Sulfamethoxazole/trimethoprim is widely distributed into body tissues. Sulfamethoxazole is distributed mainly in the extracellular body fluids while trimethoprim, which has lipophilic properties, concentrates in the tissues. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are protein bound in the blood.

### Biotransformation

Sulfamethoxazole/trimethoprim is metabolised in the liver. Trimethoprim is metabolised to oxide and hydroxylated metabolites, while sulfamethoxazole is acetylated and conjugated with glucuronic acid.

### Elimination

Sulfamethoxazole/trimethoprim is rapidly excreted in the urine.

## 5.3 Preclinical safety data

### Genotoxicity

No data available.

### Carcinogenicity

No data available.

**Reproductive and developmental toxicity**

See section 4.6.

# 6. PHARMACEUTICAL PARTICUALRS

## 6.1 List of excipients

- Diethanolamine
- Propylene glycol
- Ethanol
- Sodium metabisulfite
- Sodium hydroxide (for pH-adjustment)
- Hydrochloric acid (for pH-adjustment)
- Water for injections.

## 6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

## 6.3 Shelf life

24 months.

24 hours opened stored at room temperature (refer Section 6.6).

## 6.4 Special precautions for storage

Store below 30°C. Do not refrigerate. Protect from light.

If stored at low temperatures precipitation may occur, and solutions in which precipitation has occurred should be discarded.

## 6.5 Nature and contents of container

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP is supplied as a 5 mL ampoule containing 400 mg sulfamethoxazole and 80 mg trimethoprim in packs of 5 ampoules.

## 6.6 Special precautions for disposal and other handling

**Compatibilities**

DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP has been found to be stable for 24 hours at room temperature under fluorescent light when admixed with the following solutions at a dilution of 1 in 25 and 1 in 35.

5% Glucose Injection

4% Glucose/0.18% Sodium Chloride Injection

0.9% Sodium Chloride Injection

10% Glucose Injection

2.5% Glucose/0.45% Sodium Chloride Injection

0.45% Sodium Chloride Injection

Dextran 70 6% in 0.9% Sodium Chloride Injection

Dextran 40 10% in 5% Glucose

No other agent should be added to or mixed with the infusion.

When admixed with Hartmann's Injection, DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP has been found to be stable for 8 hours at a 1 in 25 dilution and for 24 hours at a 1 in 35 dilution.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363

## 9. DATE OF FIRST APPROVAL

18 June 1987

## 10. DATE OF REVISION OF THE TEXT

14 January 2021

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.1, 4.2, 4.4 | Minor editorial changes. |
| 4.3, 4.5 | Added contraindication for concomitant administration with dofetilide |