Temocillin Sodium *(BANM, rINNM)*

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Témocilline Sodique. The disodium salt of (6*S*)-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).

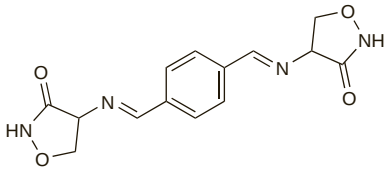
Теризидон

$C_{14}H_{14}N_4O_4$ = 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: Terivalidin; ***Braz.:*** Terizidex; ***S.Afr.:*** Terivalidin.

Tetracycline *(BAN, rINN)*

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

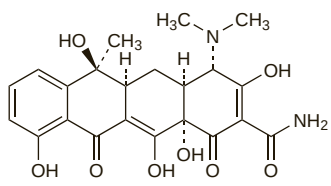
Тетрациклин

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

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 hidrochloridas; Tétracycline, chlorhydrate de; Tetracyclini hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi.

Тетрациклина Гидрохлорид

$C_{22}H_{24}N_2O_8$,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;[1,2] 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.[1] The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.[1] 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.[3] 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.[4]

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.[2] 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.[5] Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.[5] However, although this study, and an accelerated stability study carried out by WHO[6] 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.[7]

1. Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; **52:** 752–6.
2. Grobben-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; **7:** 104–8.
3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; **24:** 434–9.
4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; **6:** 201–14.
5. Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; **59:** 1160–4.
6. 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 (accessed 18/05/07)
7. 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-