Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Supristol†.

Co-trimazine *(BAN)*

Trimetoprima y sulfadiazina.
CAS — 39474-58-3.
ATC — J01EE02.

Profile

Co-trimazine, a mixture of 5 parts of sulfadiazine and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations are available in some countries which contain trimethoprim and sulfadiazine in proportions different to co-trimazine.

Co-trimoxazole *(BAN)*

Cotrimoxazol; Ko-trimoksazol.
CAS — 8064-90-2.
ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Stability. Diluted infusion solutions of co-trimoxazole have a limited stability and eventually form a precipitate: this happens more rapidly at higher concentrations. The manufacturers recommend a dilution of 480 mg in 130 mL, which is usually stable for up to 6 hours, but more concentrated solutions should be used within shorter periods of time, and a dilution of 480 mg in 80 mL should be used within 1 hour. The usual diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, have been stated to be compatible for adequate periods.

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components (see Sulfamethoxazole, p.340, and Trimethoprim, p.355). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, below).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] predominantly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the prescribing of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, below), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and remained predominantly in elderly patients.

1. Committee on Safety of Medicines. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al.* Co-trimoxazole toxicity. *BMJ* 1985; **291:** 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; **291**: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; **ii**: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; **ii**: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; **345:** 1118–19.
8. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Precautions

As for Sulfamethoxazole, p.340 and Trimethoprim, p.355.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of skin rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al.* Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; **25:** 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; **1:** 687–91.

G6PD deficiency. It has been suggested that co-trimoxazole should be avoided by people with G6PD deficiency.[1]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67**: 601–11.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in **patients with AIDS** being treated for *Pneumocystis carinii* pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

The occurrence of high serum concentrations of trimethoprim and sulfamethoxazole in patients has been proposed as a contributing factor to the high incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the **dose** of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] demonstrated no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine **metabolites** of sulfamethoxazole which produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p.340.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92–106.
2. Gordin FM, *et al.* Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
3. Jaffe HS, *et al.* Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; **ii**: 1109–11.
4. Mitsuyasu R, *et al.* Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535.
5. Colebunders R, *et al.* Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **107**: 599–600.
6. Sattler FR, *et al.* Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **109**: 280–7.
7. Stevens RC, *et al.* Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35**: 1884–90.
8. Para MF, *et al.* Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; **24:** 337–43.
9. McLean I, *et al.* Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; **ii**: 857–8.
10. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
11. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
12. Gibbons RB, Lindauer JA. Successful treatment of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in hypersensitive AIDS patients. *JAMA* 1985; **253**: 1259–60.
13. Toma E, Fournier S. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 954.
14. Kreuz W, *et al.* "Treating through" hypersensitivity to co-trimoxazole in children with HIV infection. *Lancet* 1990; **336**: 508–9.
15. Carr A, *et al.* Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7:** 65–71.
16. Absar N, *et al.* Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93:** 1001–5.
17. Cortese LM, *et al.* Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; **30:** 184–6.
18. Caumes E, *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133:** 465–9.
19. Demoly P, *et al.* Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; **102:** 1033–6.
20. Lin D, *et al.* Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/07/08).
21. Woods WG, *et al.* Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia. *J Pediatr* 1984; **105**: 639–44.
22. Drysdale HC, Jones LF. Co-trimoxazole prophylaxis in leukaemia. *Lancet* 1982; **i**: 448.
23. Dib EG, *et al.* Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 2004; **350:** 88–9.

Interference with diagnostic tests. Co-trimoxazole has been reported[1,2] to cause a small reduction in serum-thyroxine and tri-iodothyronine concentrations, probably due to the sulfonamide component.[2] Although co-trimoxazole had not been shown to be a cause of hypothyroidism (since all concentrations remained within the normal range), tests of thyroid function might need to be interpreted with care in patients on such treatment.

1. Cohen HN, *et al.* Effects on human thyroid function of sulphonamide and trimethoprim combination drugs. *BMJ* 1980; **281**: 646–7.
2. Cohen HN, *et al.* Trimethoprim and thyroid function. *Lancet* 1981; **i**: 676–7.

Porphyria. Both sulfonamides and trimethoprim have been associated with acute attacks of porphyria, and are considered unsafe in porphyric patients.

Interactions

Any of the drug interactions reported with sulfamethoxazole (p.341) or trimethoprim (p.356) may occur with co-trimoxazole.

Rifampicin. For reference to potential interaction between co-trimoxazole and rifampicin, see p.327.

Antimicrobial Action

The actions and spectrum of activity of co-trimoxazole are essentially those of its components, sulfamethoxazole (p.341) and trimethoprim (p.356).

Because they act at different points of the folate metabolic pathway a potent synergy exists between its components *in vitro* with an increase of up to about 10-fold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The optimum effect against most organisms is seen at a ratio of 1 part trimethoprim to 20 of sulfamethoxazole; although co-trimoxazole is formulated as a 1 to 5 ratio, differences in the pharmacokinetics of the two drugs mean that the ratio of the peak concentrations is approximately 1:20. However, it is not clear that the optimum ratio is achieved at all sites and, given that both drugs are present in therapeutic concentrations, the contribution of synergy to the effects of co-trimoxazole *in vivo* is uncertain.

Resistance to co-trimoxazole develops more slowly *in vitro* than to either component alone. Resistance has increased, and although initially slow, a more rapid increase was seen in many countries during the 1980s, occurring in both Gram-positive and Gram-negative organisms. Resistance has occurred notably among Enterobacteriaceae. Resistant strains of *Brucella melitensis, Haemophilus influenzae*, streptococci, and *Vibrio cholerae* have been reported rarely. Although resistant organisms are usually resistant to both components of the mixture, strains resistant to either the sulfonamide or trimethoprim, and with a reduced sensitivity to co-trimoxazole, have been reported.

◊ References.

1. Martin JN, *et al.* Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis* 1999; **180:** 1809–18.
2. Huovinen P. Resistance to trimethoprim-sulfamethoxazole. *Clin Infect Dis* 2001; **32:** 1608–14.

Pharmacokinetics

As for sulfamethoxazole (p.341) and trimethoprim (p.356). When co-trimoxazole is given orally, plasma concentrations of trimethoprim and sulfamethoxazole are generally around the optimal ratio of 1:20, although they may vary from 1:2 to 1:30 or more. The ratio of the two drugs is usually much lower in the tissues (often around 1:2 to 1:5) since trimethoprim, the more lipophilic drug, penetrates many tissues better than sulfamethoxazole and has a much larger volume of distribution. In urine the ratio may vary from 1:1 to 1:5 depending on the pH.

Uses and Administration

Co-trimoxazole is a mixture of the sulfonamide, sulfamethoxazole, and the diaminopyrimidine, trimethoprim, in the proportion of 5 parts of sulfamethoxazole to 1 part of trimethoprim. It has been used in infections due to susceptible organisms, particularly those of the urinary, respiratory, and gastrointestinal tracts, although the indications for its use are restricted in the UK (see below). Its main uses now are in pneumocystis pneumonia, toxoplasmosis, and nocardiosis.

Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally in combination with other drugs), cat scratch disease, chancroid, *Burkholderia cepacia* (*Pseudomonas cepacia*) infections in cystic fibrosis, some forms of AIDS-associated diarrhoea such as the protozoal infection isosporiasis, gonorrhoea, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients. For details of the bacterial infections listed above and their treatment, see under Choice of Antibacterial, p.162.

Co-trimoxazole is usually given orally in an adult dose of 960 mg (trimethoprim 160 mg and sulfamethoxazole 800 mg) twice daily; in severe infections 2.88 g daily in 2 divided doses has been given. Lower doses are given for long-term treatment and in patients with renal impairment (see Administration in Renal Impairment, below).

Doses of co-trimoxazole to be given twice daily to children are: from 6 weeks to 5 months of age, 120 mg; 6 months to 5 years, 240 mg; 6 to 12 years, 480 mg. Alternatively, children may be given a dose of 24 mg/kg twice daily. Co-trimoxazole should not generally be given to infants below 6 weeks of age because of the risk of kernicterus from the sulfonamide component (see Pregnancy, p.341, under Precautions of Sulfamethoxazole), although it may be used in infants from 4 weeks of age for the treatment or prophylaxis of pneumocystis pneumonia.

Higher doses of co-trimoxazole of up to 120 mg/kg daily given in 2 to 4 divided doses for 14 to 21 days are used in the treatment of pneumocystis pneumonia in adults and children over 4 weeks of age; serum concentrations should be monitored and folate supplementation possibly considered (but see Pneumocystis Pneumonia, below). For prophylaxis in adults with AIDS, the usual dose of co-trimoxazole (960 mg twice daily) may be given, but has been associated with a high incidence of adverse effects (see Immunocompromised Patients, under Precautions, above). Alternatively the following dose regimens may be used: 960 mg daily (7 days each week); 960 mg daily on alternate days (3 days each week); or 960 mg twice daily on alternate days (3 days each week). Children may be given standard doses (see above) for prophylaxis; doses are given on 3 alternate or consecutive days per week or for 7 days per week. Prophylactic doses in children have also been given in terms of body-surface area; the *BNFC* suggests a dose of 450 mg/m^2 (to a maximum of 960 mg) twice daily for three days of the week, given either consecutively or on alternate days.

For serious infections, if oral use is not possible, co-trimoxazole may begin by intravenous infusion diluted immediately before use in a suitable diluent. The contents of each ampoule containing 480 mg of co-trimoxazole in 5 mL are added to 125 mL of diluent and infused over 60 to 90 minutes, unless fluid restriction is required, in which case only 75 mL of diluent may be used. Dosage is similar to that by mouth.

◊ The place of co-trimoxazole in therapy was reviewed by the UK CSM in 1995 (see also Incidence of Adverse Effects, above).[1] As a result they recommended that its use should be limited to: pneumocystis pneumonia, toxoplasmosis, and nocardiosis; urinary-tract infections and acute exacerbations of chronic bronchitis, but only when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer it to a single antibacterial; and acute otitis media in children, but again only when there is good reason to prefer it.

1. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Administration in renal impairment. Doses of co-trimoxazole, both orally and intravenously, should be reduced in patients with renal impairment. The following recommendations for adults and children over 12 years of age are based on creatinine clearance (CC):

- CC above 30 mL/minute: the standard dose
- CC 15 to 30 mL/minute: half the standard dose
- CC below 15 mL/minute: not recommended.

Blastocystis infection. For a mention of the use of co-trimoxazole in the treatment of *Blastocystis hominis* infection, see p.823.

Cyclosporiasis. Patients with *Cyclospora* infection (p.824) have responded to treatment with co-trimoxazole.[1-3]

1. Pape JW, *et al.* Cyclospora infection in adults infected with HIV: clinical manifestations, treatment and prophylaxis. *Ann Intern Med* 1994; **121:** 654–7.
2. Hoge CW, *et al.* Placebo-controlled trial of co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. *Lancet* 1995; **345:** 691–3. Correction. *ibid.*: 1060.
3. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Granulomatous diseases. Although co-trimoxazole appears to be effective in reducing the incidence of bacterial infection in patients with chronic granulomatous disease,[1-3] a disorder of leucocyte function associated with recurrent life-threatening infection and granuloma formation, its use in systemic vasculitis is much more controversial. There have been a number of reports of benefit from co-trimoxazole in patients with Wegener's granulomatosis (p.1515),[4-7] but even where benefit has been reported relapse appears to be common,[6] and an analysis[8] of the experience of the USA National Institutes of Health in 158 patients, was sceptical of its value: only 1 of 9 patients given 960 mg twice daily by mouth had any prolonged improvement.

Some evidence later emerged that addition of co-trimoxazole to maintenance regimens in patients already in remission reduces the incidence of relapse,[9] although another study suggested that it might actually increase the risk of relapse.[10]

1. Mouy R, *et al.* Incidence, severity, and prevention of infections in chronic granulomatous disease. *J Pediatr* 1989; **114:** 555–60.
2. Margolis DM, *et al.* Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. *J Infect Dis* 1990; **162:** 723–6.
3. Gallin JI, Malech HL. Update on chronic granulomatous diseases of childhood: immunotherapy and potential for gene therapy. *JAMA* 1990; **263:** 1533–7.
4. DeRemee RA, *et al.* Wegener's granulomatosis: observations on treatment with antimicrobial agents. *Mayo Clin Proc* 1985; **60:** 27–32.
5. Bowden FJ, Griffiths H. Co-trimoxazole in the treatment of Wegener's granulomatosis. *Med J Aust* 1989; **151:** 303–4.
6. Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991; **151:** 1649–52.
7. Ohtake T, *et al.* Generalized Wegener's granulomatosis responding to sulfamethoxazole-trimethoprim monotherapy. *Intern Med* 2001; **40:** 666–70.
8. Hoffman GS, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116:** 488–98.
9. Stegeman CA, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335:** 16–20.
10. de Groot K, *et al.* Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; **39:** 2052–61.

Isosporiasis. A regimen of oral co-trimoxazole 960 mg four times daily for 10 days followed by 960 mg twice daily for 3 weeks was reported to be initially effective in patients with AIDS suffering from isosporiasis (p.824), and produced resolution of diarrhoea within 2 days of beginning treatment; it was, however, associated with a high rate of recurrence.[1] A shorter regimen followed by indefinite prophylaxis may be preferable in persons with AIDS; in a small randomised controlled study, co-trimoxazole 960 mg twice daily for 7 days, followed by 10 weeks' prophylaxis, was effective in HIV-infected patients with isosporiasis.[2]

1. DeHovitz JA, *et al.* Clinical manifestations and therapy of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1986; **315:** 87–90.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132:** 885–8.

Nocardiosis. Co-trimoxazole is used in the treatment of nocardiosis (p.181). There is no consensus on the optimum dosage; doses of 2.88 to 3.84 g daily in divided doses for up to 3 months have been used.

Pneumocystis pneumonia. Co-trimoxazole is the preferred drug[1-3] for both the treatment and prophylaxis of pneumocystis pneumonia (p.521). A single dose of 480 mg daily may be effective and better tolerated for prophylaxis than a daily dose of 960 mg.[4] However, some still prefer the latter dose schedule[5] which is also the one preferred by the CDC in the USA[1] and is a licensed dose for prophylaxis in both the UK and USA. Various studies[4-10] have shown intermittent dosing is also effective for the prophylaxis of pneumonia and is better tolerated than daily dosing; the dose has usually been 960 mg three times each week on alternate days[4-9] although 960 mg twice daily three times each week has also been given.[10] The addition of folinic acid has no

effect on tolerability and may be associated with a higher rate of therapeutic failure (see HIV Infection and AIDS, p.1944).

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5108.pdf (accessed 18/05/05)
2. CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-14): 1–63. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5314.pdf (accessed 04/04/05)
3. CDC. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2004; **53** (RR-15): 1–112. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5315.pdf (accessed 04/04/05) Correction. *MMWR* 2005; **54:** 311. [dose of amphotericin B/flucytosine for C. neoformans meningitis] Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5412a10.htm (accessed 13/06/05)
4. Ioannidis JPA, *et al*. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996; **156:** 177–88.
5. El-Sadr WM, *et al*. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis* 1999; **29:** 775–83.
6. Wormser GP, *et al*. Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151:** 688–92.
7. Stein DS, *et al*. Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1991; **35:** 1705–9.
8. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337:** 468–71.
9. Bozzette SA, *et al*. The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98:** 177–82.
10. Podzamczer D, *et al*. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.

Toxoplasmosis. There is some evidence that giving co-trimoxazole for prophylaxis of pneumocystis pneumonia produces an additional benefit in acting prophylactically against toxoplasmic encephalitis in persons with HIV infection or AIDS,[1-5] but the evidence (as for other drugs) has been largely anecdotal or from small retrospective studies. In the USA, the CDC recommends[1] that co-trimoxazole 960 mg daily (as for *Pneumocystis carinii* pneumonia prophylaxis, above) be given to HIV-infected patients who are seropositive for *Toxoplasma* and have a CD4+ count below 100 cells/microlitre.

Co-trimoxazole has also produced promising results in preliminary studies for the treatment of toxoplasmic encephalitis in patients with AIDS,[6] and a systematic review[7] considered it an effective treatment, particularly in resource-poor settings where alternatives such as pyrimethamine with sulfadiazine might not be available.

For a discussion of toxoplasmosis and its management, see p.826.

1. CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; **51** (RR-8): 1–52.
2. Zangerle R, Allerberger F. Effect of prophylaxis against Pneumocystis carinii on toxoplasma encephalitis. *Lancet* 1991; **337:** 1232.
3. Carr A, *et al*. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992; **117:** 106–11.
4. Beaman MH, *et al*. Prophylaxis for toxoplasmosis in AIDS. *Ann Intern Med* 1992: **117:** 163–4.
5. Podzamczer D, *et al*. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122:** 755–61.
6. Torre D, *et al*. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42:** 1346–9.
7. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).

Preparations

BP 2008: Co-trimoxazole Intravenous Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; ***USP 31:*** Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Adrenol; Bacticel; Bactrim; Cotrizol-G; Danferane; Diocla†; Dosulfin Fuerte; Netocur; Novidrine; Sulfagrand; Tritenk; Urisept NF; ***Austral.:*** Bactrim; Cosig†; Resprim; Septrin; Trimoxazole; ***Austria:*** Bactrim; Cotribene; Eusaprim; Oecotrim; Trimetho comp; ***Belg.:*** Bactrim; Cotrim; Eusaprim; Steroprim†; ***Braz.:*** Assepium; Bac-Sulfitrin; Bacfar; Bacprotin; Bactris†; Bacteracin; Bactrim; Bactrisan; Bactrizol; Bactropin; Batrox; Baxapril†; Benectrin; Binoctrin†; Clotrizol†; Dientrin; Duoctrin†; Ectrin; Espectrin†; Espectroprima†; Gamactrin; Imuneprim; Infectrin; Lifactrin†; Linurin†; Lupectrim†; Metoprin; Neotrin; Pulkrin; Qiftrin†; Quimio-Ped†; Roytrin†; Selectrin; Septiolan†; Teutrin; Tricban; Trimexazol; Trimezol†; Uropol; ***Canad.:*** Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Septra; ***Chile:*** Bacterol; Bactrimel; Introcin†; Septrin; Trelibec; ***Cz.:*** Apo-Sulfatrim†; Berlocid†; Biseptol; Bismoral; Nopil†; Oriprim†; Primotren; Sumetrolim; Supracombin†; ***Denm.:*** Sulfotrim†; ***Fin.:*** Cotrim; ***Fr.:*** Bactrim; Eusaprim†; ***Ger.:*** Bactoreduct†; Berlocid; Cotrim; Cotrim-Diolan; CotrimHefa; Cotrimhexal; Cotrimox-Wolff; Cotrimstada; Drylin; Eusaprim; Kepinol; Microtrim†; Sigaprim†; Supracombin†; TMS; ***Gr.:*** Bactrimel; Bioprim†; Septrin; ***Hong Kong:*** Chemitrim†; Chemoprim; Cotrim; Dhatrin; Letus; Septrin; ***Hung.:*** Sumetrolim; ***India:*** Bactrim; Ciplin; Colizole; Cotrimol†; Oriprim; Sepmax; Septran; Tabrol; Trisulfose; ***Indon.:*** Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim; Cotrimol; Dumotrim; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim; Meprotrin; Nufaprim; Ottoprim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim; Sultrimmix; Trimezol; Triminex; Trimoxsul; Trixzol; Trizole; Ulfaprim; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.:*** Duobact†; Septrin; ***Israel:*** Diseptyl; Resprim; Septrin; ***Ital.:*** Abacin†; Bactrim; Chemitrim; Eusaprim; Gantrim†; ***Jpn:*** Bactramin; ***Malaysia:*** Bacin; Baserin†; Chemix; Cotrim; Resprim; Trimexazole; Virin†; ***Mex.:*** Andoprim; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric; Bactide; Bactilen; Bactiver; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Kaltrim; Maxtrim; Metoxiprim; Microbactim†; Mixange; Octiban; Pisatrina; Polibatrin; Pribac; Protaxol; Protrim; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultiprim†; Syraprim†; Thriazol; Tribakin; Trime/Sulfa†; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimzol; Trinelax†; Trisufin†; Vanadyl; ***Neth.:*** Bactrimel; Eusaprim†; Sulfotrim; ***Norw.:*** Bactrim; Trimetoprim-Sulfa†; ***NZ:*** Apo-Sulfatrim; Trisul; ***Philipp.:*** Bacidal; Bactille; Bactrim; Bacxal; Baczole; Bantizol; Chromo-Z; Combi-Methoxan; Costazole; Cozole; Drilozole; Fedimed; Forteprim; Globaxol; Ivatrim; Kassemox; Lictora; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Synermed; Triforam; Trim-S; Trimephar; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim; Zolmed; ***Pol.:*** Bactrim; Biseptol; Groseptol†; Septrin; Two-Septol; ***Port.:*** Bactrim; Cotrim†; Metomide†; Microcetim; Septrin; ***Rus.:*** Biseptol (Бисептол); Oriprim (Ориприм); Rancotrim (Ранкотрим); ***S.Afr.:*** Acuco; Bactrim; Bencole; Casicot; Cocydal; Cozole; Durobac; Fabubac†; Lagatrim; Meditrim; Mezenol†; Purbac; Septran; Spectrim; Trimethox; Trimzol; Xerazole; Xeroprim†; ***Singapore:*** Apo-Sulfatrim; Bacin; BS†; Chemix; Chemoprim; Dhatrin; Septrin†; Suprim; Trimezole†; ***Spain:*** Broncomega†; Busetal†; Eduprim†; Gobens Trim; Momentol; Septrin; ***Swed.:*** Bactrim; Eusaprim; ***Switz.:*** Agoprim†; Bactrim; Cotrim; Escoprim; Groprim; Lagatrim; Mediprim; Nopil; Sigaprim†; Supracombin†; ***Thai.:*** Actin; Bacin; Bacta†; Bactrim; Baczole; Chemoprim†; Co-Tasian; Co-Trimed; Conprim; Cotamox; Ko-Cap; Ko-Kure; Ladar; Lastrim; Letus; M-Trim; Mano-Trim; Med-Sultrim†; Mega-Prim; Metrim; Metxaprim; Mycosamthong; Po-Trim; Pulvicin†; Septrin†; Spectrim; Sulbacta; Sulfometh; Suntrim; Tampo†; Toprim†; Trimexazole; Triprim; Trixzol; Zoleprim†; ***Turk.:*** Bactrim; Bakton; Kemoprim; Metoprim; Mikrosid; Septrin; Trifen; Trimoks; ***UAE:*** Trimol; ***UK:*** Fectrim; Septrin; ***USA:*** Bactrim; Cotrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.:*** Bactrimel; Bactron†; Co-Sultrin; Forcrim; Trimecor; Trimetoprim Sulfa†; Tripur.

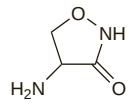
Multi-ingredient: ***Arg.:*** Bacti-Uril; Bactrim Balsamico; Dosulfin Bronquial; Enterobacticel; Netocur Balsamico; Neumobacticel; Uro-Bactrim†; ***Braz.:*** Assepium Balsamico; Benectrin Balsamico; Diazol; Dispeptrin; Ectrin Balsamico; Metoprin Balsamico; Selectrin Balsamico; Uro-Baxapril†; Urectrin; ***Chile:*** Entero Micinovo; Uro-Micinovo; ***Hung.:*** Cotripharm; ***Mex.:*** Bactrim Compositum; Brogamax; Guayaprin; Octex; Sadocin; Trimexole Compositum; ***Singapore:*** Co-Trimexazole; Trimaxazole; ***Spain:*** Bactopumon; Balsoprim; Bronco Aseptilex Fuerte; Broncovir; Bronquicisteina; Bronquidiazina CR; Bronquimar; Bronquimucil†; Cotrazol; Eduprim Mucolitico; Neumopectolina†; Pulmo Menal†; Pulmosterin Duo.

Cycloserine *(BAN, rINN)*

Cicloserina; D-Cycloserin; Cyclosérine; D-Cycloserine; Cycloserinum; Cykloserin; SC-49088; Sikloserin; Sykloseriini. (+)-(*R*)-4-Aminoisoxazolidin-3-one.

Циклосерин

$C_3H_6N_2O_2$ = 102.1.
CAS — 68-41-7.
ATC — J04AB01.
ATC Vet — QJ04AB01.



Description. Cycloserine is an antimicrobial substance produced by the growth of certain strains of *Streptomyces orchidaceus* or *S. garyphalus*, or obtained by synthesis.

Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Cycloserine). A white to pale yellow, crystalline powder, odourless or has a faint odour. It is hygroscopic and deteriorates upon absorbing water. Freely soluble in water. pH of a 10% solution in water is between 5.5 and 6.5. Store in airtight containers.

Adverse Effects and Treatment

The most frequent adverse effects with cycloserine involve the CNS and include anxiety, confusion, disorientation, depression, psychoses possibly with suicidal tendencies, aggression, irritability, and paranoia. Vertigo, headache, drowsiness, speech difficulties, tremor, paresis, hyperreflexia, dysarthria, paraesthesia, coma, and convulsions may also occur. Neurological reactions are dose related and may be reduced by keeping plasma concentrations below 30 micrograms/mL. It has been reported that up to 30% of patients have experienced adverse effects. These reactions usually subside when cycloserine is stopped or the dosage is reduced. Pyridoxine has been used in an attempt to treat or prevent neurological reactions but its value is unproven.

Hypersensitivity reactions including skin reactions and photosensitivity occur rarely. Serum aminotransferase values may be raised, especially in patients with a history of liver disease. Folate and vitamin B_{12} deficiency, megaloblastic anaemia, and sideroblastic anaemia have been reported occasionally when cycloserine has been used with other antituberculous drugs. Heart failure has occurred in patients receiving daily doses of 1 g or more.

Precautions

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cycloserine,[1] and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Morton RF, *et al*. Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. Cycloserine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Patients receiving cycloserine and taking alcohol are at increased risk of convulsions; for reference to increased blood-alcohol concentrations in patients receiving cycloserine, see p.1627.

Neurotoxic effects may be potentiated by use of cycloserine with ethionamide, and concurrent use of cycloserine and isoniazid may result in increased CNS toxicity, such as dizziness and drowsiness.

Antimicrobial Action

Cycloserine interferes with bacterial cell wall synthesis by competing with D-alanine for incorporation into the cell wall. It has variable activity against Gram-positive and Gram-negative bacteria including *Escherichia coli* and *Staphylococcus aureus*.

Cycloserine is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistance develops if cycloserine is used alone.

Pharmacokinetics

Cycloserine is readily and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations of 10 micrograms/mL have been obtained 3 to 4 hours after a dose of 250 mg, rising to 20 to 30 micrograms/mL on repeating the dose every 12 hours. The plasma half-life is about 10 hours and is prolonged in patients with renal impairment.

Cycloserine is widely distributed into body tissues and fluids, including the CSF, placenta, and breast milk, producing fetal blood concentrations approaching those in maternal serum.

Cycloserine is excreted largely unchanged by glomerular filtration. About 50% of a single 250-mg dose is excreted unchanged in the urine within 12 hours and about 70% is excreted within 72 hours. As negligible amounts of cycloserine appear in the faeces, it is assumed that the remainder of a dose is metabolised to unidentified metabolites. It is removed by haemodialysis.

Pregnancy and breast feeding. Cycloserine has been shown to pass to the fetus, into amniotic fluid,[1] and into breast milk.[2] Concentrations in breast milk after 250 mg four times daily have been reported to range from 6 to 19 micrograms/mL.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Morton RF, *et al*. Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; **3:** 169–72.

Uses and Administration

Cycloserine is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p.196) as part of a multidrug regimen when resistance to primary drugs has developed. It has been used in urinary-tract infections, although less toxic drugs are preferred.

The usual adult oral dose in tuberculosis is 250 mg twice daily for 2 weeks, followed by 0.5 to 1 g daily in divided doses. Dosage in patients with mild to moderate renal impairment should be reduced and doses for all patients should be adjusted by monitoring plasma concentrations (see Precautions, above).

For details of doses in infants, children, and adolescents, see below.

Cycloserine has been tried for the adjunctive treatment of schizophrenia. L-Cycloserine has been investigated for the treatment of Gaucher disease (p.2249).