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# **WHO MODEL PRESCRIBING INFORMATION**



## **DRUGS USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS AND PREVENTION OF RHEUMATIC FEVER**

World Health Organization  
Geneva

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Model Prescribing  
Information

Drugs Used in the Treatment of  
Streptococcal Pharyngitis and  
Prevention of Rheumatic Fever



World Health Organization  
Geneva  
1999

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## CONTENTS

Preface .....	1
Introduction .....	2
Management of group a streptococcal upper respiratory tract infection	4
Diagnosis .....	4
Antimicrobial treatment of Group A streptococcal pharyngitis	5
1. Primary prevention of rheumatic fever .....	5
2. Secondary prophylaxis of rheumatic fever .....	8
Table 1. Treatment of Group A Streptococcal Pharyngitis ( <i>Primary Prevention</i> of Rheumatic Fever). .....	11
Table 2. Prevention of Recurrences of Rheumatic Fever by Prevention of Group A Streptococcal Infections in Individuals who have had an initial attack of Rheumatic Fever ( <i>Secondary Prophylaxis</i> ). .	13
Drug Data sheets	
Benzathine Benzylpenicillin .....	14
Phenoxymethylpenicillin .....	15
Erythromycin .....	16
Sulfadiazine or Sulfisoxazole .....	17



## **PREFACE**

The Revised Drug Strategy of the World Health Organization adopted in World Health Assembly Resolution WHA39.27 and revised in Resolution WHA49.14 in May 1996, calls for the preparation of model prescribing information to complement the WHO Model List of Essential Drugs. This will provide source material for adaptation by national authorities - particularly in developing countries - wishing to develop national drug formularies, drug compendia and similar material.

This information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug appropriate to circumstances prevailing in each of WHO's Member States. Also, some countries have already formally adopted texts of their own that have a statutory connotation.

This WHO Model Prescribing Information was written by the Division of Drug Management and Policies. It describes the WHO currently recommended drugs, doses and dosage regimens for the treatment of streptococcal pharyngitis and prevention of rheumatic fever.

## **INTRODUCTION**

Rheumatic fever and rheumatic heart disease were widely prevalent in countries throughout the world at the beginning of the second half of the twentieth century. However, during the ensuing decades the disease's major impact has been centred in developing countries, which constitute a majority of the world's population. As with so many other health problems, these are countries which can least afford the economic and social costs. Particularly frustrating has been the fact that rheumatic fever and rheumatic heart disease are theoretically preventable. If group A beta-haemolytic streptococcal infections of the upper respiratory tract are prevented or are effectively treated, neither initial nor recurrent attacks of rheumatic fever occur.

The medical and public health issues are further complicated by the fact that group A streptococcal infections are universally endemic. As there is no available vaccine for group A infections, prevention measures remain dependent upon accurate clinical diagnosis and appropriate antibiotic treatment. Rheumatic fever prevention programmes utilizing recommended clinical and laboratory techniques for diagnosis and antibiotic treatment of group A streptococcal infections are cost-effective. It is the purpose of this brochure to outline currently accepted and effective methods of management of group A streptococcal upper respiratory tract infections.

## **EPIDEMIOLOGY OF GROUP A STREPTOCOCCAL UPPER RESPIRATORY TRACT INFECTIONS**

There is an incontrovertible relationship between group A beta-haemolytic streptococcal upper respiratory infections and development of rheumatic fever. The only significant reservoir of these organisms is the human. For incompletely defined reasons, the infection has a predilection for children between the ages of five and 15 years, but adults are also susceptible. Although capable of causing epidemics in newborn nurseries and infection in younger children, the majority of streptococcal infections occur in school-age children. Adult infections have been most frequently observed in



unique epidemiologic situations such as schools, military bases and residential institutional facilities.

Group A streptococcal infections appear to be quite frequent and therefore result in a high incidence of rheumatic fever in socially and economically disadvantaged populations, especially where crowding is frequent. Group A streptococcal upper respiratory tract infection is spread by droplets, thus accounting for its high transmissibility in such situations. Most outbreaks are associated with respiratory tract transmission, but food-borne outbreaks (often associated with dairy products and eggs) have been documented. In contrast to other infectious agents due only to a single strain (e.g. type b *Hemophilus influenzae*), there are approximately 100 recognized serotypes of group A streptococci. Therefore, although infection with a given serotype is thought to confer long lasting type-specific immunity the abundance of serotypes makes the threat of a new infection continuous. The result of endemic and epidemic infections is a continuous world-wide public health problem.

Complicating the understanding of the epidemiology and pathogenesis of group A streptococcal infections associated with rheumatic fever, is the fact that some specific serotypes appear to have more "rheumatogenic" potential than do others. Epidemiologic observations suggest that these serotypes are more often associated with the development of rheumatic fever. Serotypes associated with rheumatic fever (e.g. M- types 1, 3, 5, 6, 18, 24) are most often found to infect the upper respiratory tract. In contrast, serotypes which most frequently cause superficial skin infection (pyoderma) and are not associated with rheumatic fever are among the higher numbered M-types (e.g. types 49, 55, 57 and 60). Whether there are actually biologic differences in these latter serotypes which make them less of a threat to cause rheumatic fever remains incompletely understood. These epidemiologic observations may also be responsible for the belief that rheumatic fever follows only upper respiratory tract infection and not skin infection. This is in contrast to acute post-streptococcal glomerulonephritis,

which may follow either upper respiratory tract or skin infection. The understanding of differences between skin and throat infections remains incomplete.

## **MANAGEMENT OF GROUP A STREPTOCOCCAL UPPER RESPIRATORY TRACT INFECTION**

### ***Diagnosis***

Young children, school-age children, and adults may present with significantly different clinical findings. An accurate clinical diagnosis of group A streptococcal upper respiratory tract infection can be very difficult emphasizing the advantage of laboratory confirmation of the infection whenever possible. Although usually described as of sudden onset with high fever (often greater than 38°C), severe pain on swallowing, and often accompanied by abdominal pain, nausea and vomiting, these classical signs and symptoms are frequently not present, especially in endemic situations. Likewise, in very young children (those below three years of age) the presentation of streptococcal upper respiratory tract infection is often different. These children initially present with a low-grade fever, irritability and a serous discharge from the anterior nares. This latter syndrome has been referred to as "streptococcosis".

As difficult as it may be to clinically establish a diagnosis of acute streptococcal tonsillitis or pharyngitis, the signs and symptoms of this bacterial infection typically are quite different from those associated with viral upper respiratory tract infections (i.e. the common cold). Hoarseness, coughing, runny eyes and coryza rarely are associated with group A streptococcal infections. Although many children have palpable anterior cervical lymph nodes (*lymphadenopathy*), the characteristic finding of true group A streptococcal upper respiratory tract infections is that of tender anterior cervical lymph nodes (*lymphadenitis*).

This lack of precision in confirming a clinical diagnosis has reinforced the need, whenever possible, of the diagnostic microbiology or immunology laboratory. The throat culture continues to be the "gold standard" for

determining the presence of group A streptococci in the upper respiratory tract. However, failure to properly sample the posterior pharynx tonsils or tonsillar fossae may result in false-negative cultures. Similarly, prior administration of antibiotics may also result in a false-negative culture. Rapid antigen detection tests are available which allow the detection of group A streptococcal antigens from the throat swab. Generally, rapid tests have acceptable specificity but their sensitivity has been reported to be unacceptably low in some studies. This has led to the recommendation that if a rapid antigen test is 'negative' in a patient suspected of having a streptococcal infection, throat culture is advisable. Rapid antigen tests are not widely available in many countries and when they are, their cost tends to exceed that of a throat culture. Group A streptococcal antibody tests such as antistreptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNase B) are very useful in confirming the diagnosis of rheumatic fever or acute glomerulonephritis. However, they are not useful nor are they indicated for the management of patients with acute group A streptococcal pharyngitis. At the time of presentation with acute pharyngitis there will have been insufficient time to mount a rise in antibody titre.

### ***Antimicrobial treatment of Group A streptococcal pharyngitis***

#### *1. Primary prevention of rheumatic fever*

*Primary prevention* is the treatment of acute streptococcal pharyngitis in order to prevent the initial attack of rheumatic fever. In general, once the diagnosis has been made, antibiotic therapy is indicated. In some countries where the incidence of streptococcal pharyngitis and rheumatic fever is especially high, a national decision may be taken to treat all children presenting with acute pharyngitis with an antibiotic without obtaining a throat culture. However, it should be recognized that this may lead to indiscriminate use of antibiotics in sore throat with the obvious disadvantage of antibiotic-associated adverse effects and unnecessary ecologic pressure on indigenous flora leading to bacterial resistance. Examples of both are available in the literature.

#### *Penicillins*

Penicillin remains the treatment of choice for group A streptococcal upper

respiratory tract infections. In fact, penicillin is the only antibiotic that has ever been evaluated in controlled studies which clearly demonstrate that rheumatic fever can be prevented by antibiotic therapy. Since the success of penicillin in preventing rheumatic fever has been associated with eradication of the group A streptococcus from the upper respiratory tract, other classes of antibiotics (e.g. cephalosporins) which also are capable of eradicating the organism from the upper respiratory tract have been deemed appropriate for primary prophylaxis. However, they often remain more expensive.

A single injection of intramuscular benzathine benzylpenicillin, a long acting repository form of the antibiotic, is the most effective treatment in eradicating group A streptococci, probably due to its long duration of action. It can also be used for mass prophylaxis.

Oral penicillin (phenoxymethylpenicillin) therapy for streptococcal pharyngitis has to continue for 10 days; studies indicated that 10 days of therapy were associated with higher eradication rates of the organism from the upper respiratory tract. Other penicillins including ampicillin, amoxicillin and the semi-synthetic penicillins have also proved effective in eradicating group A streptococci. However, because 10 days of oral therapy has been the recommended duration, adherence remains a problem for patients taking an oral antibiotic. Reduced adherence to prescribed oral medications for the purpose of rheumatic fever prevention is common. Educational efforts by health care professionals to promote adherence can significantly enhance efficacy.

#### *Macrolides*

For penicillin-allergic patients, antibiotic treatment with oral erythromycin for 10 days has been traditionally used. Newer macrolides are available and are reported to be associated with fewer adverse effects but they are generally more expensive. Short course therapy with these newer macrolides has been reported to be effective, but more definitive data are required prior to recommending short courses of these antibiotics for primary prevention at the present time.

### *Cefalosporins*

The first and second generation cefalosporins have been used to treat group A streptococcal infections, because they have been shown to be capable of eradicating the organism from the upper respiratory tract. As a rule, the cefalosporins are more expensive than penicillin V. Short course therapy (less than 10 days) with some cefalosporins is also under evaluation but more data are required before they can be recommended.

### *Resistance*

No clinical isolate of group A streptococci has ever shown resistance to penicillin but resistance to macrolide antibiotics (e.g. erythromycin) used as alternative therapy for individuals with documented penicillin allergy is increasing in some countries and sporadic resistance has been documented in many parts of the world (e.g. in Japan during the 1960s and 1970s and more recently in some countries of Europe). In most parts of the world, however, group A streptococcal resistance to the macrolides remains at less than five percent of isolates. Clinical use of macrolides should be influenced by local resistance rates. Resistance to sulfa drugs and to tetracyclines is known to occur; often as many as 30% or greater of the organisms prove resistant making sulfa drugs and tetracyclines unsuitable for the therapy of group A streptococcal upper respiratory tract infections (or any other group A streptococcal infection).

### *Recommended antibiotics*

Table 1 shows commonly recommended antibiotics for the treatment of acute streptococcal pharyngitis for primary prevention of rheumatic fever.

It usually is not necessary to re-culture patients' throats after a full course of antibiotic therapy unless there is a unique epidemiologic situation such as an epidemic of streptococcal infections or unless the patient has had rheumatic fever or lives in a household with someone who has had rheumatic fever. If individuals are symptomatic following a complete course of antibiotic therapy in which compliance was assured, a second course of antibiotic therapy may be indicated. In these relatively rare instances, laboratory documentation of the organism is advantageous.

## 2. *Secondary prophylaxis of rheumatic fever*

For all individuals who have had an initial attack of rheumatic fever, whether or not they have rheumatic heart disease, continuous administration of an antibiotic is mandatory to prevent acquisition and infection of the upper respiratory tract by group A streptococci. *Secondary prophylaxis* has been documented to reduce significantly the risk of recurrent attacks with their attendant morbidity and mortality.

Antibiotic regimens for secondary prophylaxis differ. The regular intramuscular injection of repository penicillin (benzathine benzylpenicillin) is the most effective available treatment. Although classically given every four weeks, recent data indicate that 1,200,000 units of benzylbenzathine penicillin given every three weeks is more effective in preventing recurrences of rheumatic fever, especially in high-risk patients.

Several technical factors related to the benzathine benzylpenicillin injection can affect its bioavailability. For this reason it is recommended that health workers responsible for administering the injection are trained in the technique of giving injections. The injection should be deep into the muscle as recommended. More superficial injections allow the benzathine benzylpenicillin to remain in the subcutaneous tissue leading to decreased absorption and lower serum levels. Care should be taken, particularly in adults that the whole content of the vial is fully removed and injected.

Although the activity of benzathine benzylpenicillin remains stable in the vial for several years if adequately stored, the activity may be affected by the presence of preservatives, metal ions or bicarbonate in the vial. The physical properties of the solution, if not optimum, may also affect its degree of solubility and hence its absorption from the injection site. All of the above affects the biological activity of benzathine benzylpenicillin. Since different brands are produced in the market, continuous quality assurance is important to optimize not only its chemical activity but also its biological activity. This is needed to reduce variations between different brands and to assure effective serum penicillin levels.

For patients for whom the regular and repeated injections of benzathine benzylpenicillin are not given, an alternative but lesser effective method is the use of daily oral phenoxymethylpenicillin. The potential problems with oral prophylaxis that should be considered are:

- Adherence is difficult;
- Even when adherence can be assured, the rheumatic fever recurrence rates have been shown to be higher with this regimen than with intramuscular benzathine benzylpenicillin;

For patients known to be allergic to penicillin, an oral sulfonamide is recommended for secondary prophylaxis. It is **not** effective for treating established group A streptococcal infection. For individuals who cannot take either penicillin or sulfadiazine, erythromycin in a dose of 250 mg twice daily may be used. However, there are recent reports of group A streptococcal resistance to erythromycin.

#### *Duration of secondary prophylaxis*

There are several variables that affect the likelihood of recurrences of rheumatic fever, including the time since the most recent attack, the age of the patient and the risk posed by the environment. The duration of secondary prophylaxis should be adapted to the individual patient but some general principles can be stated. Patients without carditis in a previous attack should have prophylaxis for a minimum of five years after the last attack, and at least until age 18 and often longer if risk factors are high. Patients with cardiac involvement in the initial attack should continue prophylaxis at least until the age of 25 years, and longer if environmental conditions or other risk factors warrant it.

For patients with chronic valvular rheumatic heart disease, secondary prophylaxis for prolonged periods, even for life, has sometimes been recommended. It is prudent for the physician to consider each patient individually in determining the duration.

Antibiotic prophylaxis for secondary rheumatic fever should be continued through pregnancy. However, sulfonamides present a risk to the fetus and an alternative antibiotic (penicillin or erythromycin) should be substituted. The teenage years present a special problem, particularly with adherence. Special efforts must be made at this crucial period when the risk of recurrence is great.

\*The general principles for secondary prophylaxis are :

Patient	Duration
No carditis/RHD	To 18 years and at least five years after the last attack
Documented carditis	At least to 25 years and often longer
Chronic carditis	For life
With artificial valves	For life

\* see text for details



Table 1. Treatment of Group A Streptococcal Pharyngitis (*Primary Prevention of Rheumatic Fever*).

Antibiotic	Route	Dose	Duration of Rx
<u>For non penicillin allergic patients:</u> Benzathine benzylpenicillin	IM	< 30 kg 600,000 IU > 30 kg 1,200,000 IU	A single injection
Phenoxymethylpenicillin	Oral	< 30 kg 250 mg 2 or 3 times daily > 30 kg, 500 mg 2 or 3 times daily	10 days
<u>For penicillin allergic patients:</u> Erythromycin ethylsuccinate	Oral	40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days
Erythromycin estolate	Oral	20-40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days

Comments:

- 1) Oral ampicillin or amoxicillin has been used. They must be given for 10 days.
- 2) Oral cephalosporins (first or second generation) are also effective but usually are more expensive. They must be given for 10 days
- 3) Newer orally administered macrolides have been reported to be effective in eradicating group A streptococci when given for less than 10 days. At this time data are not sufficiently conclusive to support unqualified recommendation for a shortened course of therapy.

- 4) Mixtures of benzathine benzylpenicillin with procaine benzylpenicillin G have been used. The mixture tends to cause less discomfort, but doses must be calculated based upon the amount of benzathine benzylpenicillin in the mixture.
- 5) Sulfonamides or tetracycline are **not** acceptable therapy for group A streptococcal pharyngitis.

Table 2. Prevention of Recurrences of Rheumatic Fever by Prevention of Group A Streptococcal Infections in Individuals who have had an initial attack of Rheumatic Fever (*Secondary Prophylaxis*).

Antibiotic	Route	Dose
Benzathine benzylpenicillin	IM	For children <30 kg: 600,000 IU every 3-4 weeks For children ≥ 30 kg and adults: 1,200,000 IU every 3-4 weeks
Phenoxymethylpenicillin	Oral	250 mg 2 times daily
Sulfonamide (e.g. sulfadiazine, sulfadoxine or equivalent)	Oral	< 30 kg 500 mg daily > 30 kg 1.0 g daily
Erythromycin	Oral	250 mg 2 times daily

Comments:

- 1) Studies have shown injections of benzathine benzylpenicillin every three weeks are superior to every four weeks in preventing recurrences in those individuals considered to be at high risk of recurrence of rheumatic fever.
- 2) Sulfonamides are contraindicated in the third trimester of pregnancy because of transplacental passage of the drugs and potential competition with bilirubin for albumin-binding sites.
- 3) Erythromycin, although not studied for secondary prophylaxis, may be used for individuals who can not take either penicillin or a sulfonamide.
- 4) It should be remembered that patients are susceptible to recurrences even after surgery for rheumatic heart disease and secondary prophylaxis should be continued (see text). This is different from prophylaxis for prevention of infective endocarditis.

## **BENZATHINE BENZYL PENICILLIN**

*powder for injection 1.44 g (2.4 million IU) in 5 ml vial*

Benzylpenicillin is a natural substance derived from *Penicillium notatum*. It consists of a thiazolidone ring connected to a beta-lactam ring. It is bactericidal against *streptococci*, *neisseriae*, many anaerobes and spirochaetes.

After intramuscular injection, peak plasma concentrations are usually reached within 12-24 hours and are usually detectable for 1-4 weeks. It is widely distributed throughout the body and is excreted mainly in the urine.

**Uses:** Streptococcal pharyngitis. Primary and secondary prophylaxis of rheumatic fever.

### **Dosage and administration:**

Primary prophylaxis: Children < 30 kg 600,000 IU, a single injection  
Children ≥ 30 kg and adults 1,200,000 IU, a single injection

Secondary prophylaxis: Children < 30 kg 600,000 IU, every 3-4 weeks  
Children ≥ 30 kg and adults 1,200,000 IU, every 3-4 weeks

The vial is diluted in sterile water to allow for a homogeneous suspension to be obtained to avoid obstruction of the injecting needle. A needle gauge of #19 or #20 is preferred. Smaller bore needles have been noted to be more easily obstructed. The injection should be deep into the gluteus maximus muscle. More superficial injections allow the benzathine benzylpenicillin to remain in the subcutaneous tissue leading to decreased absorption and lower serum levels. Care should be taken that the whole content of the vial is fully removed and injected.

**Contraindications:** Known hypersensitivity to penicillin or cephalosporins.

**Precautions:** Facilities should be available for treating anaphylaxis whenever penicillin is used. A careful history should be taken with regard to previous allergic reactions.

If skin rashes develop, the patient another antimicrobial should be given.

**Important caution:** Many hypersensitivity reactions are reported with penicillin ranging from skin rashes to immediate anaphylaxis which may be

fatal. The overall incidence of hypersensitivity reactions is from 2 to 5 %. Anaphylaxis is very rare and occurs in about 1/10 000 injections. Death has been reported in about 1/30 - 50 000 injections. It should be emphasized that many anaphylactic reactions occur in severely ill rheumatic heart disease patients who are at risk of life-threatening arrhythmias. They may have an arrhythmia associated with shock mimicking anaphylaxis.

**Use in pregnancy:** There is no evidence of teratogenicity with benzathine benzylpenicillin. It can be used during pregnancy.

**Adverse reactions:** The most common adverse effect of these substances are hypersensitivity reactions that range in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection.

Accidental injection into a peripheral nerve causes pain and dysfunction.

Nephropathy manifested as interstitial nephritis has been reported.

Neutropenia and thrombocytopenia have occurred rarely.

**Storage:** Powder for injection should be stored at temperatures between 2 and 8° C and protected from moisture.

### **PHENOXYMETHYLPENICILLIN**

*tablet, 250 mg, 500 mg (as potassium)*

*powder for oral suspension, 250 mg, 125 mg (as potassium salt)/5 ml*

Phenoxymethylpenicillin is a semisynthetic derivative of penicillin for oral use. It is active against a wide variety of Gram-positive and Gram-negative cocci. Most strains of streptococci remain susceptible.

It is well absorbed from the gastrointestinal tract and distributed widely in tissues. It is excreted in the urine. It crosses the placenta and is excreted in breast milk.

**Uses:** Treatment of streptococcal pharyngitis.  
Secondary prophylaxis of rheumatic fever.

#### **Dosage and administration**

Children: < 30 kg 250 mg , 2 or 3 times daily

Adults and children: > 30 kg, 500 mg, 2 or 3 times daily

**Contraindications:** Known hypersensitivity to penicillin or cephalosporins.

**Precautions:** Facilities should be available for treating anaphylaxis whenever penicillin is used for the first time.

A careful history should be taken with regard to previous allergic reactions. If skin rashes develop, the patient should be given another antimicrobial.

**Use in pregnancy:** Phenoxymethylpenicillin can be used in pregnancy.

**Adverse reactions:** The most common adverse effects of these substances are hypersensitivity reactions that range in severity from skin rashes to immediate anaphylaxis.

Mild diarrhoea can also occur.

**Storage:** Preparations should be stored in well closed containers.

## **ERYTHROMYCIN**

*enteric coated tablets 250 mg (as stearate or ethylsuccinate)*

*oral suspension 125 mg (as stearate or ethylsuccinate)/5 ml*

Erythromycin is a macrolide antimicrobial produced by *Streptomyces erythreus*. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli.

Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half life is approximately 90 minutes. It is partially demethylated in the liver and excreted largely via the bile and faeces.

**Uses:** Streptococcal pharyngitis in penicillin-allergic patients

### **Dosage:**

Primary prophylaxis of rheumatic fever: Adults: 40 mg/kg/day (max. 1.5 g/day) 3 times daily

Children: 20-40 mg/kg/day (max. 1.0 g/day) 3 times daily

Secondary prophylaxis of rheumatic fever: 250 mg 2 times daily

**Contraindications:** Known hypersensitivity to erythromycin.

**Precautions:** Hepatic function should be monitored in patients with a previous history of liver disease.

**Adverse effects:** Erythromycin is well tolerated by most patients at the dosages required for these conditions.

Large oral doses may produce nausea, vomiting and diarrhoea.

Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

**Drug interactions:** Erythromycin, chloramphenicol, and clindamycin which have a similar bacteriostatic action tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

**Storage:** Capsules and tablets should be stored in tightly closed containers.

### **SULFADIAZINE or SULFISOXAZOLE**

*tablet, 500 mg*

*injection, 250 mg (sodium salt)*

Sulfadiazine and sulfisoxazole are intermediate acting sulfonamides with a broad spectrum of activity against a wide range of Gram-positive and Gram-negative organisms. They are readily absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is 10 -12 hours. After partial acetylation in the liver it is excreted in the urine.

#### **Uses:**

Secondary prevention of rheumatic fever:

**Dosage:** Secondary prophylaxis: adults 1 g daily in 2 divided doses.

Children: 150 mg/kg daily in divided doses

**Contraindications:** Hypersensitivity to sulfonamides; severe renal or hepatic function impairment; porphyria; pregnancy during the first trimester.

**Precautions:** The blood count should be monitored regularly throughout therapy to detect signs of bone-marrow depression.

Any patient suspected of being sensitive to sulfonamides should never

receive them again. Presumptive signs include skin rashes and evidence of haemolysis such as dark urine and purpura.

Sulfadiazine is less soluble in urine than many other sulfonamides. High urinary output must be maintained to avoid crystallization. Patients should be advised to drink 1.0-1.5 litres of alkaline water daily.

Concomitant administration of other drugs that interfere with folic acid metabolism (other than pyrimethamine) should be avoided whenever possible.

**Use in pregnancy:** Sulfadiazine is contraindicated during the first trimester. Administration of sulfonamides can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern, based on data derived from premature neonates, that they may promote kernicterus. Although they readily cross the placental barrier there is no conclusive evidence that the fetus is at risk.

**Adverse effects:** Nausea, vomiting, diarrhoea and headache sometimes occur.

Sulfonamide-induced hypersensitivity reactions, although uncommon, can be severe. They include rare life-threatening cutaneous reactions such as erythema multiform (Stevens-Johnson syndrome) and toxic epidermal necrolysis. Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

**Overdosage:** Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

**Storage:** Preparations should be stored protected from light.









