

ble in alcohol; sparingly soluble or slightly soluble in dichloromethane. Protect from light.

Profile

Marbofloxacin is a fluoroquinolone antibacterial used in veterinary medicine.

Mecillinam (BAN, rINN)

Aminocillin (USAN); FL-1060; Mecilinam; Mécillinam; Mecillinamum; Mesillinami; Ro-10-9070. (6R)-6-(Perhydroazepin-1-yl-methyleneamino)penicillanic acid.

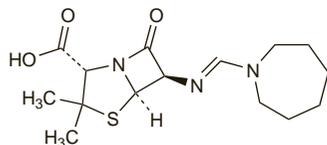
Мециллинам

$C_{15}H_{23}N_3O_3S = 325.4$.

CAS — 32887-01-7.

ATC — J01CA11.

ATC Vet — QJ01CA11.



Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

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

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Mecillinam is a derivative of amidinopenicillanic acid. Unlike benzylpenicillin and related antibiotics, it is active against many Gram-negative bacteria, in particular Enterobacteriaceae including *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Salmonella*, and *Shigella* spp. The susceptibility of *Proteus* spp. varies; *Serratia marcescens* is generally resistant. It is less active against *Neisseria* spp. and *Haemophilus influenzae*. *Pseudomonas aeruginosa* and *Bacteroides* spp. are considered to be resistant. It is much less active against Gram-positive bacteria; enterococci including *Enterococcus faecalis* are resistant.

Mecillinam interferes with the synthesis of the bacterial cell wall by binding with a different penicillin-binding protein from benzylpenicillin. This difference in mode of action may explain the synergism against many Gram-negative organisms that has been reported *in vitro* between mecillinam and various penicillins or cephalosporins.

Mecillinam is inactivated by beta-lactamases, but is more stable than ampicillin.

Pharmacokinetics

Mecillinam is poorly absorbed from the gastrointestinal tract. Peak plasma concentrations of about 6 and 12 micrograms/mL have been achieved half an hour after intramuscular doses of 200 and 400 mg, respectively. The usual plasma half-life of about 1 hour has been reported to be prolonged to 3 to 5 hours or more in severe renal impairment. Between 5 and 10% of mecillinam is bound to plasma proteins. Mecillinam is widely distributed into body tissues and fluids; little passes into the CSF unless the meninges are inflamed. It crosses the placenta into the fetal circulation; little appears to be distributed into breast milk.

Mecillinam is metabolised to only a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular filtration and tubular secretion. Renal tubular secretion can be reduced by probenecid. Some mecillinam is excreted in bile where high concentrations are achieved.

Mecillinam is removed by haemodialysis.

Uses and Administration

Mecillinam is a semisynthetic penicillin with a substituted amidino group at the 6-position of the penicillanic acid nucleus. It is given by slow intravenous injection, by intravenous infusion, or intramuscularly, in the treatment of susceptible Gram-negative infections (see under Antimicrobial Action, above).

For urinary-tract infections a dose of 800 mg is given every 6 to 8 hours. A total dose of up to 60 mg/kg daily may be used in very severe infections.

Mecillinam has been used with other beta lactams to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

The pivallyloxymethyl ester of mecillinam, pivmecillinam, is used orally (see p.317).

Preparations

Proprietary Preparations (details are given in Part 3)

Denm.: Selexid; **Gr.:** Selexid; **Norw.:** Selexid; **Swed.:** Selexid.

Meclocycline (BAN, USAN, rINN)

GS-2989; Meclociclina; Mélocycline; Meclocyclinum; Meklocylin; Meklosykliini; NSC-78502. (4S,4aR,5S,5aR,6S,12aS)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyl-6-deoxy-5β-hydroxy-6-methylene-tetracycline.

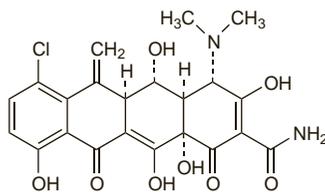
МекЛОЦИКЛИН

$C_{22}H_{21}ClN_2O_8 = 476.9$.

CAS — 2013-58-3.

ATC — D10AF04.

ATC Vet — QD10AF04.



Meclocycline Sulfosalicylate (USAN)

Meclociclina, sulfosalicilato de; Meclocycline Sulphosalicylate. Meclocycline 5-sulphosalicylate.

$C_{22}H_{21}ClN_2O_8 \cdot C_7H_6O_6S = 695.0$.

CAS — 73816-42-9.

ATC — D10AF04.

ATC Vet — QD10AF04.

Pharmacopoeias. In US.

USP 31 (Meclocycline Sulfosalicylate). pH of a 1% solution in water is between 2.5 and 3.5. Store in airtight containers. Protect from light.

Profile

Meclocycline is a tetracycline antibacterial derived from oxytetracycline (p.312). It is applied topically as the sulfosalicylate for the treatment of acne vulgaris and superficial skin infections. Potency is expressed in terms of meclocycline. Preparations containing the equivalent of 1 or 2% are available. Meclocycline sulfosalicylate has also been given as a pessary in the treatment of vulvovaginal infections.

Preparations

USP 31: Meclocycline Sulfosalicylate, Cream.

Proprietary Preparations (details are given in Part 3)

Ger.: Meclosorb; **Ital.:** Mecloclerm; Mecloclerm Antiacne; Mecloclerm Ovuli; Mecloclerm Polvere Aspersoriai; Mecloclerm Semplici.

Multi-ingredient: Ital.: Anti-Acne; Mecloclerm F; Mecloclerm†.

Meleumycin

Pharmacopoeias. In Chin.

Profile

Meleumycin, a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens*, consists of a mixture of midecamycin A₁ and kitasamycin A₆. It has actions and uses similar to those of erythromycin (p.269) and is given orally in the treatment of susceptible infections.

Meropenem (BAN, USAN, rINN)

ICI-194660; Meropenem; Méropénem; Meropenemum; SM-7338. (4R,5S,6S)-3-[(3S,5S)-5-Dimethylcarbamoylpyrrolidin-3-ylthio]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Меропенем

$C_{17}H_{25}N_3O_5 \cdot 3H_2O = 437.5$.

CAS — 96036-03-2 (meropenem); 119478-56-7 (meropenem trihydrate).

ATC — J01DH02.

ATC Vet — QJ01DH02.

Pharmacopoeias. In Chin., Jpn, and US.

USP 31 (Meropenem). Colourless to white crystals. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone and in ether; soluble in dimethylformamide and in 5% monobasic potassium phosphate solution. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Adverse Effects and Precautions

As for Imipenem, p.286.

Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have

less potential to induce seizures than imipenem (see also below).

Effects on the nervous system. *Animal* studies have indicated that meropenem induces fewer seizures than imipenem-cilastatin and clinical data from the manufacturer have substantiated this.¹ Comparison of data² from 4872 patients with a variety of infections (including meningitis) treated with meropenem with that from 4752 patients who received other antibacterials, principally cephalosporin-based regimens or imipenem-cilastatin, showed that meropenem was not associated with any greater risk of seizures than the other antibacterials and was likely to have less neurotoxic potential than imipenem-cilastatin, making it a suitable drug to use in the treatment of meningitis.

1. Norby SR, et al. Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995; **36** (suppl A): 207-23.

2. Norby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand J Infect Dis* 1999; **31**: 3-10.

Interactions

Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-valproate concentrations (sometimes with loss of seizure control) attributed to meropenem, see p.510.

Antimicrobial Action

As for Imipenem, p.287.

Meropenem is slightly more active than imipenem against Enterobacteriaceae and slightly less active against Gram-positive organisms.

Pharmacokinetics

After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.

Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Meropenem is removed by haemodialysis.

References

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- Blumer JL, et al. Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children. *Antimicrob Agents Chemother* 1995; **39**: 1721-5.
- Novelli A, et al. Clinical pharmacokinetics of meropenem after the first and tenth intramuscular administration. *J Antimicrob Chemother* 1996; **37**: 775-81.
- Thalhammer F, et al. Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* 1999; **43**: 523-7.
- Giles LJ, et al. Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. *Crit Care Med* 2000; **28**: 632-7.
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- Ververs TF, et al. Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous veno-venous hemofiltration. *Crit Care Med* 2000; **28**: 3412-16.
- van Enk JG, et al. Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23**: 198-201.
- Goldstein SL, et al. Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. *Pediatr Nephrol* 2001; **16**: 1015-18.
- Ariano RE, et al. Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39**: 32-8.

13. Isla A, *et al.* Meropenem and continuous renal replacement therapy: in vitro permeability of 2 continuous renal replacement therapy membranes and influence of patient renal function on the pharmacokinetics in critically ill patients. *J Clin Pharmacol* 2005; **45**: 1294–1304.
14. Novelli A, *et al.* Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44**: 539–49.
15. Du X, *et al.* Population pharmacokinetics and pharmacodynamics of meropenem in pediatric patients. *J Clin Pharmacol* 2006; **46**: 69–75.

Uses and Administration

Meropenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p.287). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections including intra-abdominal infections, gynaecological infections, meningitis, respiratory-tract infections (including in cystic fibrosis patients), septicaemia, skin and skin structure infections, urinary-tract infections, and infections in immunocompromised patients. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is equivalent to about 1 g of anhydrous meropenem. It is given by slow injection over 3 to 5 minutes or by infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours. A dose of 2 g every 8 hours is given for meningitis; doses of up to 2 g every 8 hours have also been used in cystic fibrosis. For details of reduced doses in renal impairment, see below.

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

Reviews.

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- Edwards SJ, *et al.* Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005; **21**: 785–94.
- Linden P. Safety profile of meropenem: an updated review of over 6000 patients treated with meropenem. *Drug Safety* 2007; **30**: 657–68.
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Administration in children. Use of meropenem is licensed in both the UK and the USA for infants and children over 3 months of age and weighing less than 50 kg. The usual dose is 10 to 20 mg/kg every 8 hours. A dose of 40 mg/kg is given every 8 hours for meningitis; doses of 25 to 40 mg/kg every 8 hours have been used in children aged 4 to 18 years with cystic fibrosis.

In addition, the *BNFC* suggests the following doses for those under 3 months of age:

- neonates under 7 days of age: 20 mg/kg every 12 hours (or 40 mg/kg every 12 hours in severe infections and in meningitis)
- neonates 7 to 28 days of age: 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in severe infections and in meningitis)
- infants 1 to 3 months of age: 10 mg/kg every 8 hours (or 20 mg/kg every 8 hours in severe infections; 40 mg/kg every 8 hours in meningitis)

Administration in renal impairment. Doses of meropenem should be reduced in patients with renal impairment. The following doses may be given to adults based on creatinine clearance (CC):

- CC 26 to 50 mL/minute: the usual dose given every 12 hours
- CC 10 to 25 mL/minute: one-half the usual dose every 12 hours
- CC less than 10 mL/minute: one-half the usual dose every 24 hours
- haemodialysis patients: the usual dose after the dialysis session

Preparations

USP 31: Meropenem for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Meroefectil; Merotenk; Merozen; Merpem; Zeropenem; **Austral.:** Merrem; **Austria:** Optinem; **Belg.:** Meronem; **Braz.:** Meronem; Meroxil; **Canad.:** Merrem; **Chile:** Meronem; **Cz.:** Meronem; **Denm.:** Meronem; **Fin.:** Meronem; **Ger.:** Meronem; **Gr.:** Meronem; **Hong Kong:** Meronem;

Hung.: Meronem; **India:** Meronem; **Indon.:** Merofen; Meronem; Ronem; Tripnem; **It.:** Meronem; **Israel:** Meronem; **Ital.:** Merrem; **Jpn.:** Meropen; **Malaysia:** Meronem; **Mex.:** Merrem; **Neth.:** Meronem; **Norw.:** Meronem; **NZ:** Merrem; **Philipp.:** Meronem; **Pol.:** Meronem; **Port.:** Meronem; **Rus.:** Meronem (Меронем); **S.Afr.:** Meronem; **Singapore:** Meronem; **Spain:** Meronem; **Swed.:** Meronem; **Switz.:** Meronem; **Thai.:** Meronem; **Turk.:** Meronem; **UK:** Meronem; **USA:** Merrem; **Venez.:** Meronem.

Metampicillin Sodium (HNNM)

Metampicilina sódica; Métampicilline Sodique; Natrii Metampicillinum. Sodium (6R)-6-(D-2-methyleneamino-2-phenylacetamido)penicillanate.

Натрий Метампицилин

$C_{17}H_{18}N_3NaO_4S = 383.4$.

CAS — 6489-97-0 (metampicillin); 6489-61-8 (metampicillin sodium).

ATC — J01CA14.

ATC Vet — QJ01CA14.

Profile

Metampicillin has actions and uses similar to those of ampicillin (p.204).

After oral doses it is almost completely hydrolysed to ampicillin. When given parenterally, however, a proportion of the dose exists in the circulation as unchanged metampicillin which has some antibacterial activity of its own.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient Arg.: Gentocelinaf.

Methacycline (BAN, USAN)

Metacycline (pINN); GS-2876; Metaciclina; Métacycline; Metacyclinum; Metacyklin; Metasykliini. (4S,4aR,5S,5aR,6S,12aS)-4-Dimethylamino-1,4,4a,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-5 β -hydroxy-6-methylenetetraacycline.

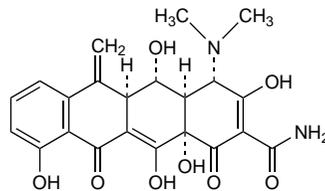
Метациклин

$C_{22}H_{22}N_2O_8 = 442.4$.

CAS — 914-00-1.

ATC — J01AA05.

ATC Vet — QJ01AA05.



Methacycline Hydrochloride (BANM)

Metacycline Hydrochloride (pINN); Hidrocloruro de metaciclina; Métacycline, Chlorhydrate de; Metacyclini Chloridum; Metacyclini Hydrochloridum; Metacyklin chlorowodorek; Méthylène-cycline Chlorhydrate; 6-Methyleneoxytetracycline Hydrochloride.

Метациклина Гидрохлорид

$C_{22}H_{22}N_2O_8 \cdot HCl = 478.9$.

CAS — 3963-95-9.

ATC — J01AA05.

ATC Vet — QJ01AA05.

Pharmacopoeias. In *Chin.*, *Pol.*, and *US*.

USP 31 (Methacycline Hydrochloride). A yellow to dark yellow crystalline powder. Soluble 1 in 100 of water, 1 in 300 of alcohol, and 1 in 25 of 0.1N sodium hydroxide; very slightly soluble in chloroform and in ether. pH of a solution in water containing the equivalent of methacycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Profile

Methacycline is a tetracycline derivative with uses similar to those of tetracycline (p.347). Like demeclocycline, it is excreted more slowly than tetracycline and effective blood concentrations are maintained for longer periods; the plasma elimination half-life is about 14 hours.

Methacycline hydrochloride is given orally in a usual adult dose of 600 mg daily in 2 divided doses, preferably 1 hour before or 2 hours after meals.

Preparations

USP 31: Methacycline Hydrochloride Capsules; Methacycline Hydrochloride Oral Suspension.

Proprietary Preparations (details are given in Part 3)

Fr.: Lysocline; Physiomycline; **Ital.:** Esaronidil; Rotilen; Staffilon.

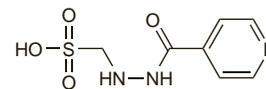
Methaniazide (HNN)

Isoniazid Mesylate; Isoniazid Methanesulfonate; Metaniazida; Méthaniazide; Methaniazidum. 2-Isonicotinoylhydrazinomethanesulphonate.

Метаниазида

$C_7H_9N_3O_4S = 231.2$.

CAS — 13447-95-5 (methaniazide); 6059-26-3 (methaniazide calcium); 3804-89-5 (methaniazide sodium).



Profile

Methaniazide is a derivative of isoniazid (p.288). It has been used orally and by injection as the calcium and sodium salts respectively in the treatment of tuberculosis.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Neo-Tizide; **India:** Erbazidef.

Multi-ingredient India: Strepto-Erbazidef.

Methenamine (HNN)

Aminoform; E239; Esametilentetrammina; Esammina; Formine; Heksamin; Hexamethylenamine; Hexamine; Metenamiini; Meténamin; Metenamim; Metenammina; Metenaminas; Metenammina; Methenamin; Méthénamine; Methenaminum; Urotropine. Hexamethylenetetramine; 1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}.0]decane.

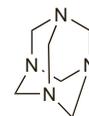
Метенамин

$C_6H_{12}N_4 = 140.2$.

CAS — 100-97-0.

ATC — J01XX05.

ATC Vet — QJ01XX05.



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

Ph. Eur. 6.2 (Methenamine). A white, or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Methenamine). Colourless, practically odourless, lustrous crystals or white crystalline powder. Soluble 1 in 1.5 of water, 1 in 12.5 of alcohol, 1 in 10 of chloroform, and 1 in 320 of ether. Its solutions are alkaline to litmus.

Methenamine Hippurate (BAN, USAN, HNNM)

Heksamin Hippurat; Hexamine Hippurate; Hipurato de metenammina; Metenamin Hippurat; Méthénamine, Hippurate de; Methenamini Hippuras. Hexamethylenetetramine hippurate.

Метенamina Гиппурат

$C_6H_{12}N_4 \cdot C_9H_9NO_3 = 319.4$.

CAS — 5714-73-8.

ATC — J01XX05.

ATC Vet — QJ01XX05.

Pharmacopoeias. In *US*.

Methenamine Mandelate (HNNM)

Heksamin Mandelat; Hexamine Amygdalate; Hexamine Mandelate; Mandelato de metenammina; Metenamin Mandelat; Méthénamine, Mandelate de; Methenamini Mandelas. Hexamethylenetetramine mandelate.

Метенamina Манделат

$C_6H_{12}N_4 \cdot C_8H_8O_3 = 292.3$.

CAS — 587-23-5.

ATC — J01XX05.

ATC Vet — QJ01XX05.

Pharmacopoeias. In *US*.

USP 31 (Methenamine Mandelate). A white, practically odourless crystalline powder. Very soluble in water; soluble 1 in 10 of alcohol, 1 in 20 of chloroform, and 1 in 350 of ether. Its solutions have a pH of about 4.

Adverse Effects and Precautions

Methenamine and its salts are generally well tolerated but may cause gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. Skin rashes, pruritus, and occasionally other hypersensitivity reactions, may occur.

Comparatively large amounts of formaldehyde may be formed during prolonged use or when large doses are given. This may produce irritation and inflammation of the urinary tract, especially the bladder, as well as painful and frequent micturition, haematuria, and cystitis.