pressed in terms of the base. The usual adult dose is 500 mg two or three times daily.

Preparations

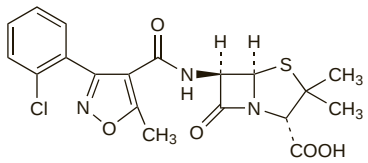
Proprietary Preparations (details are given in Part 3)
Belg.: Rixapen.

Cloxacillin *(BAN, rINN)*

Cloxacilina; Cloxacilline; Cloxacillinum; Kloksasilliini; Kloxacillin. (6*R*)-6-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

Клоксациллин

$C_{19}H_{18}ClN_3O_5S$ = 435.9.
CAS — 61-72-3.
ATC — J01CF02.
ATC Vet — QJ01CF02; QJ51CF02; QS01AA90.



Cloxacillin Benzathine *(BANM)*

Cloxacilina benzatina. The *N,N'*-dibenzylethylenediamine salt of cloxacillin.

$C_{16}H_{20}N_2.(C_{19}H_{18}ClN_3O_5S)_2$ = 1112.1.
CAS — 23736-58-5; 32222-55-2.
ATC — J01CF02.
ATC Vet — QJ01CF02.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP(Vet)*.
BP(Vet) 2008 (Cloxacillin Benzathine). A white or almost white powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers.
USP 31 (Cloxacillin Benzathine). White or almost white, almost odourless, crystals or crystalline powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; sparingly soluble in acetone; soluble in chloroform and in methyl alcohol. pH of a 1% suspension in water is between 3.0 and 6.5. Store in airtight containers.

Cloxacillin Sodium *(BANM, USAN, rINNM)*

BRL-1621; Cloxacilina sódica; Cloxacilline sodique; Cloxacillinum natricum; Cloxacillinum Natricum Monohydricum; Kloksacilino natrio druska; Kloksacylina sodowa; Kloksasilliininatrium; Kloxacilin sodná sůl monohydrát; Kloxacillinnatrium; Kloxacillin-nátrium; Natrii Cloxacillinum; P-25.

Натрий Клоксациллин

$C_{19}H_{17}ClN_3NaO_5S,H_2O$ = 475.9.
CAS — 642-78-4 (anhydrous cloxacillin sodium); 7081-44-9 (cloxacillin sodium monohydrate).
ATC — J01CF02.
ATC Vet — QJ01CF02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Cloxacillin Sodium). Semi-synthetic product derived from a fermentation product. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.
USP 31 (Cloxacillin Sodium). A white, odourless, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers at a temperature not exceeding 25°.

Incompatibility. Cloxacillin sodium has been reported to be incompatible with aminoglycosides and a number of other antimicrobials.

Adverse Effects and Precautions

As for Flucloxacillin, p.277.

Effects on the kidneys. References.

1. García-Ortiz R, *et al.* Cloxacillin-induced acute tubulo interstitial nephritis. *Ann Pharmacother* 1992; **26:** 1241–2.

Effects on the liver. References.

1. Enat R, *et al.* Cholestatic jaundice caused by cloxacillin: macrophage inhibition factor test in preventing rechallenge with hepatotoxic drugs. *BMJ* 1980; **280:** 982–3.
2. Konikoff F, *et al.* Cloxacillin-induced cholestatic jaundice. *Am J Gastroenterol* 1986; **81:** 1082–3.
3. Goland S, *et al.* Severe cholestatic hepatitis following cloxacillin treatment. *Postgrad Med J* 1998; **74:** 59–60.

Sodium content. Each g of cloxacillin sodium contains about 2.1 mmol of sodium.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

As for Flucloxacillin, p.277.

Pharmacokinetics

Cloxacillin is incompletely absorbed from the gastrointestinal tract, and absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 15 micrograms/mL is attained in fasting subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 micrograms/mL have been observed 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentration. About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

Cloxacillin crosses the placenta and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and in bone.

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and up to 10% in the bile. Cloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations in patients with cystic fibrosis have been attributed to both enhanced tubular secretion and enhanced nonrenal clearance of cloxacillin.

Uses and Administration

Cloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Cloxacillin is given orally as the sodium salt and doses are expressed in terms of the equivalent amount of cloxacillin; 1.09 g of cloxacillin sodium is equivalent to about 1 g of cloxacillin. It should be given at least 30 minutes before meals as the presence of food in the stomach reduces absorption.

Usual oral doses are 250 to 500 mg four times daily. Children up to 2 years may be given a quarter of the daily adult dose and those over 2 years half the daily adult dose, in divided doses every 6 hours.

Cloxacillin sodium has also been given by intramuscular or slow intravenous injection or infusion. Other routes have included intra-articular or intrapleural injection, and inhalation.

Cloxacillin may be used with other antibacterials, including ampicillin, to produce a wider spectrum of activity.

Cloxacillin benzathine is used in veterinary medicine.

Preparations

USP 31: Cloxacillin Sodium Capsules; Cloxacillin Sodium for Oral Solution.

Proprietary Preparations (details are given in Part 3)

Belg.: Penstaphon; ***Canad.:*** Apo-Cloxi; Novo-Cloxin; Nu-Cloxi; ***Chile:*** Cloxapen†; ***Fin.:*** Ekvacillin†; Staflocil; ***Fr.:*** Orbenine; ***Gr.:*** Anaclosil; Orbenin; Staphyclox; ***Hong Kong:*** Apo-Cloxi; Cloxil†; Cloxin; Lidoxin; Monoclox; Prostaphlin-A; ***India:*** Bioclox; Iclox†; ***Indon.:*** Meixam; ***Israel:*** Loxavit; Orbenil; ***Malaysia:*** Monoclox; Oxacil†; Proxin†; ***Neth.:*** Orbenin†; ***Norw.:*** Ekvacillin; ***Philipp.:*** Avastoph; Caxin; Ciclox; Cloxigen; Eloxil; Encloxil; Eraclox; Excelox; Jogen; Lewinex; Medix; Orbenin; Oxaclen; Pannox; Patriflex; Prostaphilin-A; Solaze; Vamcloxil; ***Pol.:*** Syntarpen; ***S.Afr.:*** Cloxin; Orbenin; ***Singapore:*** Axocillin†; Cloxacap†; Lidoxin; Monoclox†; ***Spain:*** Anaclosil; Orbenin; ***Swed.:*** Ekvacillin; ***Thai.:*** Cloxa; Cloxalin; Cloxam; Cloxanbin; Cloxapan†; Cloxasian; Cloxgen; Cloxil; Cloxillin†; Corbin; Greater-Gloxa; K-Cil; Lidoxin; Loxzalin; Meiclox; Orbenin; Serviclox†; Socloxin; Syntoclox; Theraclox; Vaclox.

Multi-ingredient: *Cz.:* Ampiclox†; ***Hong Kong:*** Ampiclox†; APT-Ampicloxa; Pamedox; Roscilox; ***India:*** ABClox; Adilox; Amclo†; Ampilox; Ampilox-LB; Amplus; Ampoxin; Ampoxin-LB; Bicidal Plus; Campilox; Clax; Hipenox; Imox-Clo; Imox-Clo LB; Megaclox; Megaclox LB; Megapen; Novaclox; Novaclox LB; Suprimox; Symbiotik; ***Irl.:*** Ampiclox†; ***Ital.:*** Amplium; ***S.Afr.:*** Ampiclox; Apen; Cloxam; Megamox; Ranclosil†; ***Thai.:*** Ampiclox; Viccillin-S.

Colistin Sulfate *(plNNM)*

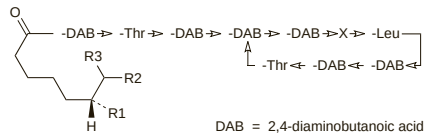
Colistin Sulphate *(BANM)*; Colistine, sulfate de; Colistini sulfas; Kolistiinisulfaatti; Kolistino sulfatas; Kolistinsulfat; Kolistin-sulfát; Kolistyny siarczan; Kolisztin-szulfát; Polymyxin E Sulphate; Sulfato de colistina.

Колистина Сульфат

CAS — 1066-17-7 (colistin); 1264-72-8 (colistin sulfate).

ATC — A07AA10; J01XB01.

ATC Vet — QA07AA10; QJ01XB01.



DAB = 2,4-diaminobutanoic acid

polymyxin	X	R1	R2	R3	Mol. Formula
E1	D-Leu	CH	CH	H	C H N O
E2	D-Leu	CH	H	H	C H N O
E3	D-Leu	H	CH	H	C H N O
E1-I	D-Ile	CH	CH	H	C H N O
E1-7MOA	D-Leu	H	CH	CH	C H N O

(colistin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Colistin Sulphate). A mixture of the sulfates of polypeptides produced by certain strains of *Bacillus polymyxa* var. *colistinus* or obtained by any other means. It contains a minimum of 77% of the sum of polymyxin E1, polymyxin E2, polymyxin E3, polymyxin E1-I, and polymyxin E1-7MOA. A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.
USP 31 (Colistin Sulfate). The sulfate salt of an antibacterial substance produced by the growth of *Bacillus polymyxa* var. *colistinus*. It has a potency of not less than 500 micrograms of colistin per mg. A white to slightly yellow, odourless, fine powder. Freely soluble in water; insoluble in acetone and in ether; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 7.0. Store in airtight containers.

Stability. Colistin base is precipitated from aqueous solution above pH 7.5.

Colistimethate Sodium *(BANM, USAN, rINN)*

Colistimetato de sodio; Colistimetato de Sódio; Colistimetato sódico; Colistiméthate sodique; Colistimethatum natricum; Colistimethatum Natrium; Colistin Sulphomethate Sodium; Colistinéméthanesulfonate Sodique; Kolistimetaattinatrium; Kolistimetatnatrium; Kolistimetato natrio druska; Kolistimethát sodná sůl; Kolistymetat sodowy; Kolisztimetát-nátrium; Pentasodium Colistinmethanesulfonate; Sodium Colistimethate; Sodium Colistinmethanesulphonate; W-1929.

Колистиметат Натрий

CAS — 30387-39-4 (colistimethate); 8068-28-8 (colistimethate sodium).
ATC — A07AA10; J01XB01.
ATC Vet — QA07AA10; QJ01XB01.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Colistimethate Sodium). It is prepared from colistin by the action of formaldehyde and sodium bisulfite. The potency is not less than 11 500 units/mg, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.
USP 31 (Colistimethate Sodium). A white to slightly yellow, odourless, fine powder. It has a potency equivalent to not less than 390 micrograms of colistin per mg. Freely soluble in water; insoluble in acetone and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 6.5 and 8.5.

Stability. After the death of a patient with cystic fibrosis who had been given a liquid solution of colistimethate premixed for inhalation with a nebuliser (see Cystic Fibrosis, under Adverse Effects, below) the US FDA warned[1] that such premixing of colistimethate in an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution and increases the potential for lung toxicity. When colistimethate is mixed with water and buffer it undergoes spontaneous hydrolysis to colistin; polymyxin E1, a component of colistin, has been shown to cause pulmonary inflammation in *animal* studies. Inhalation solutions of colistimethate should therefore be given promptly after preparation.

1. FDA. Colistimethate (marketed as Coly-Mycin M and generic products) (issued 28 June 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/colistimethateHCP.htm (accessed 18/01/08)

Units

The first International Standard Preparation (1968) for colistin contains 20 500 units/mg of colistin sulfate and the first International Reference Preparation (1968) for colistimethate contains 12 700 units/mg of colistimethate.