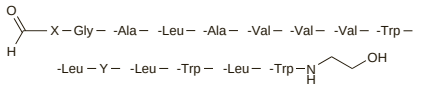
(Целестодерм-В с Гарамицином); Dexa-Gentamicin (Декса-Гентамицин); Triderm (Тридерм); ***S.Afr.:*** Celestoderm-V with Garamycin†; Diprogenta; Garasone†; Palacos R with Garamycin; Quadriderm; Septopal; ***Singapore:*** B-Tasone-G; Beprogent; Celestoderm-V with Garamycin†; Combiderm; Conazole; Dexamytrex; Diprogenta; Garasone; Gentriderm; Gentrisone; Infectoflam; Modaderm; Neoderm; Quadriderm†; Refobacin Bone Cement R; Refobacin-Palacos R†; Septopal†; Tri-Micon; Triderm; Voltamicin†; ***Spain:*** Celestoderm Gentamicina; Cuatroderm; Diprogenta; Epitelizante; Flugen; Flutenal Gentamicina; Gentadexa; Interderm; Novoter Gentamicina; ***Swed.:*** Celeston valerat med gentamicin; Septopal†; ***Switz.:*** Diprogenta; Indobiotic†; Infectoflam; Ophtasone; Quadriderm; Septopal; Triderm; Voltamicin; ***Thai.:*** Beprogent; Beprogenta; Dexamytrex; Diprogenta†; Genquin; Gental-F; Infectoflam; Pred Oph; Refobacin-Palacos R; Septopal; ***Turk.:*** Indobiotic; ***UK:*** Collatamp EG; Gentisone HC; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal; Vipsogal; ***USA:*** Pred G; ***Venez.:*** Betaderm con Gentamicina; Celestoderm con Gentalyn; Diprogenta; Garabet; Garasone; Gentidexa; Gentisor†; Propiogenta†; Quadriderm; Triderm; Tridetarmon.

Gramicidin *(BAN, rINN)*

Gramicidin D; Gramicidin (Dubos); Gramicidina; Gramicidinas; Gramicidine; Gramicidinum; Gramisidiini; Gramisidin.

Грамицидин

CAS — 1405-97-6.
ATC — R02AB30.
ATC Vet — QR02AB30.



Gramicidin	X	Y	Mol. Formula
A1	-Val	-Trp	C H N O
A2	-Ile	-Trp	C H N O
B1	-Val	-Phe	C H N O
C1	-Val	-Tyr	C H N O
C2	-Ile	-Tyr	C H N O

NOTE. The name gramicidin was formerly applied to tyrothricin.

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

Ph. Eur. 6.2 (Gramicidin). It consists of a family of antimicrobial linear polypeptides usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Bacillus brevis*. The main component is gramicidin A1, together with gramicidins A2, B1, C1, and C2 in particular. The potency is not less than 900 units/mg calculated with reference to the dried substance. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Gramicidin). An antibacterial substance produced by the growth of *Bacillus brevis* (Bacillaceae); it may be obtained from tyrothricin. It has a potency of not less than 900 micrograms of gramicidin per mg, calculated on the dried basis. A white or practically white, odourless, crystalline, powder. Insoluble in water; soluble in alcohol. Store in airtight containers.

Profile

Gramicidin has properties similar to those of tyrothricin (p.358) and is too toxic to be given systemically. It is used topically for the local treatment of susceptible infections usually with other antibacterials such as neomycin and polymyxin B, and often with a corticosteroid as well.

Preparations

USP 31: Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Gramicidin Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Antibiocort†; Aseptobron N; Biotaer Nasal; Bucoangin N; Caext; Carnot Colutorio; Desenfriol Caramelos†; Gargaletas; Gramibiotic†; Graneodin; Graneodin N; Kenacomb; Nasomicina; Neo Coltirot; Neo Pelvicillin; Pantometil; Proetztotal; ***Austral.:*** Kenacomb; Neosporin; Otocomb Otic; Otodex; Sofradex; Soframycin; ***Austria:*** Mycostatin V; Topsym polyvalent; Volon A antibiotikahaltig; ***Belg.:*** Mycolog; Polyspectran Gramicidine; ***Braz.:*** Fonergin; Londerm-N; Mud; Neolon-D; Omcilon A M; Onciplus; ***Canad.:*** Antibiotic Cream†; Kenacomb†; Neosporin; Opticort; Optimyxin; Optimyxin Plus; Polycidin†; Polysporin; Polysporin Complete Antibiotic; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polytopic; ratio-Triacomb; Sofracort; Soframycin; Triacomb†; Viaderm-KC; ***Chile:*** Gnifoftal†; Oftabiotico; ***Cz.:*** Sofradex†; ***Denm.:*** Kenalog Comp med Mycostatin; Sofradex; ***Fin.:*** Bafucin; Polysporin; Sofradex; ***Ger.:*** Polyspectran; ***Gr.:*** Kenacomb; Neo-Priphen; ***Hong Kong:*** Kenacomb; Neosporin; Polyoph; Sofradex; Triacomb; ***Hung.:*** Polyspor; ***India:*** Kenacomb; Kenalog-S; Neosporin; Sofracort; ***Indon.:*** Blecidex; Isotic Enpigi; Neosyd; Sofradex; ***Irl.:*** Graneodin; Kenacomb; Neosporin†; Sofradex; Soframycin†; ***Israel:*** Dermacombin; Kenacomb†; ***Ital.:*** Eta Biocortilen VC; Vasosterone Antibiotico; ***Malaysia:*** Kenacomb; Pocin G; Sofradex; ***Mex.:*** Biotarson N; Biotarson O; Kenacomb; Neosporin; Nicobio†; Polixin; Poly-Micron; Septilisin; Sulned; ***Neth.:*** Mycolog; Polyspectran G†; Sofradex; ***Norw.:*** Sofradex; ***NZ:*** Kenacomb; Sofradex; Soframycin; Viaderm-KC; ***Philipp.:*** Kenacomb; Lidex NGN; Neosporin; Novasorin; ***Pol.:*** Dicortineff; Triacomb; ***Port.:*** Dropcina; Kenacomb; ***S.Afr.:*** Kenacomb; Neosporin†; Sofradex; ***Singapore:*** Kenacomb†; Sofradex; ***Spain:*** Flodermol; Fludronef; Intradermo Cort Ant Fung†; Midacina; Oftalmowell; Spectrocin†; Tivitis; Trigon Topico; ***Swed.:*** Bafucin; ***Switz.:*** Angidine; Mycolog N; Mycolog†; Neosporin; Sofradex; Topsym polyvalent; Tyrothricine + Gramicidine; ***Thai.:*** Dermacombin; Kenacomb; Neosporin†; Opsacin†; Polyoph; Sofradex; Topifram; Xanalin; ***Turk.:*** Neosporin; ***UAE:*** Panderm; ***UK:*** Graneodin†; Neosporin; Sofradex; Tri-Adcortyl; ***USA:*** Neosporin; Ocu-Spor-G; Ocutricin; Polymycin; ***Venez.:*** Kenacomb.

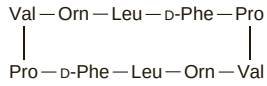
Gramicidin S *(rINN)*

Gramicidin C; Gramicidina S; Gramicidine S; Gramicidinum S; Soviet Gramicidin.

Грамицидин С

$C_{60}H_{92}N_{12}O_{10}$ = 1141.4.

CAS — 113-73-5.



Profile

Gramicidin S is an antibacterial polypeptide, produced by *Bacillus brevis*, and has similar properties to tyrothricin (p.358). It is unsuitable for systemic use and is used topically for the local treatment of susceptible infections and as lozenges for infections of the mouth and throat. The hydrochloride is used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)

Rus.: Grammidin.

Multi-ingredient: ***Indon.:*** FG Ointment; FG Troches.

Halquinol *(BAN)*

Chlorhydroxyquinoline; Chlorquinol; Halquinols *(USAN)*; SQ-16401. A mixture of the chlorinated products of quinolin-8-ol containing 57 to 74% of 5,7-dichloroquinolin-8-ol (chloroxine, p.242), 23 to 40% of 5-chloroquinolin-8-ol (cloxiquine, p.530), and not more than 4% of 7-chloroquinolin-8-ol.

CAS — 8067-69-4.

Profile

Halquinol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p.254). It is used topically in infected skin conditions.

Preparations

Proprietary Preparations (details are given in Part 3)

UK: Valpeda.

Multi-ingredient: ***Denm.:*** Kenacutan; ***Norw.:*** Kenacutan; ***Swed.:*** Kenacutan.

Ibafloxacin *(BAN, USAN, rINN)*

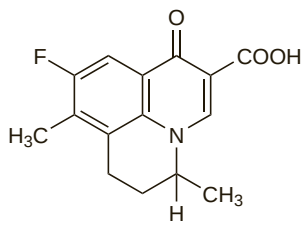
Ibafloksasiini; Ibafloxacine; Ibafloxacino; Ibafloxacinum; R-835; S-25930. 9-Fluoro-6,7-dihydro-5,8-dimethyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

Ибафлоксацин

$C_{15}H_{14}FNO_3$ = 275.3.

CAS — 91618-36-9.

ATC Vet — QJ01MA96.



Profile

Ibafloxacin is a fluoroquinolone antibacterial that is used in veterinary medicine for the treatment of susceptible infections in cats and dogs.

Imipenem *(BAN, USAN, rINN)*

N-Formimidoyl Thienamycin; Imipemide; Imipeneemi; Imipénem; Imipenem monohydrát; Imipenemas; Imipenemum; Imipenemum Monohydricum; MK-787; MK-0787. (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-(2-iminomethylaminoethylthio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Имипенем

$C_{12}H_{17}N_3O_4S,H_2O$ = 317.4.

CAS — 64221-86-9 (anhydrous imipenem); 74431-23-5 (imipenem monohydrate).

Description. Imipenem is the *N*-formimidoyl derivative of thienamycin, an antibiotic produced by *Streptomyces cattleya*.

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

Ph. Eur. 6.2 (Imipenem). A white, almost white, or pale yellow powder. Sparingly soluble in water; slightly soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 7.0. Store in airtight containers at a temperature of 2° to 8°.

USP 31 (Imipenem). A white to tan-coloured crystalline powder. Sparingly soluble in water; slightly soluble in methyl alcohol. Store at a temperature not exceeding 8°.

Incompatibility and stability. Imipenem is unstable at alkaline or acidic pH and the commercially available injection of imipenem with cilastatin sodium for intravenous use is buffered to provide, when reconstituted, a solution with pH 6.5 to 7.5. Licensed product information advises against mixing with other antibacterials.

References.

1. Bigley FP, *et al.* Compatibility of imipenem-cilastatin sodium with commonly used intravenous solutions. *Am J Hosp Pharm* 1986; **43**: 2803–9.
2. Smith GB, *et al.* Stability and kinetics of degradation of imipenem in aqueous solution. *J Pharm Sci* 1990; **79**: 732–40.

Adverse Effects

Imipenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination.

Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). Hypersensitivity reactions such as skin rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as *Enterococcus faecium*, strains of *Pseudomonas aeruginosa* with acquired resistance, and *Candida* may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive Coombs' test, have been noted.

Local reactions such as pain or thrombophlebitis may occur after injection.

Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses. Mental disturbances and confusion have also been reported.

Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to *animals*. A harmless reddish coloration of urine has been observed in children.

Effects on the nervous system. References.

1. Eng RH, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1989; **149**: 1881–3.
2. Brown RB, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1990; **150**: 1551.
3. Job ML, Dretler RH. Seizure activity with imipenem therapy: incidence and risk factors. *DICP Ann Pharmacother* 1990; **24**: 467–9.
4. Leo RJ, Ballow CH. Seizure activity associated with imipenem use: clinical case reports and review of the literature. *DICP Ann Pharmacother* 1991; **25**: 351–4.
5. Duque A, *et al.* Vertigo caused by intravenous imipenem/cilastatin. *DICP Ann Pharmacother* 1991; **25**: 1009.
6. Lucena M, *et al.* Imipenem/cilastatin-associated hiccups. *Ann Pharmacother* 1992; **26:** 1459.
7. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Safety* 1996; **15:** 87–90.

Hypersensitivity. A retrospective analysis[1] involving a total of 211 patients appeared to show that those with a history of reported or documented penicillin allergy had an 11% incidence of hypersensitivity reactions when treated with a carbapenem antibacterial compared with 2.7% for those without such a history of

penicillin allergy. There was no difference in the occurrence of allergic-type reactions between imipenem-cilastatin and meropenem.

1. Prescott WA, *et al.* Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004; **38:** 1102–7.

Superinfection. References.

1. Gray JW, *et al.* Enterococcal superinfection in paediatric oncology patients treated with imipenem. *Lancet* 1992; **339**: 1487–8.

Precautions

Imipenem-cilastatin should not be given to patients known to be hypersensitive to it, and should be given with caution to patients known to be hypersensitive to penicillins, cephalosporins, or other beta lactams because of the possibility of cross-sensitivity.

It should be given with caution to patients with renal impairment, and the dose reduced appropriately. Particular care is necessary in patients with CNS disorders such as epilepsy.

Interactions

Seizures have been reported in patients given ganciclovir with imipenem-cilastatin.

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

Antimicrobial Action

Imipenem is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of activity *in vitro*, including activity against Gram-positive and Gram-negative aerobic and anaerobic organisms, and is stable to hydrolysis by beta-lactamases produced by most bacterial species. Cilastatin, the enzyme inhibitor given with imipenem, appears to have no antibacterial activity.

Most Gram-positive cocci are sensitive to imipenem including most streptococci, and both penicillinase- and non-penicillinase-producing staphylococci, although its activity against meticillin-resistant *Staphylococcus aureus* is variable. Imipenem has good to moderate activity against *Enterococcus faecalis*, but most *E. faecium* are resistant. *Nocardia*, *Rhodococcus*, and *Listeria* spp. are also sensitive.

Among Gram-negative bacteria, imipenem is active against many of the Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella*, and *Yersinia* spp. Its activity against *Pseudomonas aeruginosa* is similar to that of ceftazidime. Imipenem is also active against *Acinetobacter* spp. and *Campylobacter jejuni*, and also against *Haemophilus influenzae* and *Neisseria* spp., including beta-lactamase-producing strains.

Many anaerobic bacteria, including *Bacteroides* spp., are sensitive to imipenem, but *Clostridium difficile* is only moderately susceptible.

Imipenem is not active against *Chlamydia trachomatis*, *Mycoplasma* spp., fungi, or viruses.

There have been reports of antagonism between imipenem and other beta lactams *in vitro*. Imipenem and aminoglycosides often act synergistically against some isolates of *Ps. aeruginosa*.

Imipenem is a potent inducer of beta-lactamases of some Gram-negative bacteria, but generally remains stable to them. Acquired resistance has been reported in *Ps. aeruginosa* during therapy with imipenem.

Resistance. References.

1. Ballestero S, *et al.* Carbapenem resistance in Pseudomonas aeruginosa from cystic fibrosis patients. *J Antimicrob Chemother* 1996; **38:** 39–45.
2. Rasmussen BA, Bush K. Carbapenem-hydrolyzing β-lactamases. *Antimicrob Agents Chemother* 1997; **41:** 223–32.
3. Livermore DM. Acquired carbapenemases. *J Antimicrob Chemother* 1997; **39:** 673–6.
4. MacKenzie FM, *et al.* Emergence of a carbapenem-resistant Klebsiella pneumoniae. *Lancet* 1997; **350:** 783.
5. Pikis A, *et al.* Decreased susceptibility to imipenem among penicillin-resistant Streptococcus pneumoniae. *J Antimicrob Chemother* 1997; **40:** 105–8.
6. Mainardi J-L, *et al.* Carbapenem resistance in a clinical isolate of Citrobacter freundii. *Antimicrob Agents Chemother* 1997; **41:** 2352–4.
7. Modakkas EM, Sanyal SC. Imipenem resistance in aerobic gram-negative bacteria. *J Chemother* 1998; **10:** 97–101.
8. Tsakris A, *et al.* Outbreak of infections caused by Pseudomonas aeruginosa producing VIM-1 carbapenemase in Greece. *J Clin Microbiol* 2000; **38:** 1290–2.
9. Fierobe L, *et al.* An outbreak of imipenem-resistant Acinetobacter baumannii in critically ill surgical patients. *Infect Control Hosp Epidemiol* 2001; **22:** 35–40.
10. Nagy E, *et al.* Occurrence of metronidazole and imipenem resistance among Bacteroides fragilis group clinical isolates in Hungary. *Acta Biol Hung* 2001; **52:** 271–80.
11. Gulay Z, *et al.* Clonal spread of imipenem-resistant Pseudomonas aeruginosa in the intensive care unit of a Turkish hospital. *J Chemother* 2001; **13:** 546–54.

Pharmacokinetics

Imipenem is not appreciably absorbed from the gastrointestinal tract and is given parenterally.

Imipenem is excreted primarily in the urine by glomerular filtration and tubular secretion and undergoes partial metabolism in the kidneys by dehydropeptidase I, an enzyme in the brush border of the renal tubules, to inactive, nephrotoxic metabolites, with only 5 to 45% of a dose excreted in the urine as unchanged active drug. Imipenem is given with cilastatin sodium (p.243), a dehydropeptidase inhibitor, resulting in increased urinary-imipenem concentrations. Cilastatin does not affect serum concentrations of imipenem.

The pharmacokinetics of imipenem and cilastatin are similar and both have plasma half-lives of about 1 hour; half-lives, especially those of cilastatin, may be prolonged in neonates and in patients with renal impairment. When imipenem with cilastatin is given in doses of 500 or 750 mg intramuscularly, peak plasma-imipenem concentrations of 10 and 12 micrograms/mL respectively are achieved at about 2 hours and prolonged absorption results in plasma-imipenem concentrations of above 2 micrograms/mL for 6 to 8 hours. The bioavailability of imipenem after intramuscular injection is about 75%. Up to 20% of imipenem and 40% of cilastatin is bound to plasma proteins. Imipenem is widely distributed in body tissues and fluids and crosses the placenta. Information on penetration into the CSF is limited, but concentrations appear to be relatively low.

When given with cilastatin about 70% of an intravenous dose of imipenem is recovered unchanged in the urine within 10 hours. A total of 50% of an intramuscular dose is recovered in the urine and urinary concentrations above 10 micrograms/mL are maintained for 12 hours after a dose of 500 or 750 mg. Cilastatin is also excreted mainly in the urine, the majority as unchanged drug and about 12% as *N*-acetyl cilastatin. Both imipenem and cilastatin are removed by haemodialysis.

About 1% of imipenem is excreted via the bile in the faeces.

◊ Reviews.

1. Drusano GL. An overview of the pharmacology of imipenem/cilastatin. *J Antimicrob Chemother* 1986; **18** (suppl E): 79–92.
2. Watson ID, *et al.* Clinical pharmacokinetics of enzyme inhibitors in antimicrobial chemotherapy. *Clin Pharmacokinet* 1988; **15**: 133–64.
3. Mouton JW, *et al.* Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39:** 185–201.

The elderly. References.

1. Finch RG, *et al.* Pharmacokinetic studies of imipenem/cilastatin in elderly patients. *J Antimicrob Chemother* 1986; **18** (suppl E): 103–7.

Hepatic impairment. References.

1. Rolando N, *et al.* The penetration of imipenem/cilastatin into ascitic fluid in patients with chronic liver disease. *J Antimicrob Chemother* 1994; **33:** 163–7.

Pregnancy and the neonate. References.

1. Reed MD, *et al.* Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990; **34:** 1172–7.
2. Heikkilä A, *et al.* Pharmacokinetics and transplacental passage of imipenem during pregnancy. *Antimicrob Agents Chemother* 1992; **36:** 2652–5.

Renal impairment. References.

1. Verbist L, *et al.* Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. *J Antimicrob Chemother* 1986; **18** (suppl E): 115–20.
2. Alarabi AA, *et al.* Pharmacokinetics of intravenous imipenem/cilastatin during intermittent haemofiltration. *J Antimicrob Chemother* 1990; **26:** 91–8.
3. Pietroski NA, *et al.* Steady-state pharmacokinetics of intramuscular imipenem-cilastatin in elderly patients with various degrees of renal function. *Antimicrob Agents Chemother* 1991; **35:** 972–5.
4. Konishi K, *et al.* Removal of imipenem and cilastatin by hemodialysis in patients with end-stage renal failure. *Antimicrob Agents Chemother* 1991; **35:** 1616–20.
5. Chan CY, *et al.* Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1991; **27:** 225–32.
6. Tegeder I, *et al.* Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 1997; **41:** 2640–5.

Uses and Administration

Imipenem is a carbapenem beta-lactam antibacterial, differing from the penicillins in that the 5-membered ring is unsaturated and contains a carbon rather than a sulfur atom. Since imipenem is metabolised in the kidney by the enzyme dehydropeptidase I it is always given with cilastatin (p.243), an inhibitor of the enzyme; this enhances urinary concentrations of active drug and was found to protect against the nephrotoxicity of high doses of imipenem seen in *animal* studies.

Imipenem is used for the treatment of infections caused by susceptible organisms. They include infections in immunocompromised patients (with neutropenia), intra-abdominal infections, bone and joint infections, skin and soft-tissue infections, urinary-tract infections, biliary-tract infections, hospital-acquired pneumonia, and septicaemia. It may also be used for the treatment of gonorrhoea and for surgical infection prophylaxis. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of these infections and their treatment, see under Choice of Antibacterial, p.162. It is not indicated for CNS infections.

Administration and dosage. Commercial preparations contain imipenem and cilastatin, as the sodium salt, in a ratio of 1 to 1. Doses of the combination are expressed in terms of the amount of anhydrous imipenem. Imipenem is given by intravenous infusion or deep intramuscular injection. When given intravenously, doses of 250 or 500 mg are infused over 20 to 30 minutes, and doses of 750 mg or 1 g over 40 to 60 minutes. The usual intravenous dose in adults and children weighing more than 40 kg is 1 to 2 g daily in divided doses every 6 or 8 hours, depending on the severity of the infection, although up to a maximum daily dose of 4 g or 50 mg/kg has been given in life-threatening infections.

Children of 3 months or more and weighing less than 40 kg may be given 15 to 25 mg/kg every 6 hours by intravenous infusion; the total daily dose should not usually exceed 2 g. Higher doses of up to 4 g daily have been given to children with moderately susceptible *Pseudomonas aeruginosa* infection; up to 90 mg/kg daily has been given to older children with cystic fibrosis. Neonates and infants up to 3 months of age may be given the following doses: 4 weeks to 3 months of age, 25 mg/kg every 6 hours; 1 to 4 weeks of age, 25 mg/kg every 8 hours; up to 1 week of age, 25 mg/kg every 12 hours.

For details of reduced doses in renal impairment, see below.

For surgical infection prophylaxis in adults, imipenem 1 g may be given intravenously on induction of anaesthesia, followed by a further 1 g three hours later, with additional doses of 500 mg at 8 and 16 hours after induction if necessary.

Imipenem may be given intramuscularly in adults with mild to moderate infections in doses of 500 or 750 mg every 12 hours. A single 500-mg intramuscular dose may be given in uncomplicated gonorrhoea.

◊ General reviews.

1. Balfour JA, *et al.* Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996; **51:** 99–136.
2. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74:** 420–34.

3. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Safety* 2000; **22:** 191–4.
4. Rodloff AC, *et al.* Two decades of imipenem therapy. *J Antimicrob Chemother* 2006; **58:** 916–29.
5. Zhanel GG, *et al.* Comparative review of the carbapenems. *Drugs* 2007; **67:** 1027–52.

Administration in renal impairment. Doses of imipenem should be reduced in patients with renal impairment; in the UK, the following are the recommended maximum *intravenous* doses based on creatinine clearance (CC):

- CC 31 to 70 mL/minute: 500 mg every 6 to 8 hours
- CC 21 to 30 mL/minute: 500 mg every 8 to 12 hours
- CC 6 to 20 mL/minute: 250 mg (or 3.5 mg/kg, whichever is the lower) every 12 hours or occasionally 500 mg every 12 hours
- CC 5 mL/minute or less: should only be given imipenem if haemodialysis is started within 48 hours

Imipenem and cilastatin are cleared from the body by haemodialysis and doses should be given after a dialysis session and then every 12 hours.

Information is lacking on the safety or effectiveness of the *intramuscular* route in patients with renal impairment.

Preparations

USP 31: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Proprietary Preparations (details are given in Part 3)
Pol.: Tienam.

Multi-ingredient: ***Arg.:*** Dixabiox; Imipecil; Imistatin; Klonam†; Zienam; ***Austral.:*** Primaxin; ***Austria:*** Zienam; ***Belg.:*** Tienam; ***Braz.:*** Penexil†; Tienam; ***Canad.:*** Primaxin; ***Chile:*** Inem; Tienam; ***Cz.:*** Tienam; ***Denm.:*** Tienam; ***Fin.:*** Tienam; ***Fr.:*** Tienam; ***Ger.:*** Zienam; ***Gr.:*** Primaxin; ***Hong Kong:*** Prepenem; Tienam; ***Hung.:*** Tienam; ***India:*** Cilanem; ***Indon.:*** Pelastin; Tienam; ***Israel:*** Tienam; ***Ital.:*** Imipem; Tenacid; Tienam; ***Malaysia:*** Bacqure; Tienam; ***Mex.:*** Arzomeba; Iminen; Tienam; ***Neth.:*** Tienam; ***Norw.:*** Tienam; ***NZ:*** Primaxin; ***Philipp.:*** Anipen; Tienam; ***Port.:*** Tienam; ***Rus.:*** Tienam (Тиенам); ***S.Afr.:*** Tienam; ***Singapore:*** Tienam; ***Spain:*** Tienam; ***Swed.:*** Tienam; ***Switz.:*** Tienam; ***Thai.:*** Tienam; ***Turk.:*** Tienam; ***UK:*** Primaxin; ***USA:*** Primaxin; ***Venez.:*** Zienam.

Isepamicin *(BAN, USAN, rINN)*

HAPA-B; Isepamicina; Isépamicine; Isepamicinum; Sch-21420; Sch-21420. 4-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-(3-amino-L-lactoyl)-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine; 1*N*-(S-3-Amino-2-hydroxypropionyl)-gentamicin B.

Изепамицин

$C_{22}H_{43}N_5O_{12}$ = 569.6.
CAS — 58152-03-7; 67479-40-7.
ATC — J01GB11.
ATC Vet — QJ01GB11.

Isepamicin Sulfate *(rINNM)*

Isepamicin Sulphate *(BANM)*; Isépamicine, Sulfate d'; Isepamicini Sulfas; Isepamisin Sülfat; Sulfato de isepamicina.

Изепамицина Сульфат

$C_{22}H_{43}N_5O_{12}.2H_2SO_4$ = 765.8.
CAS — 68000-78-2.
ATC — J01GB11.
ATC Vet — QJ01GB11.

Pharmacopoeias. In *Jpn*, which specifies a variable amount of H_2SO_4.

Profile

Isepamicin is a semisynthetic aminoglycoside with actions and uses similar to those of gentamicin (p.282). It is reported not to be degraded by many of the enzymes responsible for aminoglycoside resistance. Isepamicin sulfate is given by intramuscular injection or intravenous infusion in a dose of up to 15 mg/kg daily in 2 divided doses. Once-daily dosage may be possible in selected patients. Dosage should be adjusted based on serum-isepamicin concentration monitoring. In adults, the total daily dose should not exceed 1.5 g.

◊ References.

1. Tod M, *et al.* Clinical pharmacokinetics and pharmacodynamics of isepamicin. *Clin Pharmacokinet* 2000; **38:** 205–23.

Preparations

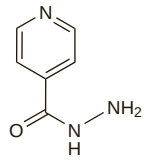
Proprietary Preparations (details are given in Part 3)
Austria: Isepacin†; ***Belg.:*** Isepacine†; ***Cz.:*** Isepacin†; ***Fr.:*** Isepalline†; ***Ital.:*** Isepacin†; ***Mex.:*** Isepacin†; ***Turk.:*** Isepacine.

Isoniazid *(BAN, pINN)*

INAH; INH; Isoniatsidi; Isoniazida; Isoniazide; Isoniazidum; Isonicotinic Acid Hydrazide; Isonicotinylhydrazide; Isonicotinylhydrazine; Izoniazid; Izoniazidas; Izoniazyd; Tubazid. Isonicotinohydrazide.

Изониазид

$C_6H_7N_3O$ = 137.1.
CAS — 54-85-3.
ATC — J04AC01.
ATC Vet — QJ04AC01.



NOTE. The name Isopyrin, which has been applied to isoniazid, has also been applied to ramifenazone.

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

Ph. Eur. 6.2 (Isoniazid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.0 to 8.0.

USP 31 (Isoniazid). Colourless, or white, odourless crystals, or white crystalline powder. Soluble 1 in 8 of water and 1 in 50 of alcohol; slightly soluble in chloroform; very slightly soluble in ether. pH of a 10% solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. It has been recommended that sugars such as glucose, fructose, and sucrose should not be used in isoniazid syrup preparations because the absorption of the drug was impaired by the formation of a condensation product.[1] Sorbitol may be a suitable substitute if necessary.

1. Rao KVN, *et al.* Inactivation of isoniazid by condensation in a syrup preparation. *Bull WHO* 1971; **45:** 625–32.

Sterilisation. Solutions of isoniazid should be sterilised by autoclaving.

Adverse Effects

Isoniazid is generally well tolerated at currently recommended doses. However, patients who are slow acetylators of isoniazid and those with advanced HIV disease appear to have a higher incidence of some adverse effects. Also patients whose nutrition is poor are at risk of peripheral neuritis which is one of the commonest adverse effects of isoniazid. Other neurological adverse effects include psychotic reactions and convulsions. Pyridoxine may be given to prevent or treat these adverse effects. Optic neuritis has also been reported.

Transient increases in liver enzymes occur in 10 to 20% of patients during the first few months of treatment and usually return to normal despite continued treatment. Symptomatic hepatitis occurs in about 0.1 to 0.15% of patients given isoniazid as monotherapy, but this can increase with age, regular alcohol consumption, and in those with chronic liver disease. The influence of acetylator status is uncertain. Elevated liver enzymes associated with clinical signs of hepatitis such as nausea and vomiting, or fatigue may indicate hepatic damage; in these circumstances, isoniazid should be stopped pending evaluation and should only be reintroduced cautiously once hepatic function has recovered. Fatalities have occurred due to liver necrosis.

Haematological effects reported on use of isoniazid include various anaemias, agranulocytosis, thrombocytopenia, and eosinophilia.

Hypersensitivity reactions occur infrequently and include skin eruptions (including erythema multiforme), fever, and vasculitis.

Other adverse effects include nausea, vomiting, dry mouth, constipation, pellagra, purpura, hyperglycaemia, lupus-like syndrome, vertigo, hyperreflexia, urinary retention, and gynaecomastia.

Symptoms of overdosage include slurred speech, metabolic acidosis, hallucinations, hyperglycaemia, respiratory distress or tachypnoea, convulsions, and coma; fatalities can occur.

Carcinogenicity. Concern about the carcinogenicity of isoniazid arose in the 1970s when an increased risk of bladder cancer in patients treated with isoniazid was reported.[1-3] However, no evidence to support a carcinogenic effect of isoniazid was found in more than 25 000 patients followed up for 9 to 14 years in studies organised by the USA Public Health Service[4] and in 3842 patients followed up for 16 to 24 years in the UK.[5]

1. Miller CT. Isoniazid and cancer risks. *JAMA* 1974; **230:** 1254.
2. Kerr WK, Chipman ML. The incidence of cancer of bladder and other sites after INH therapy. *Am J Epidemiol* 1976; **104:** 335–6.
3. Miller CT, *et al.* Relative importance of risk factors in bladder carcinogenesis. *J Chron Dis* 1978; **31:** 51–6.
4. Glassroth JL, *et al.* An assessment of the possible association of isoniazid with human cancer deaths. *Am Rev Respir Dis* 1977; **116:** 1065–74.
5. Stott H, *et al.* An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. *Tubercle* 1976; **57:** 1–15.

Effects on the blood. In addition to the effects mentioned above, rare reports of adverse effects of isoniazid on the blood include bleeding associated with acquired inhibition of fibrin stabilisation[1] or of factor XIII,[2] and red cell aplasia.[3-5]

For a reference to neutropenia, see Effects on the Blood, under Ethambutol Hydrochloride, p.274.

1. Otis PT, *et al.* An acquired inhibitor of fibrin stabilization associated with isoniazid therapy: clinical and biochemical observations. *Blood* 1974; **44:** 771–81.
2. Krumdieck R, *et al.* Hemorrhagic disorder due to an isoniazid-associated acquired factor XIII inhibitor in a patient with Waldenström's macroglobulinemia. *Am J Med* 1991; **90:** 639–45.
3. Claiborne RA, Dutt AK. Isoniazid-induced pure red cell aplasia. *Am Rev Respir Dis* 1985; **131:** 947–9.
4. Lewis CR, Manoharan A. Pure red cell hypoplasia secondary to isoniazid. *Postgrad Med J* 1987; **63:** 309–10.
5. Veale KS, *et al.* Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. *J Pediatr* 1992; **120:** 146–8.

Effects on the CNS. In addition to the peripheral neuropathy that is a well-established adverse effect of isoniazid, effects on the CNS have also been reported, including ataxia and cerebellar toxicity,[1,2] psychotic reactions[3-5] (generally characterised by delusions, hallucinations, and confusion), and seizures, particularly after overdosage.[6] Encephalopathy has been reported in dialysis patients.[7,8] Encephalopathy may also be a symptom of pellagra, which may be associated with isoniazid treatment.[9]

1. Blumberg EA, Gil RA. Cerebellar syndrome caused by isoniazid. *DICP Ann Pharmacother* 1990; **24:** 829–31.
2. Lewin PK, McGreal D. Isoniazid toxicity with cerebellar ataxia in a child. *CMAJ* 1993; **148:** 49–50.
3. Pallone KA, *et al.* Isoniazid-associated psychosis: case report and review of the literature. *Ann Pharmacother* 1993; **27:** 167–70.
4. Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother* 1998; **32:** 889–91.
5. Witkowski AE, *et al.* Isoniazid-associated psychosis. *Gen Hosp Psychiatry* 2007; **29:** 85–6.
6. Shah BR, *et al.* Acute isoniazid neurotoxicity in an urban hospital. *Pediatrics* 1995; **95:** 700–4.
7. Cheung WC, *et al.* Isoniazid induced encephalopathy in dialysis patients. *Tubercle Lung Dis* 1993; **74:** 136–9.
8. Wang HY, *et al.* Encephalopathy caused by isoniazid in a patient with end stage renal disease with extrapulmonary tuberculosis. *Ren Fail* 2003; **25:** 135–8.
9. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with isoniazid and other first-line antituberculous drugs, but sometimes hepatotoxicity may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Isoniazid and pyrazinamide are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1] Speculation that fast acetylators of isoniazid could be at increased risk of hepatotoxicity due to production of a hepatotoxic hydrazine metabolite has not been supported;[2] in fact, slow acetylators have generally been found to have a higher risk than fast acetylators.[3,4] This could reflect a reduced rate of subsequent metabolism to non-toxic compounds. In addition, concentrations of hydrazine in the blood have not been found to correlate with acetylator status.[5,6]

A multicentre study[7] considered the incidence of hepatotoxicity from a short-term regimen of daily isoniazid, rifampicin, and pyrazinamide for 8 weeks in the initial phase followed by daily isoniazid and rifampicin for 16 weeks in the continuing phase. Analysis from 617 patients showed an incidence of hepatotoxic reactions of 1.6%; the incidence of elevated aspartate aminotransferase was 23.2%. In the same study, 445 patients on a 9-month regimen of daily isoniazid and rifampicin had a 1.2% incidence of hepatotoxicity and 27.1% incidence of elevated liver enzymes. A similar incidence of hepatitis of 1.4% among 350 patients on a 9-month regimen of rifampicin and isoniazid has also been reported.[8] A retrospective analysis[9] of 430 children on isoniazid and rifampicin revealed hepatotoxic reactions in 3.3%, the highest incidence being in children with severe disease.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[10] for initial measurement of liver function in all patients and regular monitoring in patients with known chronic liver disease. Details are given concerning the response to deteriorating liver function depending on the clinical situation, and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced in the USA.[11,12]

The incidence of hepatotoxicity is lower in patients receiving isoniazid for prophylaxis than in those receiving treatment for active disease. During a 7-year period[13] an incidence of 0.15%