

**Temocillin Sodium** (BANM, rINNM)

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Temocilline Sodique. The disodium salt of (6S)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.

Натрий Темоциллин

$C_{16}H_{16}N_2Na_2O_7S_2 = 458.4$ .

CAS — 61545-06-0.

ATC — J01CA17.

ATC Vet — QJ01CA17.

**Profile**

Temocillin is a semisynthetic penicillin that is highly resistant to a wide range of beta-lactamases and is used for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative aerobic bacteria, including those resistant to third-generation cephalosporins.

It is given as the sodium salt and doses are expressed in terms of the base; 1.11 g of temocillin sodium is equivalent to about 1 g of temocillin. It is given by intravenous or intramuscular injection or by intravenous infusion in usual doses of 1 g every 12 hours. A dose of 12.5 mg/kg every 12 hours may be used in children. Intravenous doses may be doubled in severe infections.

In patients with renal impairment the interval between doses may need to be increased.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

**Belg.:** Negaban; **Ital.:** ISF 09338†; **UK:** Negaban.

**Terizidone** (rINN)

B-2360; Terizidona; Térizidone; Terizidonum. 4,4'-[p-Phenylenebis(methyleneamino)]bis(isoxazolidin-3-one).

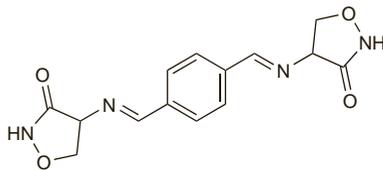
Теризидон

$C_{14}H_{14}N_4O_4 = 302.3$ .

CAS — 25683-71-0.

ATC — J04AK03.

ATC Vet — QJ04AK03.

**Profile**

Terizidone has been used in the treatment of infections of the urinary tract and of pulmonary and extrapulmonary tuberculosis.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

**Austria:** Terivaldin; **Braz.:** Terizidex; **S.Afr.:** Terivaldin.

**Tetracycline** (BAN, rINN)

Tetraciclina; Tetraciklin; Tetraciklina; Tétracycline; Tetracyclinum; Tetracyclin; Tetracyklina; Tetracykliini. A variably hydrated form of (4S,4a,5a,6S,12a)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide.

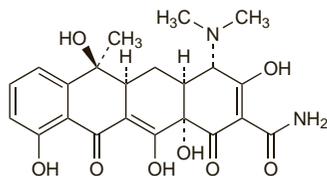
Тетрациклин

$C_{22}H_{24}N_2O_8 = 444.4$ .

CAS — 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate).

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QG01AA90; QG51AA02; QJ01AA07; QJ51AA07; QS01AA09; QS02AA08; QS03AA02.



**Pharmacopoeias.** In *Eur.* (see p.vii) and *US*.

**Ph. Eur. 6.2** (Tetracycline). A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

The symbol † denotes a preparation no longer actively marketed

**USP 31** (Tetracycline). A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

**Tetracycline Hydrochloride** (BANM, rINNM)

Hidrocloruro de tetraciclina; Tetraciklinhidroklorid; Tetraciklino hidrokloridas; Tétracycline, chlorhydrate de; Tetracyclini hydrochloridum; Tetracyclin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi.

Тетрациклина Гидрохлорид

$C_{22}H_{24}N_2O_8 \cdot HCl = 480.9$ .

CAS — 64-75-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, *US*, and *Viet*.

*US* also includes Epitetracycline Hydrochloride.

**Ph. Eur. 6.2** (Tetracycline Hydrochloride). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

**USP 31** (Tetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light.

**Tetracycline Phosphate Complex** (BAN)

Tetraciclina, complejo con fosfato.

CAS — 1336-20-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

**Description.** A complex of sodium metaphosphate and tetracycline.

**Incompatibility.** Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

**Stability.** Tetracycline undergoes reversible epimerisation in solution to the less active 4-epitetracycline;<sup>1,2</sup> the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.<sup>1</sup> The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.<sup>1</sup> Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose about 8 to 12% of their potency in 24 hours at room temperature.<sup>3</sup> Although epimerisation has been observed to be the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.<sup>4</sup>

In contrast to the case in solution, *suspensions* of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.<sup>2</sup> This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of *solid* dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37° and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.<sup>5</sup> Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.<sup>5</sup> However, although this study, and an accelerated stability study carried out by WHO<sup>6</sup> indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.<sup>7</sup>

- Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; **52**: 752–6.
- Grobbe-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; **7**: 104–8.
- Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; **24**: 434–9.
- Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chem (Sci)* 1978; **6**: 201–14.
- Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; **59**: 1160–4.
- WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser* 790 1990. Also available at: [http://libdoc.who.int/trs/WHO\\_TRS\\_790.pdf](http://libdoc.who.int/trs/WHO_TRS_790.pdf) (accessed 18/05/07).
- Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304**: 210–14.

**Adverse Effects**

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Oesophageal ulceration has been reported with doxycycline, minocycline, and tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime. Other effects that have been reported include glossitis, stomatitis, and dysphagia.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed derivatives such as doxycycline.

Renal dysfunction has been reported with tetracyclines, particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal impairment increase the severity of uraemia with increased excretion of nitrogen and loss of sodium, accompanied by acidosis and hyperphosphataemia, and may lead to excessive systemic accumulation of the tetracycline and possible liver toxicity. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and interstitial nephritis have occurred rarely.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women and in patients with renal impairment or those given high doses. However, hepatotoxicity has also occurred in patients without these predisposing factors but is rarely reported with doxycycline.

Tetracyclines are deposited both in deciduous teeth (milk teeth; primary teeth) and in permanent teeth during their formation, causing permanent discoloration and enamel hypoplasia. The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose given. Doxycycline binds less with calcium compared with other tetracyclines and these changes may occur less frequently. Tetracyclines are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women.

Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances, and papilloedema has been reported. The use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracra-

nial pressure occurs tetracycline treatment should be stopped. Transient myopia in patients taking tetracyclines may be due to changes in refractive power of the lens. Other adverse effects that have occasionally been reported with tetracyclines include increased muscle weakness in patients with myasthenia gravis and exacerbation of SLE.

Hypersensitivity to the tetracyclines is much less common than to the beta lactams, but hypersensitivity reactions, including rashes, fixed drug eruptions, exfoliative dermatitis, toxic epidermal necrolysis, drug fever, pericarditis, angioedema, urticaria, and asthma have been reported; anaphylaxis has occurred very rarely. Photosensitivity, which has been reported with most tetracyclines, occurs most frequently with demeclocycline and other long-acting derivatives, less with chlortetracycline, and very rarely with oxytetracycline and tetracycline; it appears to be phototoxic rather than photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity.

Local pain and irritation can occur when tetracyclines are given parenterally and thrombophlebitis may follow intravenous injections. A Jarisch-Herxheimer reaction occurs commonly in patients with relapsing fever treated with tetracyclines.

Although rare, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Tetracyclines may produce hypoprothrombinaemia. They have also been associated with reductions in serum-vitamin B concentrations, including a case of folate deficiency and concomitant megaloblastic anaemia.

The use of tetracyclines that are out-of-date or which have deteriorated has been associated with the development of a reversible Fanconi-type syndrome characterised by polyuria and polydipsia with nausea, glycosuria, aminoaciduria, hyperphosphaturia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria; these effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline.

**Effects on intracranial pressure.** Benign intracranial hypertension (pseudotumor cerebri) has been described in patients given tetracyclines.<sup>1</sup> Tetracycline is most commonly implicated, usually in patients being treated for acne; it has also been associated with doxycycline<sup>2,3</sup> and minocycline.<sup>4,5</sup> Presenting symptoms, such as headaches, tinnitus, visual loss, diplopia, nausea, and vomiting, usually develop from within 2 weeks to 1 year or more of starting a tetracycline. Most cases resolved when the drug was stopped although some required symptomatic treatment with diuretics (including acetazolamide), corticosteroids, and/or lumbar puncture. Nevertheless, permanent visual loss has been reported.

1. Digre KB. Not so benign intracranial hypertension. *BMJ* 2003; **326**: 613–14.
2. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ* 2003; **326**: 641–2.
3. Friedman DI, et al. Doxycycline and intracranial hypertension. *Neurology* 2004; **62**: 2297–9.
4. Weese-Mayer DE, et al. Minocycline and pseudotumor cerebri: the well-known but well-kept secret. *Pediatrics* 2001; **108**: 519–20.
5. Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and not so benign intracranial hypertension. *Aust Adverse Drug React Bull* 2003; **22**: 2–3. Also available at: <http://www.tga.gov.au/adr/aadrb/aadr0302.pdf> (accessed 07/02/07)

## Precautions

The tetracyclines are contra-indicated in patients hypersensitive to any of this group of antibacterials, since cross-sensitivity may occur.

Tetracyclines should not be used during pregnancy because of the risk of hepatotoxicity in the mother as well as the effects on the developing fetus. They should also be avoided during breast feeding and in children up to the age of 8, or according to the *BNF*, 12, years. Use in pregnancy, potentially during breast feeding, or in childhood, may result in impaired bone growth and permanent discoloration of the child's teeth.

In general the tetracyclines, with the exception of doxycycline, should be used with caution in those with renal impairment and, if they must be given, doses should be reduced. However, the *BNF* advises avoid-

ing tetracyclines, except doxycycline and minocycline, even in mild impairment. Care should also be taken if tetracyclines are given to patients with hepatic impairment and high doses should be avoided.

Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity. Care is advisable in patients with myasthenia gravis, who may be at risk of neuromuscular blockade. Tetracyclines should be avoided in those with SLE.

Serum monitoring of tetracyclines may be helpful in patients with risk factors given prolonged therapy: it has been suggested that serum concentrations of tetracycline should not exceed 15 micrograms/mL. To avoid the risk of oesophageal ulceration oral tetracyclines (notably doxycycline, see p.267) should be taken with plenty of fluid while sitting or standing, and well before going to bed.

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

**Breast feeding.** The American Academy of Pediatrics<sup>1</sup> states that, after use of tetracycline by breast-feeding mothers, there is negligible absorption by the infant and that tetracycline is therefore usually compatible with breast feeding. However, licensed product information states that adverse effects including permanent tooth discoloration and enamel hypoplasia may occur in breast-fed infants and that breast feeding is contra-indicated during treatment with tetracyclines.

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 28/05/04)

**Porphyria.** Tetracyclines are considered to be probably safe in patients with porphyria, although there is conflicting experimental evidence of porphyrinogenicity. Doxycycline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients, and results from *animals* or *in-vitro* systems suggest that oxytetracycline might be porphyrinogenic.

## Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore use of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, colestyramine, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralose are probably of little clinical significance. These interactions can be minimised by giving such products at least 1 to 3 hours apart from tetracyclines. Strontium ranelate should not be given with tetracyclines because of possible complex formation.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together; such use should be avoided. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, halofantrine, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants have also been increased in a few patients. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred after the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the effectiveness of oral contraceptives.

Because of possible antagonism of the action of the penicillins by the mainly bacteriostatic tetracyclines it has been recommended that the two types of drug

should not be used together, especially when a rapid bactericidal action is necessary.

## Antimicrobial Action

The tetracyclines are mainly bacteriostatic, with a broad spectrum of antimicrobial activity including Chlamydiaceae, *Mycoplasma* spp., *Rickettsia* spp., spirochaetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

**Mechanism of action.** Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis, and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective activity against the infecting organism.

**Spectrum of activity.** The following pathogenic organisms are usually sensitive to tetracyclines:

Gram-positive cocci including some strains of *Staphylococcus aureus* and coagulase-negative staphylococci, and streptococci including *Str. pneumoniae*, *Str. pyogenes* (group A), and some viridans streptococci. Enterococci are essentially resistant.

Other sensitive Gram-positive bacteria including strains of *Actinomyces israelii*, *Bacillus anthracis*, *Erysipelothrix rhusiopathiae*, *Listeria monocytogenes*, and among the anaerobes some *Clostridium* spp. *Noncardia* spp. are generally much less susceptible although some are sensitive to minocycline. *Propionibacterium acnes* is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations.

Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *N. gonorrhoeae* (gonococci), although some strains are resistant, and *Moraxella catarrhalis* (*Branhamella catarrhalis*). *Acinetobacter* spp. may be resistant to tetracycline, but most strains are susceptible to doxycycline and minocycline.

Other sensitive Gram-negative aerobes including *Bordetella pertussis*, *Brucella* spp., *Klebsiella granulomatis*, *Campylobacter* spp., *Eikenella corrodens*, *Francisella tularensis*, *Haemophilus influenzae* and some strains of *H. ducreyi*, *Legionella* spp., *Pasteurella multocida*, *Streptobacillus moniliformis*, and various members of the Vibrionaceae including *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Vibrio cholerae* and *V. parahaemolyticus*. Although many of the Enterobacteriaceae, including *Salmonella*, *Shigella*, and *Yersinia* spp., are susceptible, resistant strains are common; *Proteus* and *Providencia* spp. are not susceptible. *Pseudomonas aeruginosa* is not susceptible either, although some other species formerly classified as *Pseudomonas* respond, including *Burkholderia mallei*, *B. pseudomallei*, and *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*).

Among the Gram-negative anaerobes *Bacteroides fragilis* may sometimes be susceptible, although wild strains are often resistant, and *Fusobacterium* may also be sensitive.

Other organisms usually sensitive to tetracyclines include *Helicobacter pylori*, Chlamydiaceae, *Rickettsia* and *Coxiella* spp., many spirochaetes including *Borrelia burgdorferi*, *Leptospira* spp., and *Treponema pallidum*, atypical mycobacteria such as *Mycobacterium marinum*, and mycoplasmas including *Mycoplasma pneumoniae* and *Ureaplasma urealyticum*. In addition the tetracyclines are active against some protozoa including *Plasmodium falciparum* and *Entamoeba histolytica*.

Fungi, yeasts, and viruses are generally resistant.

**Resistance.** Resistance to the tetracyclines is usually plasmid-mediated and transferable. It is often inducible, and appears to be associated with the ability to prevent accumulation of the antibacterial within the bacte-

rial cell, both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries), resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as *Escherichia coli*, *Enterobacter*, *Salmonella*, and *Shigella* spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among group A streptococci, and even more so among group B streptococci; there is also resistance among pneumococci, which often show multiple drug resistance. Emergence of high-level tetracycline-resistant strains of *Neisseria gonorrhoeae* is common in some areas. Frequent resistance is also seen in clostridia, and in *Bacteroides fragilis* (among more than 60% of isolates in some countries), while increasing resistance amongst *Haemophilus ducreyi* has limited the value of tetracyclines in chancroid.

### Pharmacokinetics

Most tetracyclines are incompletely absorbed from the gastrointestinal tract, about 60 to 80% of a dose of the drug usually being available. The degree of absorption is reduced by the presence of divalent and trivalent metal ions and also certain drugs, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food (see Interactions above). However, the more lipophilic derivatives doxycycline and minocycline are almost completely absorbed (more than 90%), and they are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline.

Tetracycline 500 mg orally every 6 hours generally produces steady-state plasma concentrations of 4 to 5 micrograms/mL, whereas with doxycycline a dose of 200 mg is sufficient to produce peak concentrations of about 3 micrograms/mL. Peak plasma concentrations occur about 1 to 3 hours after oral use. Higher concentrations can be achieved after intravenous use; concentrations may be higher in women than in men.

In the circulation, tetracyclines are bound to plasma proteins to varying degrees, but reported values differ considerably, ranging from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline, about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and for doxycycline.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed, and small amounts appear in saliva and in the fluids of the eye; higher concentrations are achieved with more lipid-soluble derivatives such as minocycline and doxycycline. Tetracyclines appear in breast milk, where concentrations may be 60% or more of those in the maternal plasma. They diffuse across the placenta and appear in the fetal circulation in concentrations of about 25 to 75% of those in the maternal blood. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines have been classified in terms of their duration of action in the body, although the divisions appear to overlap somewhat. Of the 'short-acting' analogues, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours, and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocycline and methacycline, have reported half-lives of about 12 and 14 hours respectively, although various sources cite values of 7 to 17 hours, and the 'long-acting' minocycline and doxycycline have half-lives of about 16 and 18 hours, with

reported values anywhere between 11 to 26 and 12 to 24 hours respectively.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 60% of an intravenous dose of tetracycline, and up to 55% of an oral dose, is eliminated unchanged in the urine; tetracycline concentrations in the urine of up to 300 micrograms/mL may be reached 2 hours after a usual dose is taken and be maintained for up to 12 hours. Usually about 40 to 70% of a dose is excreted in the urine, but for chlortetracycline, doxycycline, and minocycline, rather less is eliminated by this route since chlortetracycline and minocycline undergo metabolism, and doxycycline is excreted mainly in the faeces. Urinary excretion is increased if urine is alkalinised.

The tetracyclines are excreted in the bile, where concentrations 5 to 25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after oral doses and lesser amounts after injection.

Tetracyclines are slowly removed by haemodialysis, except for doxycycline which is not removed; they are not removed by peritoneal dialysis.

### Uses and Administration

The tetracyclines are bacteriostatic antibacterials with a wide spectrum of activity and have been used in the treatment of a large number of infections caused by susceptible organisms. With the emergence of bacterial resistance and the development of other antibacterials their use has become more restricted, but they remain drugs of choice in rickettsial infections (including Q fever, spotted fevers, and typhus), ehrlichiosis, trench fever, chlamydial infections (including psittacosis, lymphogranuloma venereum, trachoma, non-gonococcal urethritis, and conjunctivitis), and also pharyngitis, sinusitis, or pneumonia due to *Chlamydia pneumoniae* (*Chlamydia pneumoniae*), and mycoplasmal infections (especially pneumonia caused by *Mycoplasma pneumoniae*). They are widely used as part of regimens for pelvic inflammatory disease. A tetracycline is often used with fluid and electrolyte replacement in the treatment of cholera, and is usually the treatment of choice in relapsing fever and in the early stages of Lyme disease. Tetracyclines may be of benefit in the treatment of melioidosis. They may be used for mouth infections, especially in destructive forms of periodontal disease. Tetracyclines are used, often with streptomycin or rifampicin, in the treatment of brucellosis, and may be given with streptomycin in plague, and as an alternative to streptomycin or gentamicin in the treatment of tularaemia.

Tetracyclines are used as an alternative to other drugs in the treatment of actinomycosis, infected animal bites, anthrax, chronic bronchitis, gas gangrene, gastroenteritis (due to *Campylobacter* or *Yersinia enterocolitica*), granuloma inguinale, leptospirosis, and syphilis. Opinions differ as to their value in listeriosis. There are now relatively few areas where tetracycline-resistant gonococci are uncommon, which limits the value of tetracyclines in gonorrhoea, but they are often given with antigonorrhoeal therapy to treat concomitant chlamydial infections, and they retain some value in the prophylaxis of neonatal gonococcal conjunctivitis by topical application.

For details of all these infections and their treatment, see under Choice of Antibacterial, p.162.

Tetracyclines are also used in the oral treatment of acne and rosacea (see Skin Disorders, below).

Tetracyclines have antiprotozoal actions and tetracycline or doxycycline may be given with quinine in the management of falciparum malaria resistant to chloroquine (below). Tetracyclines are the usual treatment for balantidiasis (p.823) and they have been used with an amoebicide in the treatment of severe amoebic dysen-

tery and in *Dientamoeba fragilis* infections (see Amoebiasis, p.822).

Tetracycline has been used in the management of malabsorption syndromes such as tropical sprue.

Tetracycline has been instilled as a sclerosant solution for pleurodesis and in the management of malignant effusions (p.659).

**Administration and dosage.** In the treatment of systemic infections the tetracyclines are usually given orally. They should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration. In severe acute infections they have been given by slow intravenous infusion or, rarely, by intramuscular injection; parenteral therapy should be substituted by oral dosage as soon as practicable.

Doses of tetracycline base and tetracycline hydrochloride are expressed in terms of tetracycline hydrochloride. Tetracycline (anhydrous) 231 mg is equivalent to about 250 mg of tetracycline hydrochloride. The usual adult oral dosage of tetracycline hydrochloride is 250 or 500 mg every 6 hours, preferably 1 hour before or 2 hours after meals. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects. It is also sometimes given orally with other tetracycline derivatives.

Tetracycline hydrochloride has been given by slow intravenous infusion or by intramuscular injection in severe infections. As intramuscular injections were painful, procaine hydrochloride was usually included in the solution.

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

Care is required if tetracyclines are given to the elderly. They should be avoided if possible in renal impairment (with the exception of doxycycline and minocycline) and doses reduced if they must be used. For dosage recommendations in patients with hepatic impairment, see below.

**Other routes.** Although topical application carries the risk of sensitisation and may contribute to the development of resistance, tetracycline hydrochloride has been used as a 3% ointment; a 0.2% solution has been used in acne but systemic treatment appears to produce better results. A 1% eye ointment or eye drops have been used in the treatment of ocular infections due to susceptible organisms. For the treatment of pleural effusions, 500 mg of tetracycline hydrochloride has been dissolved in 30 to 50 mL of sodium chloride 0.9% and instilled into the pleural space. For periodontal disease, fibres that release tetracycline have been inserted into the periodontal pocket.

#### Reviews.

1. Chopra I, et al. Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; **29**: 245-77.
2. Smilack JD. The tetracyclines. *Mayo Clin Proc* 1999; **74**: 727-9.
3. Voils SA, et al. Use of macrolides and tetracyclines for chronic inflammatory diseases. *Ann Pharmacother* 2005; **39**: 86-94.
4. Shlaes DM. An update on tetracyclines. *Curr Opin Investig Drugs* 2006; **7**: 167-71.
5. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54**: 258-65.

**Administration in children.** In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, tetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see above), to a maximum of 2 g daily, may be given orally. However, in the USA, it may be given to those over 8 years old in usual doses of 25 to 50 mg/kg daily by mouth in 4 divided doses.

**Administration in hepatic impairment.** Some licensed product information has stated that the dosage of tetracycline should not exceed 1 g daily in patients with known liver disease.

**Diabetic complications.** The *BNF* notes that diabetic diarrhoea in patients with autonomic neuropathy can often be managed with 2 or 3 doses of oral tetracycline 250 mg.

**Malaria.** Tetracyclines have been used with quinine to treat falciparum malaria (p.594).<sup>1</sup> They are active against both blood and tissue forms of the parasite, and high cure rates have been obtained with such combinations. The action of tetracyclines is relatively slow and they should never be used alone to treat malaria.

A usual oral regimen is a 3 to 7 day course of quinine given with 7 days of the tetracycline. The total daily dose of tetracycline should be divided, and that usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical in the field. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun; tetracycline should not be used parenterally. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones.

The dose of doxycycline given orally with quinine is 200 mg daily for at least 7 days.

Tetracyclines are not considered suitable for extended prophylactic use, although doxycycline 100 mg daily has been used for short-term prophylaxis in areas of high risk where other drugs are likely to be ineffective.

1. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (issued 28th June 2004, updated 6th March 2007). Available at: <http://www.cdc.gov/malaria/pdf/clinicalguidance.pdf> (accessed 28/03/07)

**Mouth ulceration.** Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (p.1700) and reportedly reduce ulcer pain and duration,<sup>1</sup> but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (p.1499).

1. Henriesson V, Axell T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendum dentifrice. *Acta Odontol Scand* 1985; **43**: 47–52.

**Musculoskeletal and joint disorders.** Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (p.11). Studies<sup>1,2</sup> indicate that minocycline can produce modest beneficial effects in patients with advanced disease, but the clinical significance of these improvements has been questioned.<sup>3</sup> Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;<sup>4,5</sup> continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs (DMARDs).<sup>6</sup> A systematic review,<sup>7</sup> which included these and some other studies, reported that the use of tetracyclines (doxycycline, minocycline, or tetracycline) for 3 months or longer was associated with a reduction in disease activity but not in joint damage when compared with placebo or a DMARD (hydroxychloroquine or methotrexate); the authors also noted that patients with early onset disease responded better to tetracyclines. There has been speculation over the role of infection as a cause of rheumatoid arthritis.<sup>3,8</sup> A later study<sup>9</sup> in patients with early seropositive disease found that initial therapy with methotrexate plus doxycycline was superior to methotrexate alone. It was also noted that therapeutic responses to doxycycline 100 mg twice daily and 20 mg twice daily were similar, suggesting that its anti-inflammatory effects were more important; however, further studies are needed.

Although there has been little convincing clinical evidence that any treatment can slow the progression of osteoarthritis (p.11), a placebo-controlled study involving 431 women with unilateral osteoarthritis of the knee found that treatment with doxycycline 100 mg twice daily over 30 months was associated with a reduction in the rate of joint space narrowing.<sup>10</sup> It had no effect on the contralateral knee, and did not reduce pain scores, although these were low at baseline.

The role of antibacterials is also uncertain in reactive arthritis (see Bone and Joint Infections, p.164), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.<sup>11</sup> However, another small study<sup>12</sup> found that treatment with a 4-month course of doxycycline 100 mg twice daily was not superior to a 10-day course.

1. Kloppenburg M, et al. Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; **37**: 629–36.
2. Tilley BC, et al. Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **122**: 81–9.
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; **345**: 1319–20.
4. O'Dell JR, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; **40**: 842–8.
5. O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; **44**: 2235–41.
6. O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; **42**: 1691–5.
7. Stone M, et al. Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; **30**: 2112–22.
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; **57**: 279–82.
9. O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006; **54**: 621–7.

10. Brandt KD, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; **52**: 2015–25.
11. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; **308**: 1302–3.
12. Putschky N, et al. Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006; **65**: 1521–4.

**Peptic ulcer disease.** Tetracycline has been used as part of triple therapy to eradicate *Helicobacter pylori* in patients with peptic ulcer disease (p.1702). The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.

**Periodontal disease.** For the use of doxycycline in subantimicrobial doses as an adjunct in the treatment of periodontal disease, see Administration, Subantimicrobial Doses, p.268.

**Skin disorders. ACNE.** Tetracyclines may be used topically or orally in the treatment of acne (p.1577). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium acnes*, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are:

- doxycycline 50 mg daily (the *BNF* advocates 100 mg daily)
- lymecycline equivalent to 300 mg of tetracycline daily
- minocycline 100 mg daily
- oxytetracycline 250 to 500 mg daily (the *BNF* advocates 1 g daily)
- tetracycline 1 g daily

Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 3 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance compared with tetracycline;<sup>1</sup> it has also been reported to be more effective than erythromycin against oxytetracycline-resistant acne.<sup>2</sup> However, a later randomised study<sup>3</sup> found minocycline to be comparable in efficacy to oxytetracycline, topical erythromycin with benzoyl peroxide, and topical benzoyl peroxide alone in the treatment of mild to moderate acne; in another randomised study<sup>4</sup> lymecycline also showed comparable efficacy and safety. Moreover, minocycline can cause skin pigmentation and may be associated rarely with immunologically-mediated reactions.<sup>5</sup> Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.<sup>6</sup>

For the use of doxycycline in subantimicrobial doses in patients with acne, see Administration, Subantimicrobial Doses, p.268.

1. Eady EA, et al. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; **122**: 233–44.
2. Knaggs HE, et al. The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatol Treat* 1993; **4**: 53–6.
3. Ozolins M, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004; **364**: 2188–95.
4. Bossuyt L, et al. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; **13**: 130–35.
5. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; **312**: 138.
6. Goulden V, et al. Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134**: 693–5.

**PEMPHIGUS AND PEMPHIGOID.** Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (p.1582), although there have been reports<sup>1–8</sup> suggesting that a tetracycline (often minocycline) may be of value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, et al. Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; **132**: 668–70.
2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orydnia with minocycline. *Br J Dermatol* 1995; **132**: 784–9.
3. Kolbach DN, et al. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; **133**: 88–90.
4. Loo WJ, et al. Minocycline as a therapeutic option in bullous pemphigoid. *Clin Exp Dermatol* 2001; **26**: 376–9.
5. Amato L, et al. Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; **13**: 143–6.
6. Assmann T, et al. Therapieresistent pemphigus vulgaris: Kombinationstherapie mit Methylprednisolon und Doxycyclin. *Hautarzt* 2003; **54**: 979–81.
7. Kakurai M, et al. Localized pemphigoid (pretibial type) with IgG antibody to BP180 NC16a domain successfully treated with minocycline and topical corticosteroid. *Clin Exp Dermatol* 2007; **32**: 759–61.
8. Carozzo M, et al. Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* 2008; **18**: 198–200.

**ROSACEA.** Tetracyclines are commonly used in the treatment of rosacea (p.1583). Long-term treatment is usually necessary.

Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.<sup>1</sup> However, a review<sup>2</sup> of the literature concluded that the treatment effect and optimal dose and duration of these 2 drugs have yet to be established; oxytetracycline was found to be of moderate benefit.

For the use of doxycycline in subantimicrobial doses in patients with rosacea, see p.268.

1. Frucht-Pery J, et al. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; **116**: 88–92.
2. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004; **23**: 106–9.

## Preparations

**BP 2008:** Tetracycline Capsules; Tetracycline Tablets; **USP 31:** Tetracycline Hydrochloride and Nystatin Capsules; Tetracycline Hydrochloride Capsules; Tetracycline Hydrochloride for Injection; Tetracycline Hydrochloride for Topical Solution; Tetracycline Hydrochloride Ointment; Tetracycline Hydrochloride Ophthalmic Ointment; Tetracycline Hydrochloride Ophthalmic Suspension; Tetracycline Hydrochloride Oral Suspension; Tetracycline Hydrochloride Tablets; Tetracycline Oral Suspension.

### Proprietary Preparations (details are given in Part 3)

**Arg.:** Cicloterly; Tancilina; **Austral.:** Achromycin V; Achromycin; Laticin; Tetrex; **Austria:** Achromycin; Actisite; Laticin; **Braz.:** Ambra-Sinto T; Aurecidina; Biotrex; Cinatex; Infex; Multigran; Procidina; Statinglyne; Telexin; Teracton; Teraben; Tetraclil; Tetraclina; Tetraclil; Tetragel; Tetramax; Tetramicin; Tetraspir; Tetraclil; Tetrex; Tetrib; **Canada:** Apo-Tetra; Novo-Tetra; Nu-Tetra; **Cz.:** Tetraclhel; **Fin.:** Apocidin; Oricylin; **Ger.:** Achromycin; Imex; Supramycin; Tefilin; Tetralution; **Gr.:** Cliten; Hostacylin; Imex; Muvito; Tetra; Tracilin; **Hong Kong:** Medocycline; **India:** Achromycin; Hostacylin; Restedlin; Subamycin; Tetraclil; **Indon.:** Cetacycline-P; Conmycin; Corsatet; Dumocycline; Ikacycline; Indocycline; Licolin; Sanlin; Spectrocyline; Super Tetra; Tetra; Tetraclor; Tetrix; **Irl.:** Topicycline; **Israel:** Recycline; Tevacycline; **Ital.:** Actisite; **Malaysia:** Beatacylone; Dhatarcin; Laticyn; Tracyn; **Mex.:** Acromicina; Ambotetra; Bercidina; Biotricina; Cortigrin; Dibater; Euducina; Forcicine; Istix; Laur; Mclidin; Neoprob; Ofidlin; Oxi-T; Profalin CPS; Quimocylar; Senocidin; Soldin; Te-Br; Teclizima; Tetraclil; Terranumonyl; Tetra; Tetra-Zil; Tetrapar; Tetrapres; Tetreba; Tetrex; Tetrim; Traplicina; Triclin; **Philipp.:** Monoclyne; **Port.:** Ciclobiotico; Neocilina; **Rus.:** Polcortolon TC (Полькортолон ТС); **S.Afr.:** Tetrex; **Singapore:** Beatacylone; Biotine; **Spain:** Actisite; Quimpe Antibiotico; Tetra Hubber; **Switz.:** Actisite; **Thai.:** Achromycin; Boramycin; Hydroxymycin; Lenocin; Pantocycline; Tetra Cental; Tetralin; Tetra; Tetra; **Turk.:** Imex; Tetra; Tetralet; Tetramin; Vitasilin; **UK:** Topicycline; **USA:** Achromycin V; Actisite; Bristacycline; Sumycin; **Venez.:** Alfaciolina; Clincor.

**Multi-ingredient:** **Arg.:** Dresan Biotici; Eubetal Biotici; Febrimicina; Paspasine; Solustres; **Austria:** Eftapan Tetra; Fluorex Plus; Mystedlin; **Braz.:** Anfoterin; Gino-Teracin; Monocetin; Novasutin; Parenzyme Tetraclina; Talsutin; Tericin AT; Tricangine; Tricooclin B; Trinotrex; Vagiklin; **Chile:** Talselcin; **Fin.:** Heliapak T; **Fr.:** Amphocycline; **Ger.:** Mystedlin; Polcortolon TC; **Hong Kong:** Talsutin; **Hung.:** Polcortolon TC; **Indon.:** Enciportin; Talsutin; **Ital.:** Alfaflor; Betaflorol; Colbioin; Eubetal Antibiotico; Flumeclina; Flumelot Antibiotico; Mictasone; Pensulin; Vitacaf; **Malaysia:** Talsutin; **Mex.:** Bercilina Enzimatica; Pharbrix; Quimotrip; Solfranico; Trecloran; Urovec; **Philipp.:** Vagimycin; **Pol.:** Polcortolon TC; **Port.:** Ciclobiotico; **Rus.:** Colbioin (Колбиоин); **S.Afr.:** Riosatin; Tetrex-F; Tritet; Vagmycin; **Spain:** Bristiciclina Dental; Gine Heyden; Nasopomada; Sanicel; **UK:** Detectol; **USA:** Heliada; Pylera; **Venez.:** Talsutin.

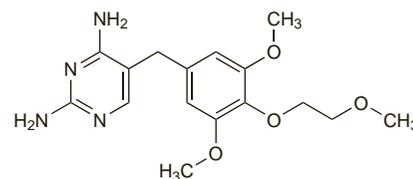
## Tetroxoprim (BAN, USAN, rINN)

Tetroxoprima; Tétroxoprim; Tetroxoprimum. 5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyldiamine.

Тетроксоприм

C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub> = 334.4.

CAS — 53808-87-0.



NOTE. Compounded preparations of tetroxoprim may be represented by the following name:

- Co-tetroxazine (BAN)—tetroxoprim 2 parts and sulfadiazine 5 parts (see p.257).

### Profile

Tetroxoprim is a dihydrofolate reductase inhibitor similar to, but less active than, trimethoprim (p.355). It has been used, with sulfadiazine, as co-tetroxazine (p.257).

Tetroxoprim embonate has been used similarly.

### Preparations

**Proprietary Preparations** (details are given in Part 3)

**Multi-ingredient:** **Ger.:** Sterinor; **Venez.:** Esterinor.