4. Kadima TA, Weiner JH. Mechanism of suppression of piperacillin resistance in enterobacteria by tazobactam. *Antimicrob Agents Chemother* 1997; **41:** 2177–83.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; **41:** 435–9.
6. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. *Clin Microbiol Infect* 2008; **14** (suppl 1): 181–4. Correction. *ibid.*; (suppl 5): 21–4.

Pharmacokinetics

Piperacillin is not absorbed from the gastrointestinal tract. It is well absorbed after intramuscular use, with peak plasma concentrations of 30 to 40 micrograms/mL 30 to 50 minutes after a dose of 2 g. The pharmacokinetics of piperacillin are reported to be nonlinear and dose-dependent. The plasma half-life is about 1 hour, but is prolonged in neonates. In patients with severe renal impairment there may be a threefold increase in half-life; in those with end-stage renal failure half-lives of 4 to 6 hours have been reported, and in those with both renal and hepatic impairment much longer half-lives may result. About 20% of piperacillin in the circulation is bound to plasma proteins.

Piperacillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

About 60 to 80% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours, achieving high concentrations. High concentrations are also found in the bile and up to 20% of a dose may be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Piperacillin is removed by haemodialysis.

Piperacillin with tazobactam. The pharmacokinetics of piperacillin do not appear to be altered by tazobactam, but piperacillin reduces the renal clearance of tazobactam.

◊ References.
1. Heikkilä A, Erkkola R. Pharmacokinetics of piperacillin during pregnancy. *J Antimicrob Chemother* 1991; **28:** 419–23.
2. Wise R, *et al.* Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. *Antimicrob Agents Chemother* 1991; **35:** 1081–4.
3. Johnson CA, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. *Clin Pharmacol Ther* 1992; **51:** 32–41.
4. Dupon M, *et al.* Plasma levels of piperacillin and vancomycin used as prophylaxis in liver transplant patients. *Eur J Clin Pharmacol* 1993; **45:** 529–34.
5. Sörgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother* 1993; **31** (suppl A): 39–60.
6. Reed MD, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother* 1994; **38:** 2817–26.
7. Bourget P, *et al.* Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. *Antimicrob Agents Chemother* 1996; **40:** 139–45.
8. Occhipinti DJ, *et al.* Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. *Antimicrob Agents Chemother* 1997; **41:** 2511–17.

Uses and Administration

Piperacillin is a ureidopenicillin that is used similarly to ticarcillin (p.353) for the treatment of infections caused by *Pseudomonas aeruginosa*, and also infections due to other susceptible bacteria. It has been used particularly in immunocompromised patients (neutropenic patients) and for biliary-tract infections (cholangitis). Other indications have included uncomplicated gonorrhoea due to penicillin-sensitive gonococci, and urinary-tract infections. It has also been used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. For the treatment of serious infections piperacillin is commonly used with an aminoglycoside, but they should be given separately because of possible incompatibility.

Administration and dosage. Piperacillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of piperacillin; 1.04 g of piperacillin sodium is equivalent to about 1 g of piperacillin. Doses should generally be reduced in moderate to severe renal impairment.

Piperacillin may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 20 to 30 minutes, or by deep intramuscular injection. Single doses of more than 2 g for adults or 500 mg for children should not be given by the intramuscular route.

For the treatment of serious or complicated infections, adults may be given piperacillin 200 to 300 mg/kg daily in divided doses intravenously; the usual dose is 3 to 4 g every 4 or 6 hours. In life-threatening infections, particularly those caused by *Pseudomonas* or *Klebsiella* spp., it should be given in a dose of not less than 16 g daily. The usual maximum daily dose is 24 g, although this has been exceeded.

For mild or uncomplicated infections, 100 to 125 mg/kg daily may be given to adults; usual doses are 2 g every 6 or 8 hours, or 4 g every 12 hours, intravenously, or 2 g every 8 or 12 hours intramuscularly.

Uncomplicated gonorrhoea may be treated by a single intramuscular dose of 2 g. Probenecid 1 g may be given orally 30 minutes before the injection.

For the prophylaxis of infection during surgery, 2 g just before the procedure, or when the umbilical cord is clamped in caesarean section, followed by at least 2 doses of 2 g at intervals of 4 or 6 hours within 24 hours of the procedure, may be given.

The intravenous route is preferred for infants and children. Those aged 1 month to 12 years may be given 100 to 300 mg/kg daily in 3 or 4 divided doses. Neonates less than 7 days old or weighing less than 2 kg may be given 150 mg/kg daily in 3 divided doses. Those more than 7 days old and weighing more than 2 kg may be given 300 mg/kg daily in 3 or 4 divided doses.

Piperacillin with tazobactam. Piperacillin has also been used with tazobactam (p.344), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. The combination is given intravenously in a ratio of piperacillin (as the sodium salt) 8 parts to 1 part of tazobactam (as the sodium salt). Doses, calculated on piperacillin content, are similar to those of piperacillin alone.

◊ References.
1. Greenwood D, Finch RG, eds. Piperacillin/tazobactam: a new β-lactam/β-lactamase inhibitor combination. *J Antimicrob Chemother* 1993; **31** (suppl A): 1–124.
2. Schoonover LL, *et al.* Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother* 1995; **29:** 501–14.
3. Perry CM, Markham A. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs* 1999; **57:** 805–43.
4. Kotapati S, *et al.* The clinical and economic benefits of administering piperacillin-tazobactam by continuous infusion. *Intensive Crit Care Nurs* 2005; **21:** 87–93.
5. Gin A, *et al.* Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. *Expert Rev Anti Infect Ther* 2007; **5:** 365–83.

Preparations

BP 2008: Piperacillin Intravenous Infusion;
USP 31: Piperacillin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Algiseptico†; Piperac†; ***Austral.:*** Pipril†; ***Austria:*** Pipril; ***Belg.:*** Pipcil†; ***Canad.:*** Pipracil†; ***Cz.:*** Pipraks†; Pipril†; ***Denm.:*** Ivacin†; ***Ger.:*** Pipera†; Pipril†; ***Gr.:*** Pipril; Zobactam; Zoracilin; ***Hong Kong:*** Pipracil†; ***Hung.:*** Pipril†; ***India:*** Pipracil; ***Irl.:*** Pipril†; ***Israel:*** Picillin†; Pipracin; Pipril†; ***Ital.:*** Avocin†; Biopiper†; Cilpier; Dipenil; Ecosette; Eril†; Farecillin; Peracil; Perasint; Picillin; Piperital; Pipersal; Pipertex; Reparcillin; Semipenil; Sintoplus; Viracillina†; ***Jpn:*** Pentcillin; ***Malaysia:*** Pipracil†; ***NZ:*** Pipril†; ***Switz.:*** Pipril†; ***Thai.:*** Peracin; Pipracil†; ***Turk.:*** Pipraks; ***USA:*** Pipracil†.

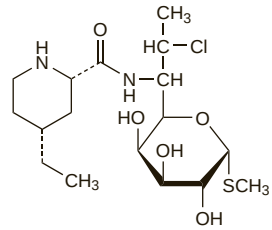
Multi-ingredient: ***Arg.:*** Pipetexina; Tazonam; ***Austral.:*** Tazocin; ***Austria:*** Tazonam; ***Belg.:*** Tazocin; ***Braz.:*** Tazocin; Tazoxil†; Tazpen†; ***Canad.:*** Tazocin; ***Chile:*** Tazonam; ***Cz.:*** Tazocin; ***Denm.:*** Tazocin; ***Fin.:*** Tazocin; ***Fr.:*** Tazocilline; ***Ger.:*** Tazobac; ***Gr.:*** Bactalin; Gramenox; Oliten; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong:*** Tazocin; ***Hung.:*** Tazocin; ***India:*** Tazact; Tazofast; Tazopen; Zosyn; ***Indon.:*** Tazocin; ***Irl.:*** Tazocin; ***Israel:*** Tazocin; ***Ital.:*** Tazobac; Tazocin; ***Malaysia:*** Tazocin; ***Mex.:*** Tasovak; Tazocin; ***Neth.:*** Tazocin; ***Norw.:*** Tazocin; ***NZ:*** Tazocin; ***Philipp.:*** Tazocin; ***Pol.:*** Tazocin; ***Port.:*** Tazobac; ***S.Afr.:*** Tazobax; Tazocin; ***Singapore:*** Tazocin; ***Spain:*** Tazocel; ***Swed.:*** Tazocin; ***Switz.:*** Tazobac; ***Thai.:*** Tazocin; ***Turk.:*** Tazocin; ***UK:*** Tazocin; ***USA:*** Zosyn; ***Venez.:*** Tazopril; Tazpen.

Pirlimycin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de pirlimicina; Pirlimycine, Chlorhydrate de; Pirlimycinhydroklorid; Pirlimycini Hydrochloridum; Pirlimysiinihydrokloridi; U-57930E. Methyl 7-chloro-6,7,8-trideoxy-6-(*cis*-4-ethyl-L-pipecolamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride monohydrate.

Пирлимицина Гидрохлорид

$C_{17}H_{31}ClN_2O_5S,HCl,H_2O$ = 465.4.
CAS — 79548-73-5 (pirlimycin); 77495-92-2 (pirlimycin hydrochloride).



(pirlimycin)

Profile

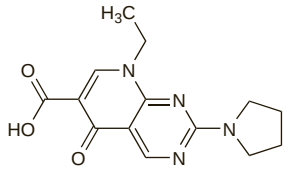
Pirlimycin is a lincosamide antibacterial used in veterinary medicine.

Piromidic Acid *(rINN)*

Acide Piromidique; Ácido piromídico; Acidum Piromidicum; PD-93; Piromidihappo; Piromidsyra. 8-Ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

Пиромидовая Кислота

$C_{14}H_{16}N_4O_3$ = 288.3.
CAS — 19562-30-2.
ATC — J01MB03.
ATC Vet — QJ01MB03.



Profile

Piromidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p.303). It has been used in the treatment of susceptible infections. There have been a number of reports of acute renal failure associated with piromidic acid.

Preparations

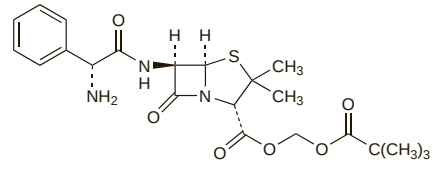
Proprietary Preparations (details are given in Part 3)
Ital.: Enteromix†.

Pivampicillin *(BAN, rINN)*

MK-191; Pivampicilin; Pivampicilina; Pivampicilinas; Pivampicilline; Pivampicillinum; Pivampisilliini. Pivaloyloxymethyl (6*R*)-6-(α-D-phenylglycylamino)penicillanate.

Пивампициллин

$C_{22}H_{29}N_3O_6S$ = 463.5.
CAS — 33817-20-8.
ATC — J01CA02.
ATC Vet — QJ01CA02.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Pivampicillin). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in methyl alcohol. It dissolves in dilute acids. Store in airtight containers.

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.

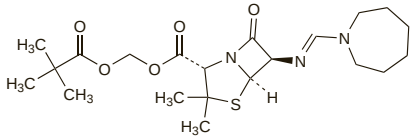
Пивмециллинам

$C_{21}H_{33}N_3O_5S$ = 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)*

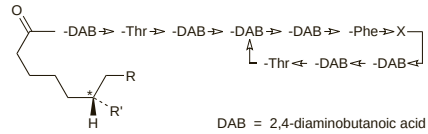
Polimiksin B Sülfat; Polimiksino B sulfatas; Polimixin-B-szulfát; Polimyksyny B siarczan; Polimyxini b sulfas; Polymyksiini-B-sulfaatti; Polymyxin B sulfat; Polymyxin B Sulphate *(BANM)*; Polymyxin-B-sulfát; Polymyxine B, sulfate de; Polymyxini B sulfas; Polymyxinum B Sulfas; Sulfato de polimixina B.

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).