Pivampicillin Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de pivampicilina; Pivampicilline, Chlorhydrate de; Pivampicillini Hydrochloridum.

Пивампициллина Гидрохлорид

$C_{22}H_{29}N_3O_6S,HCl$ = 500.0.

CAS — 26309-95-5.

ATC — J01CA02.

ATC Vet — QJ01CA02.

Adverse Effects and Precautions

As for Ampicillin, p.204. Pivampicillin is reported to cause a lower incidence of diarrhoea than ampicillin. Upper gastrointestinal discomfort may be more frequent when pivampicillin is taken on an empty stomach.

Pivaloyloxymethyl esters such as pivampicillin have been associated with the induction of carnitine deficiency (see below).

Carnitine deficiency. Carnitine deficiency (see p.1933) has been reported after the use of pivampicillin and pivmecillinam.[1] It is thought that the pivalic acid liberated on hydrolysis of these pivaloyloxymethyl esters *in vivo* is excreted as pivaloyl-carnitine with a consequent depletion in plasma and muscle concentrations of carnitine.[2] Low plasma-carnitine concentrations persisted in a patient after stopping pivampicillin, despite 6 weeks of replacement therapy with oral carnitine 1g daily. She had originally presented with skeletal myopathy when given pivampicillin for 3 months. A more intensive carnitine replacement regimen might be necessary in such patients.[3]

1. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; **ii:** 469–73.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631–3.
3. Rose SJ, *et al.* Carnitine deficiency associated with long-term pivampicillin treatment: the effect of a replacement therapy regime. *Postgrad Med J* 1992; **68:** 932–4.

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

Interactions

As for Benzylpenicillin, p.214.

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving pivampicillin and valproate.

Antimicrobial Action

Pivampicillin has the antimicrobial activity of ampicillin to which it is hydrolysed *in vivo* (p.204).

Pharmacokinetics

Pivampicillin is acid-stable and is readily absorbed from the gastrointestinal tract. On absorption it is rapidly and almost completely hydrolysed to ampicillin, pivalic acid, and formaldehyde. Plasma-ampicillin concentrations 1 hour after a dose are 2 to 3 times those attained after an equivalent dose of ampicillin. The absorption of pivampicillin is generally not significantly affected by food. About 70% of a dose is excreted in the urine as ampicillin within 6 hours.

Uses and Administration

Pivampicillin is the pivaloyloxymethyl ester of ampicillin (p.205) and has similar uses; 1.3 g of pivampicillin and 1.43 g of pivampicillin hydrochloride are each equivalent to about 1 g of ampicillin.

Pivampicillin is given orally to adults and children over 10 years of age in doses of 500 mg twice daily with food, which may be doubled in severe infections. In children aged 3 months to 1 year a dose of 20 to 30 mg/kg twice daily may be used. Children older than 1 year may be given 12.5 to 17.5 mg/kg twice daily, up to 500 mg twice daily.

In areas where gonococci remain sensitive a single dose of 1.5 g is given for gonorrhoea, with probenecid 1 g.

Pivampicillin hydrochloride has been used in some countries.

Pivampicillin has also been given with pivmecillinam (below).

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Pondocillin; ***Denm.:*** Pondocillin; ***Fr.:*** Proampi; ***Norw.:*** Pondocillin; ***Swed.:*** Pondocillin.

Pivmecillinam *(BAN, rINN)*

Amdinocillin Pivoxil *(USAN)*; FL-1039; Pivamdinocillin; Pivmecilinam; Pivmécillinam; Pivmecillinamum; Pivmesillinaami; Ro-10-9071. Pivaloyloxymethyl (6*R*)-6-(perhydroazepin-1-ylmethyleneamino)penicillanate.

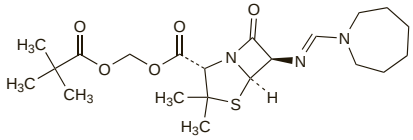
Пивмециллинам

$C_{21}H_{33}N_3O_5S$ = 439.6.

CAS — 32886-97-8.

ATC — J01CA08.

ATC Vet — QJ01CA08.



Pivmecillinam Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pivmecilinam; Pivmecilinam-hydrochlorid; Pivmecilinamo hidrochloridas; Pivmécillinam, Chlorhydrate de; Pivmecillinám-hidroklorid; Pivmecillinamhydroklorid; Pivmecillinami hydrochloridum; Pivmesillinaamihydrokloridi.

Пивмециллинама Гидрохлорид

$C_{21}H_{33}N_3O_5S,HCl$ = 476.0.

CAS — 32887-03-9.

ATC — J01CA08.

ATC Vet — QJ01CA08.

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

Ph. Eur. 6.2 (Pivmecillinam Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 2.8 to 3.8. Store at a temperature of 2° to 8°. Protect from light.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Pivaloyloxymethyl esters such as pivmecillinam have been associated with the induction of carnitine deficiency (see Pivampicillin, above).

Administration. Oesophageal injury has been associated rarely with pivmecillinam tablets.[1,2] Patients are advised to take them during a meal, while sitting or standing, and with at least half a glass of water.[3]

1. Committee on Safety of Medicines. Pivmecillinam and oesophageal injury. *Current Problems 19* 1987. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024426&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)
2. Mortimer Ö, Wiholm B-E. Oesophageal injury associated with pivmecillinam tablets. *Eur J Clin Pharmacol* 1989; **37:** 605–7.
3. Anonymous. CSM warning on pivmecillinam. *Pharm J* 1987; **238:** 443.

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

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Pivmecillinam has the antimicrobial activity of mecillinam (p.297) to which it is hydrolysed *in vivo*.

Pharmacokinetics

Pivmecillinam is well absorbed from the gastrointestinal tract and is rapidly hydrolysed to the active drug mecillinam (p.297), pivalic acid, and formaldehyde. The presence of food in the stomach does not appear to have a significant effect on absorption. Peak plasma concentrations of mecillinam of 5 micrograms/mL have been achieved 1 to 2 hours after a 400-mg dose of pivmecillinam.

About 45% of a dose may be excreted in the urine as mecillinam, mainly within the first 6 hours.

◊ References.

1. Heikkilä A, *et al.* The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women. *Br J Clin Pharmacol* 1992; **33**; 629–33.

Uses and Administration

Pivmecillinam is the pivaloyloxymethyl ester of mecillinam (p.297), to which it is hydrolysed after oral dosage. It is used in the treatment of urinary-tract infections (p.199).

Doses of pivmecillinam have often been expressed in a confusing manner since no differentiation has been made between the hydrochloride, used in tablets, and the base, used in suspensions for oral use. Pivmecillinam 1.35 g and pivmecillinam hydrochloride 1.46 g are each equivalent to about 1 g of mecillinam.

Pivmecillinam should preferably be taken with food (see also Administration, under Adverse Effects and Precautions, above).

In acute uncomplicated cystitis, the initial adult dose is 400 mg orally followed by 200 mg three times daily for 8 doses. In chronic or recurrent bacteriuria, 400 mg may be given 3 or 4 times daily. The dose for children (weighing less than 40 kg) with urinary-tract infections is 20 to 40 mg/kg daily in 3 or 4 divided doses.

Pivmecillinam has been given with other beta lactams, particularly pivampicillin (p.316), to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

For parenteral use, mecillinam is given.

◊ References.

1. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; **46** (suppl S1): 35–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Selexid; ***Belg.:*** Selexid†; ***Canad.:*** Selexid†; ***Denm.:*** Selexid; ***Fin.:*** Selexid; ***Fr.:*** Selexid; ***Norw.:*** Selexid; ***NZ:*** Selexid; ***Port.:*** Selecid†; ***Swed.:*** Selexid; ***UK:*** Selexid.

Polymyxin B Sulfate *(rINNM)*

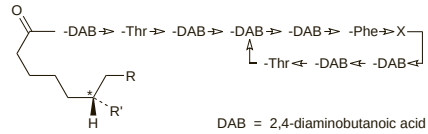
Polimiksin B Sülfat; Polimiksino B sulfatas; Polimixin-B-szulfát; Polimyksyny B siarczan; Polimyxini b sulfas; Polymyksiini-B-sulfaatti; Polymyxin B sulfat; Polymyxin B Sulphate *(BANM)*; Polymyxin-B-sulfát; Polymyxine B, sulfate de; Polymyxini B sulfas; Polymyxinum B Sulfas; Sulfato de polimixina B.

Полимиксина В Сульфат

CAS — 1404-26-8 (polymyxin B); 1405-20-5 (polymyxin B sulfate); 4135-11-9 (polymyxin B1); 34503-87-2 (polymyxin B2); 71140-58-4 (polymyxin B3).

ATC — A07AA05; J01XB02; S01AA18; S02AA11; S03AA03.

ATC Vet — QA07AA05; QJ01XB02; QS01AA18; QS02AA11; QS03AA03.



Polymyxin	R	R'	X	Mol. Formula
B1	CH	CH	-Leu	C H N O
B2	H	CH	-Leu	C H N O
B3	CH	H	-Leu	C H N O
B1-I	CH	CH	-Ile	C H N O

(polymyxin B)

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

Ph. Eur. 6.2 (Polymyxin B Sulphate). A mixture of the sulfates of polypeptides produced by the growth of certain strains of *Bacillus polymyxa* or obtained by any other means. A white or almost white, hygroscopic powder. Soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 31 (Polymyxin B Sulfate). The sulfate salt of a kind of polymyxin, a substance produced by the growth of *Bacillus polymyxa* (Bacillaceae), or a mixture of two or more such salts. A white to buff-coloured, powder, odourless or has a faint odour. It has a potency of not less than 6000 Polymyxin B units/mg, calculated on the dried substance. Freely soluble in water; slightly soluble in alcohol. pH of a 0.5% solution in water is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported with many other drugs including antibacterials. Polymyxin B sulfate is rapidly inactivated by strong acids and alkalis.

Units

The second International Standard Preparation (1969) of polymyxin B sulfate contains 8403 units/mg.

NOTE. The available forms of polymyxin B sulfate are generally less pure than the International Standard Preparation. Doses have sometimes been stated in terms of pure polymyxin base; 100 mg of pure polymyxin B is considered to be equivalent to 1 million units (1 mega unit).

Adverse Effects, Treatment, and Precautions

When given parenterally, the major adverse effects of the polymyxins are dose-related neurotoxicity and nephrotoxicity. Hypersensitivity reactions are rare, although rashes and fever have been reported, and polymyxins cause histamine release, which may lead to bronchoconstriction and other anaphylactoid symptoms. Polymyxins should be avoided in patients with a history of hypersensitivity to any of the group.

Neurotoxic reactions can occur in up to 7% of patients with normal renal function and include peripheral effects such as circumoral and 'stocking-glove' pattern paraesthesias, visual disturbances, and dizziness, ataxia, confusion, drowsiness, and other CNS effects. The polymyxins are potent neuromuscular blockers, and respiratory paralysis and apnoea may result, especially in overdosage and in patients with renal impairment or pre-existing disorders of neuromuscular transmission such as myasthenia gravis, in whom particular care is needed; certain medications may also increase the risk (see Interactions, below). Neostigmine or calcium salts are usually of little value in reversing neuromuscular blockade and artificial ventilation may be required if it develops.

Nephrotoxicity may occur in up to 20% of patients after parenteral use and may be marked by nitrogen retention, haematuria, proteinuria, and tubular necrosis. Electrolyte disturbances are common. Baseline renal function levels should be established before starting parenteral polymyxin B therapy and renal function and blood concentrations of polymyxins should be monitored frequently during therapy. Patients with pre-existing renal impairment and nitrogen retention are at particular risk and require dosage reduction. Signs of decreasing urine output and increasing nitrogen retention are an indication for stopping the drug in all patients. Although polymyxin B is said to be more nephrotoxic than colistin on a weight-for-weight basis, their effects on the kidney seem to be similar at therapeutically equivalent doses.

Polymyxin B is irritant; pain after intramuscular injection may be severe and thrombophlebitis can occur after intravenous injection. Meningeal irritation, manifest as fever, headache, stiff neck, and increased cell count and protein levels in the CSF, may follow intrathecal doses.

Ear drops containing polymyxins should not be used in patients with perforated ear drums, due to the increased risk of ototoxicity. Topical application to large areas of skin should be avoided because of the risk of systemic absorption resulting in neurotoxicity and nephrotoxicity, particularly in children, the elderly, and patients with renal impairment.

Interactions

Polymyxins may enhance the action of neuromuscular blockers (p.1903) possibly resulting in respiratory depression and apnoea, and concurrent use should be avoided. Additive neurotoxicity and/or nephrotoxicity may occur if polymyxins are given with other potentially neurotoxic and/or nephrotoxic drugs including aminoglycosides and cefaloridine; concurrent use should also be avoided.

Antimicrobial Action

Polymyxin B and the other polymyxin antibacterials act primarily by binding to membrane phospholipids and disrupting the bacterial cytoplasmic membrane. Polymyxin B has a bactericidal action on most Gram-negative bacilli except *Proteus* spp. It is particularly effective against *Pseudomonas aeruginosa*. Of the other Gram-negative organisms, *Acinetobacter* spp., *Escherichia coli*, *Enterobacter* and *Klebsiella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, *Salmonella*, and *Shigella* spp. are sensitive. Classical *Vibrio cholerae* 01 is sensitive but the El Tor and O139 biotypes are resistant. *Serratia*, *Burkholderia*, and *Providencia* spp., and *Bacteroides fragilis* are usually resistant. It is not active against *Neisseria* spp., obligate anaerobes, and Gram-positive bacteria. Some fungi such as *Coccidioides immitis* are susceptible but most are resistant.

Antimicrobial synergy has been reported with other drugs, including chloramphenicol, tetracyclines, and the sulfonamides and trimethoprim.

The action of polymyxin B is reduced by divalent cations such as calcium and magnesium, and so activity *in vivo* is less marked than *in vitro*.

Acquired resistance to polymyxin B is uncommon, although adaptive resistance may develop in enterobacteria exposed to sublethal concentrations. There is complete cross-resistance between polymyxin B and colistin.

Pharmacokinetics

Polymyxin B sulfate is not absorbed from the gastrointestinal tract, except in infants who may absorb up to 10% of a dose. It is not absorbed through mucous membranes, or intact or denuded skin.

Peak plasma concentrations after intramuscular injection usually occur within 2 hours, but are variable and polymyxin B sulfate is partially inactivated by serum. It is widely distributed and extensively bound to cell membranes in the tissues; it does not appear to be highly bound to serum proteins. Accumulation may occur after repeated doses. There is no diffusion into the CSF and it does not cross the placenta. Polymyxin B is reported to have a serum half-life of about 6 hours but this is prolonged in renal impairment; values of 2 to 3 days have been reported in patients with a creatinine clearance of less than 10 mL/minute.

Polymyxin B sulfate is excreted mainly by the kidneys by glomerular filtration, about 60% of a dose being recovered unchanged in the urine, but there is a time lag of 12 to 24 hours before polymyxin B is recovered in the urine.

Polymyxin B is not removed to an appreciable extent by peritoneal dialysis or haemodialysis.

Uses and Administration

Polymyxin B sulfate is used topically, often with other drugs, in the treatment of skin, ear, and eye infections due to susceptible organisms. Eye drops containing polymyxin B with neomycin and gramicidin have been used for the prophylaxis of infection in patients undergoing ocular surgery and, with propamidine isetionate, for the treatment of acanthamoeba keratitis (p.822). Polymyxin B has been given orally with other drugs in regimens for selective digestive-tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p.175). Polymyxin B has also been used parenterally for the treatment of infections due to susceptible Gram-negative bacteria, especially *Pseudomonas aeruginosa*, but other drugs are generally preferred. Polymyxin B has been given intrathecally in meningeal infection, and by subconjunctival injection for eye infections.

For topical application polymyxin B is usually available as a 0.1% solution or ointment (10 000 units per mL or per g respectively) combined with other drugs. Intravenous doses range from 15 000 to 25 000 units/kg daily, by infusion and may be given every 12 hours. The intramuscular route has also been used despite the severe pain which may be associated with it; doses range from 25 000 to 30 000 units/kg daily, and may be given every 4 or 6 hours.

Doses should be reduced in patients with renal impairment (see below).

Intrathecal doses of 50 000 units may be given once daily for 3 to 4 days, then on alternate days for at least 2 weeks after the CSF cultures become negative.

For details of doses in children, including infants, see below.

For subconjunctival injection, doses of up to 100 000 units daily may be used for infections of the cornea and conjunctiva.

◊ References.

1. Evans ME, *et al.* Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Ann Pharmacother* 1999; **33:** 960–7.
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Arnold TM, *et al.* Polymyxin antibiotics for gram-negative infections. *Am J Health-Syst Pharm* 2007; **64:** 819–26.
4. Zavascki AP, *et al.* Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. *J Antimicrob Chemother* 2007; **60:** 1206–15.

Administration in children. Up to 40 000 units/kg daily of polymyxin sulfate may be given to infants with normal renal function by intravenous infusion or by intramuscular injection, although the latter is not recommended routinely because of severe pain at injection sites. Doses as high as 45 000 units/kg daily have been tried in premature and full-term neonates. For suggested doses in children with renal impairment see below.

In children under 2 years of age, intrathecal doses of 20 000 units once daily for 3 to 4 days or 25 000 units on alternate days may be given, followed by the latter dose for at least 2 weeks after the CSF cultures become negative.

Older children may be given the usual adult dose (see above).

Administration in renal impairment. Parenteral doses of polymyxin sulfate should be reduced in adults and children with renal impairment; a maximum intravenous dose of 15 000 units/kg daily has been suggested.

Preparations

BP 2008: Polymyxin and Bacitracin Eye Ointment;
USP 31: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Polymyxin B for Injection; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder; Polymyxin B Sulfate and Hydrocortisone Otic Solution; Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Braz.: Polixil B†; ***Philipp.:*** Aerosporin; ***Port.:*** Oto-Synalar N.

Multi-ingredient: ***Arg.:*** Belbar; Ginal Cent; Ginkan; Irix Biotic; Isoptomax; Linfol Cicatrizante; Mailen; Min O; Nebapol B†; Neoftalm; Neoftalm Dexa; Neolag; O-Biol P; Otosporin; Otosporin L; Ovumix; Pantometil; Pentol; Poenbioptal NF; Polygynax; Polyplex; Septigyn; Sincerum Biotic L; Terramicina con Polimixina B†; Trimepol; Trimepol D; Vagicural Plus; ***Austral.:*** Neosporin; ***Austria:*** Neocones; Otosporin; Polytrim; ***Belg.:*** De Icin†; Dexa-Polyspectran New; Maxitrol; Ophtalmotrim†; Otosporin†; Panotile; Polydexa; Polygynax†; Polyspectran Gramicidine; Polytrim; Predmycin P; Statrol; Synalar Bi-Otic; Terra-Cortril + Polymyxine B; Terramycine + Polymyxine B; ***Braz.:*** Anaseptil; Colpolase; Elotin; Ginec†; Lidosporin; Maxitrol; Nepodex; Otauril†; Otocort†; Otomixyn; Otosporin; Otosynalar; Panotil; Poliginax; Polipred; Polysporin; Predmicin; Terramicina c/Polimixina; ***Canad.:*** Antibiotic Cold Sore Ointment; Antibiotic Cream†; Antibiotique Onguent; Bacimyxin; Band-Aid Antibiotic; Bioderm; Cortimyxin; Cortisporin; Dioptrol†; Johnson & Johnson First Aid Ointment†; Lidomyxin; Lidosporin; Maxitrol; Neosporin; Neotopic†; Optimyxin; Optimyxin Plus; Ozonol Antibiotic Plus; PMS-Polytrimethoprim; Polycidin†; Polyderm; Polysporin; Polysporin Complete Antibiotic; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polytopic; Polytrim; ***Chile:*** Dermabiotico; Gotalgic; Grifoftal-D; Grifoftal†; Maxitrol; Oftabiotico; Otazol†; Oticum; Otolisan; Otoseptil; Unguento Dermico Antibiotico†; ***Cz.:*** Maxitrol; Otosporin; Polygynax; Pulpomixine; Statrol†; ***Denm.:*** Hydrocortison med Terramycin og Polymyxin-B; Terramycin Polymyxin B; ***Fin.:*** Maxitrol; Polysporin; Terra-Cortril P; ***Fr.:*** Antibio-Synalar; Antibiotulle Lumiere; Atebemyxine; Auricularum; Cebemyxine; Corticotulle Lumiere†; Framyxone; Maxidrol; Novomyxine†; Panotile; Polydexa; Polyfra; Polygynax; Polygynax Virgo; Primyxine†; Sterimycine†; ***Ger.:*** Antibiotulle Lumiere†; Corticotulle Lumiere†; Dexa Polyspectran; Farco-Tril†; Isopto Max; Kombi-Stulln N; Panotile N†; Polygynax†; Polyspectran; Polyspectran HC; Terracortril†; Terramycin†; ***Gr.:*** Fotocollyre; Isopto Maxitrol; Oxacycle-P; Paroticin; Statrol†; Terramycin; ***Hong Kong:*** Aplosyn-Otic; Cebemyxine; Maxitrol; Neosporin; Otosporin; Otozambon; PMS-Baximycin†; Polydex-N; Polydexa; Polyfax†;

Polygynax; Polyoph; Terramycin with Polymyxin B; ***Hung.:*** Oftalmotrim†; Otosporin; Polyspor; ***India:*** Chlormixin; Dexosyn Plus; Neosporin; Neosporin-H; Ocupol; Ocupol-D; ***Indon.:*** Inmatrol; Isotic Enpigi; Isotic Neolysson; Isotic Nepafrin; Kenetrol; Kloramixin; Kloramixin D; Maxitrol; Nelicort; Neocortic; Neofen; Neosyd; Oregan; Osatrol; Otolin; Otopain; Otopraf; Otozambon; Polidemisin; Polifrisin; Terramycin Poly; Ximex Optixitrol; ***Irl.:*** Maxitrol; Neosporin†; Otosporin; Polyfax; ***Israel:*** Auricularum; Bamyxin; Desoren; Dex-Otic; Maxitrol; Phenimixin; Tarocidin; Tarocidin D; Terramycin; ***Ital.:*** Anauran; Cicatrene; Mixotone; Otosporin†; Rinojet SF†; ***Malaysia:*** Bacitracin-N; Maxitrol; Oftalmotrim; Pocin G; Pocin H; Terramycin; ***Mex.:*** Alosol; Biodexan; Biofrin; Biotriamin; Cortisporin; Dexsul; Hidropolicin; Maxitrol; Neobacigrin; Neosporin; Nicobio†; Polixin; Poly-Micron; Rinadex Compuesto; Septilisin; Sulned; Synalar N; Synalar O; Synalar Oftalmico; Terramicina; Tribiot; ***Neth.:*** Maxitrol; Otosporin; Panotile; Polyspectran G†; Polytrim; Synalar Bi-Otic†; Terra-Cortril Gel Steraject met polymyxine-B†; Terra-Cortril met polymyxine-B; ***Norw.:*** Maxitrol; Terra-Cortril Polymyxin B; Terramycin Polymyxin B; ***NZ:*** Maxitrol; ***Philipp.:*** Aplosyn-Otic; BNP Ointment; Cortisporin; Hydrospor; Isonep; Isonep H; Maxirap; Maxitrol; Maxoptic; Neosporin; Novasorin; Postop; Postotic; Predmycin-P; Statrol; Synalar Otic; Syntemax; Terramycin; Terramycin Plus; Trimycin; Trimycin-H; ***Pol.:*** Atecortin; Dexadent; Maxitrol; Multibiotic; Neotopic; Tribiotic; ***Port.:*** Conjunctilone; Conjunctilone-S; Oftalmotrim; Otosporin; Polisulfade; Polydexa; ***Rus.:*** Anauran (Анауран); Maxitrol (Макситрол); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Polygynax (Полижинакс); ***S.Afr.:*** Maxitrol; Neosporin†; Otosporin; Polysporin; Polytrim†; Terra-Cortril; Terramycin; ***Singapore:*** Maxitrol; Polybamycin; Polydexa; Polygynax; Predmycin-P†; Terramycin; ***Spain:*** Bacisporin; Blastoestimulina; Creanolona; Dermisone Tri Antibiotic; Liquipom Dexa Antib; Maxitrol; Neocones; Oftalmotrim; Oftalmotrim Dexa†; Oftalmowell; Otix; Otosporin; Panotile; Phonal; Poly Pred; Pomada Antibiotica; Synalar Nasal; Synalar Otico; Terra-Cortril; Terramicina; Tivitis; Tulgrasum Antibiotico; Vinciseptil Otico; ***Swed.:*** Isopto Biotic†; Terracortril med polymyxin B; Terramycin Polymyxin B; ***Switz.:*** Baneopol; Maxitrol; Mycinopred; Neosporin; Otosporin; Panotile; Polydexa; Spersapolymyxin; Terracortril†; ***Thai.:*** Banocin; Maxitrol; My-B; Neosporin†; Opsacin†; Otosamthong; Otosporin†; Polyoph; Predmycin†; Primoptic†; Spersapolymyxin; Terramycin; Terrasil†; Xanalin; ***Turk.:*** Cebemyxine; Geotril; Heksa; Neosporin; Oftalmotrim; Polimisin; Polycilline; Polytrim; Sekamisin; Terramycin; ***UK:*** Gregoderm†; Maxitrol; Neosporin; Otosporin; Polyfax; Polytrim†; ***USA:*** Ak-Poly-Bac; Ak-Spore; Ak-Trol†; Betadine First Aid Antibiotics + Moisturizer; Betadine Plus First Aid Antibiotics & Pain Reliever; Cortatrigen; Cortimycin; Cortisporin; Dexacidin†; Dexacine†; Dexasporin; Ear-Eze; Lanabiotic†; LazerSporin-C; Maxitrol; Mycitracin†; Neocin; Neopolydex; Neosporin; Neosporin + Pain Relief; Neosporin GU; Neosporin†; Neotricin HC; Opticair†; Ocu-Spor-B; Ocu-Spor-G; Ocu-Trol; Ocutricin; Otic-Care; OtiTricin; Otobiotic; Otocort; Otomycin-HPN; Otosporin; Pediotic; Poly-Dex; Poly-Pred; Polycin-B; Polymycin; Polysporin†; Polytracin; Polytrim; Spectrocin Plus†; Terak; Terramycin with Polymyxin B; Tri-Biozene; UAD-Otic; ***Venez.:*** Dermabiotic; Maxicort; Maxitrol; Neo-Synalar†; Ofterra; Otocort; Poli-Otico; Terramicina con Polimixina B.

Pristinamycin *(BAN, rINN)*

Pristinamicina; Pristinamycine; Pristinamycinum; RP-7293.

Пристинамицин

CAS — 270076-60-3.
ATC — J01FG01.
ATC Vet — QJ01FG01.

Profile

Pristinamycin is a streptogramin antibacterial produced by the growth of *Streptomyces pristina spiralis*, with actions and uses similar to those of virginiamycin (p.361). It is given orally in the treatment of susceptible infections, particularly staphylococcal infections, in a dose of 2 to 4 g daily in divided doses.

◊ Pristinamycin is a naturally occurring mixture of two synergistic components, pristinamycin I which is a macrolide, and pristinamycin II which is a depsipeptide.[1] It has been available for many years as an oral antistaphylococcal drug, and also acts against streptococci. It is effective against strains showing resistance to erythromycin; resistance to pristinamycin is rare,[2,3] although resistance in staphylococci has been reported in the past.[4,5] It is effective against meticillin-resistant *Staphylococcus aureus* (MRSA)[6,7] but its usefulness in severe infection is limited by its poor solubility, which prevents development of an intravenous formulation. Oral pristinamycin has been shown to be as effective as standard therapy with intravenous then oral penicillin in the treatment of erysipelas.[8]

Mixtures of water-soluble derivatives of pristinamycins I and II, such as quinupristin/dalfopristin (p.322), are in clinical use or under investigation.

1. Hamilton-Miller JMT. From foreign pharmacopoeias: 'new' antibiotics from old? *J Antimicrob Chemother* 1991; **27:** 702–5.
2. Weber P. Streptococcus pneumoniae: absence d'émergence de résistance à la pristinamycine. *Pathol Biol (Paris)* 2001; **49:** 840–5.
3. Leclercq R, *et al.* Activité in vitro de la pristinamycine vis-à-vis des staphylocoques isolés dans les hôpitaux français en 1999-2000. *Pathol Biol (Paris)* 2003; **51:** 400–4.
4. Loncle V, *et al.* Analysis of pristinamycin-resistant Staphylococcus epidermidis isolates responsible for an outbreak in a Parisian hospital. *Antimicrob Agents Chemother* 1993; **37:** 2159–65.
5. Allignet J, *et al.* Distribution of genes encoding resistance to streptogramin A and related compounds among staphylococci resistant to these antibiotics. *Antimicrob Agents Chemother* 1996; **40:** 2523–8.
6. Dancer SJ, *et al.* Oral streptogramins in the management of patients with methicillin-resistant Staphylococcus aureus (MRSA) infections. *J Antimicrob Chemother* 2003; **51:** 731–5.
7. Ng J, Gosbell IB. Successful oral pristinamycin therapy for osteoarticular infections due to methicillin-resistant Staphylococcus aureus (MRSA) and other Staphylococcus spp. *J Antimicrob Chemother* 2005; **55:** 1008–12.
8. Bernard P, *et al.* Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* 2002; **325:** 864–6.

Preparations

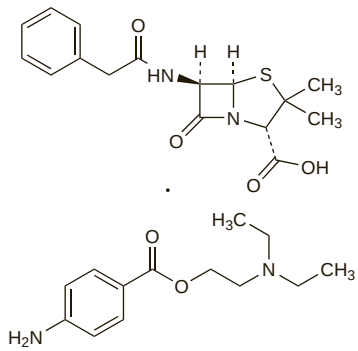
Proprietary Preparations (details are given in Part 3)
Fr.: Pyostacine; ***Israel:*** Pyostacine.

Procaine Benzylpenicillin *(BAN, rINNM)*

Bensylpenicillinprokain; Bentsyylipenisilliinprokaiini; Benzilpenicilinas prokainas; Benzilpenicillin-prokain; Benzylopenicylina prokainowa; Benzylpenicillin Novocaine; Benzylpénicilline Procaïne; Benzylpenicillinum procainum; Penicillin G Procaine; Procaína bencilpenicilina; Procaïne Benzylpénicilline; Procaine Penicillin G; Procaini Benzylpenicillinum; Procainum Benzylpenicillinum; Prokain Benzilpenisilin; Prokain Penisilin G; Prokain-benzylpenicilin. 2-(4-Aminobenzoyloxy)ethyldiethylammonium (6*R*)-6-(2-phenylacetamido)penicillanate monohydrate.

Прокаин Бензилпенициллин

$C_{13}H_{20}N_2O_2,C_{16}H_{18}N_2O_4S,H_2O$ = 588.7.
CAS — 54-35-3 (anhydrous procaine benzylpenicillin); 6130-64-9 (procaine benzylpenicillin monohydrate).
ATC — J01CE09.
ATC Vet — QJ01CE09; QJ51CE09.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Benzylpenicillin, Procaine). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol. A 0.33% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.
USP 31 (Penicillin G Procaine). White crystals or white, very fine, microcrystalline powder, odourless or practically odourless. Slightly soluble in water; soluble in alcohol and in chloroform. It is rapidly inactivated by acids, by alkali hydroxides, and by oxidising agents. pH of a saturated solution in water is between 5.0 and 7.5.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Procaine benzylpenicillin should not be given to patients known to be hypersensitive to either of its components. Procaine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Severe, usually transient, reactions with symptoms of severe anxiety and agitation, confusion, psychotic reactions including visual and auditory hallucinations, seizures, tachycardia and hypertension, cyanosis, and a sensation of impending death have occasionally been reported with procaine benzylpenicillin and may be due to accidental intravascular injection. Since similar reactions have also occurred with other depot penicillin preparations that do not contain procaine, its presence is unlikely to be the major cause of such reactions, but may be a contributory factor, especially after injection of high doses. These reactions have been termed non-allergic, pseudoallergic, pseudoanaphylactic, or Hoigné's syndrome; the term 'embolic-toxic reaction' has also been proposed.

Interactions

As for Benzylpenicillin, p.214.

Pharmacokinetics

When procaine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in 1 to 4 hours, and effective concentrations of benzylpenicillin are usually maintained for 12 to 24 hours. However, plasma concentrations are lower than those after an equivalent dose of benzylpenicillin potassium or sodium.

Distribution into the CSF is reported to be poor.

Uses and Administration

Procaine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p.214) to which it is hydrolysed gradually following deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations produced, its use should be restricted to infections caused by microorganisms that are highly sensitive to penicillin. Procaine benzylpenicillin should not be used as the sole treatment for severe acute infections, or when bacteraemia is present.

Procaine benzylpenicillin is used mainly in the treatment of syphilis; other indications have included pneumonia (in children in developing countries), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Doses of procaine benzylpenicillin may sometimes be expressed in terms of equivalent units of benzylpenicillin. Procaine benzylpenicillin 600 mg is equivalent to about 360 mg of benzylpenicillin (600 000 units). Procaine benzylpenicillin is given by deep intramuscular injection in usual doses of 0.6 to 1.2 g daily.

Patients with syphilis are given procaine benzylpenicillin 1.2 g daily for 10 to 14 days; infants up to 2 years of age with congenital syphilis may be given 50 mg/kg daily. Treatment may be continued for 3 weeks in patients with late syphilis.

Procaine benzylpenicillin is also used in combined preparations with other penicillins, including benzylpenicillin and benzathine benzylpenicillin.

Preparations

USP 31: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Procaine for Injectable Suspension; Penicillin G Procaine Injectable Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Mudapenil†; Penicil Dermol†; ***Austral.:*** Cilicaine Syringe; ***Cz.:*** Pendepon Compositum; ***Ger.:*** Jenacillin O†; ***Hung.:*** Retardillin; ***Mex.:*** Benzotripen; Farmabep; Promizol; Sodilin; Unicil 3/1; Unicil 6:3:3; ***NZ:*** Cilicaine; ***S.Afr.:*** Bio-Cillin; Novocillin†; Procillin; ***Spain:*** Aquicilina; Farmaproina; ***Turk.:*** Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Penadur 6.3.3; Penkain-K; Procillin; ***USA:*** Crysticillin; ***Venez.:*** Pebencil†; Pronapen; Silcopen†.

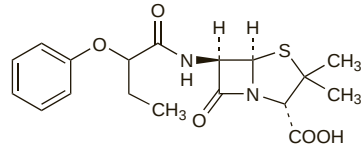
Multi-ingredient: ***Austria:*** Fortepen; Retarpen compositum; ***Braz.:*** Benapen; Benzapen G; Despacilina; Drenovac†; Expectovac†; Ginurovac†; Linfocilin†; Odontovac†; Ortocilin†; Pencil 400; Penkaron; Wycillin; ***Chile:*** Karbasalin†; ***Ger.:*** Bipensaar; Jenacillin A†; Retacillin compositum; ***Hong Kong:*** Penicillin G Procaine Fortified; ***Hung.:*** Promptcillin Forte; ***India:*** Bistrepen; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Hidrocilina; Lugaxil; Pecivax; Pendiben Compuesto; Penicil; Penipot; Penisodina; Penprocilina; Procilin; Respicil; Robencaxil; Suipen; ***Neth.:*** Penidural D/F†; ***Port.:*** Atralcilina; Lentocilin; Penadur 6.3.3†; ***Rus.:*** Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Aquicilina D A; Benzetacil Compuesta; Cepacilina 633; ***USA:*** Bicillin C-R; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Propicillin Potassium *(BANM, pINNM)*

Kalii Propicillinum; Potassium α-Phenoxypropylpenicillin; Propicilina potásica; Propicilline Potassique; Propicillinum Kalicum. A mixture of the D(+)- and L(−)-isomers of potassium (6*R*)-6-(2-phenoxybutyramido)penicillanate.

Калия Пропициллин

$C_{18}H_{21}KN_2O_5S$ = 416.5.
CAS — 551-27-9 (propicillin); 1245-44-9 (propicillin potassium).
ATC — J01CE03.
ATC Vet — QJ01CE03.



(propicillin)