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

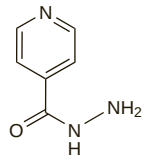
Proprietary Preparations (details are given in Part 3)
Austria: Isepacin†; ***Belg.:*** Isepacine†; ***Cz.:*** Isepacin†; ***Fr.:*** Isepalline†; ***Ital.:*** Isepacin†; ***Mex.:*** Isepacin†; ***Turk.:*** Isepacine.

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%

was recorded in 11 141 patients who started prophylactic therapy, whereas it was 1.25% amongst 1427 patients receiving treatment. A similar study[14] in a slightly older patient population reported an incidence of 0.56%. No cases of hepatotoxicity were reported in 556 HIV-infected patients taking a 3-month prophylactic regimen of isoniazid and rifampicin for latent tuberculosis.[15] A meta-analysis[16] concluded that daily isoniazid and rifampicin for 3 months appeared to be as safe as treatment with isoniazid alone for 6 to 12 months.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; **11:** 699–707.
2. Gurumurthy P, *et al.* Lack of relationship between hepatic toxicity and acetylator phenotype in three thousand South Indian patients during treatment with isoniazid for tuberculosis. *Am Rev Respir Dis* 1984; **129:** 58–61.
3. Dickinson DS, *et al.* Risk factors for isoniazid (INH)-induced liver dysfunction. *J Clin Gastroenterol* 1981; **3:** 271–9.
4. Pande JN, *et al.* Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; **51:** 132–6.
5. Gent WL, *et al.* Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients. *Eur J Clin Pharmacol* 1992; **43:** 131–6.
6. Donald PR, *et al.* Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis. *Ann Pharmacother* 1994; **28:** 1340–3.
7. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
8. Dutt AK, *et al.* Short-course chemotherapy for extrapulmonary tuberculosis: nine years' experience. *Ann Intern Med* 1986; **104:** 7–12.
9. O'Brien RJ, *et al.* Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 1983; **72:** 491–9.
10. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
11. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
12. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/sections/publications/statements/resources/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 05/10/07)
13. Nolan CM, *et al.* Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; **281:** 1014–18.
14. Fountain FF, *et al.* Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005; **128:** 116–23.
15. Whalen CC, *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; **337:** 801–8.
16. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; **40:** 670–6.

Effects on the pancreas. Cases of isoniazid-induced pancreatitis have been rarely reported;[1-4] pancreatitis resolved in these patients once treatment with isoniazid was stopped, and recurred on rechallenge. It is recommended if isoniazid-induced pancreatitis is proven that the drug should be permanently avoided.[4] Chronic pancreatic insufficiency, after an acute episode, was reported in a patient given isoniazid, rifampicin, ethambutol, and pyrazinamide and was considered to be a drug hypersensitivity reaction.[5]

1. Chan KL, *et al.* Recurrent acute pancreatitis induced by isoniazid. *Tubercle Lung Dis* 1994; **75:** 383–5.
2. Rabassa AA, *et al.* Isoniazid-induced acute pancreatitis. *Ann Intern Med* 1994; **121:** 433–4.
3. Stephenson I, *et al.* Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. *Am J Gastroenterol* 2001; **96:** 2271–2.
4. Chow KM, *et al.* Recurrent acute pancreatitis after isoniazid. *Neth J Med* 2004; **62:** 172–4.
5. Liu BA, *et al.* Pancreatic insufficiency due to antituberculous therapy. *Ann Pharmacother* 1997; **31:** 724–6.

Effects on the skin and hair. Isoniazid causes cutaneous drug reactions in less than 1% of patients.[1,2] These reactions include urticaria, purpura, acneform syndrome,[3] a lupus erythematosus-like syndrome[4] (see below), and exfoliative dermatitis.[5] Pellagra is also associated with isoniazid.[6] Isoniazid was considered the most likely cause of alopecia in 5 patients receiving antituberculosis regimens which also included rifampicin, ethambutol, and pyrazinamide.[7]

1. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976; **235:** 918–23.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.
3. Thorne N. Skin reactions to systemic drug therapy. *Practitioner* 1973; **211:** 606–13.
4. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136:** 508–11.
5. Rosin MA, King LE. Isoniazid-induced exfoliative dermatitis. *South Med J* 1982; **75:** 81.
6. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; **48:** 628–34.
7. FitzGerald JM, *et al.* Alopecia side-effect of antituberculosis drugs. *Lancet* 1996; **347:** 472–3.

Lupus. Antinuclear antibodies have been reported to occur in up to 22% of patients receiving isoniazid; however, patients are usually asymptomatic and overt lupoid syndrome is rare.[1,2] The incidence of antibody induction has been reported to be higher in slow acetylators than in fast acetylators,[3] but the difference was not statistically significant and acetylator phenotype is not considered an important determinant of the risk of isoniazid-induced lupus.[1,4,5] The syndrome appeared to be due to isoniazid itself rather than its metabolite acetylisoniazid.[6]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; **123:** 460–3.
2. Siddiqui MA, Khan IA. Isoniazid-induced lupus erythematosus presenting with cardiac tamponade. *Am J Ther* 2002; **9:** 163–5.
3. Alarcon-Segovia D, *et al.* Isoniazid acetylation rate and development of antinuclear antibodies upon isoniazid treatment. *Arthritis Rheum* 1971; **14:** 748–52.
4. Clark DWJ. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs* 1985; **29:** 342–75.
5. Rychlik-Sych M, *et al.* Acetylation genotype and phenotype in patients with systemic lupus erythematosus. *Pharmacol Rep* 2006; **58:** 22–9.
6. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; **ii:** 422–4.

Treatment of Adverse Effects

Pyridoxine hydrochloride 10 mg daily is usually recommended for prophylaxis of peripheral neuritis associated with isoniazid although up to 50 mg daily may be used. A dose of 50 mg three times daily may be given for treatment of peripheral neuritis if it develops.

Nicotinamide has been given, usually with pyridoxine, to patients who develop pellagra.

Isoniazid doses of 1.5 g or more are potentially toxic and doses of 10 to 15 g may be fatal without appropriate treatment. Treatment of overdosage is symptomatic and supportive and consists of activated charcoal, correction of metabolic acidosis, and control of convulsions. Large doses of pyridoxine may be needed intravenously for control of convulsions (see below) and should be given with diazepam. Isoniazid is removed by haemodialysis or peritoneal dialysis.

Overdosage. In adults an initial intravenous dose of pyridoxine hydrochloride equivalent to the estimated amount of isoniazid ingested (or, if the amount ingested is unknown, pyridoxine hydrochloride 5 g) has been recommended by the UK National Poisons Information Service for the management of convulsions; diazepam should also be given. For children the recommended dose of pyridoxine hydrochloride is 70 mg/kg (to a maximum of 5 g). If convulsions continue or recur, this dose may be repeated. Oral activated charcoal (50 g for adults and 10 to 15 g in children) may be considered if this is given within 1 hour of ingestion of isoniazid.

Pyridoxine deficiency. Pyridoxine deficiency associated with isoniazid in doses of 5 mg/kg daily is uncommon. Patients at risk of developing pyridoxine deficiency include those with diabetes, uraemia, alcoholism, HIV infection, and malnutrition.[1,2] Supplementation with pyridoxine should be considered for these at-risk groups as well as for pregnant women and patients with seizure disorders.[1] For the prophylaxis of peripheral neuritis it is common practice to give pyridoxine 10 mg daily, although 6 mg daily might be sufficient.[3] However, in one patient a dose of pyridoxine 10 mg daily failed to prevent psychosis, the symptoms of which only resolved after stopping isoniazid and increasing the pyridoxine dosage to 100 mg daily.[4]

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. Snider DE. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 1980; **61:** 191–6.
4. Chan TYK. Pyridoxine ineffective in isoniazid-induced psychosis. *Ann Pharmacother* 1999; **33:** 1123–4.

Precautions

Isoniazid should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50 mg daily may be used. If symptoms of hepatitis develop, such as malaise, fatigue, anorexia, and nausea, isoniazid should be stopped pending evaluation.

Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and the British Thoracic Society has recommended that isoniazid treatment be suspended if serum aminotransferase concentrations are elevated to more than 5 times the normal upper limit or the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. Careful monitoring should be considered for black and Hispanic women, in whom there may be an increased risk of fatal hepatitis.

When visual symptoms occur during isoniazid treatment periodic eye examinations have been suggested.

Breast feeding. Peak concentrations of isoniazid in breast milk were 6 micrograms/mL after a dose of 5 mg/kg and were 16.6 micrograms/mL after a 300-mg dose.[1] However, drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. Adverse effects on breast-fed infants have not been reported and the American Academy of Pediatrics thus considers isoniazid to be usually compatible with breast feeding,[2] although such infants should be monitored for toxic reactions.

1. Snider D, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. Isoniazid is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Pregnancy and the neonate. In a review[1] of antituberculous treatment in pregnant patients it was reported that over 95% of 1480 pregnancies in which isoniazid had been given resulted in a normal term infant. Slightly more than 1% of the infants/fetuses were abnormal and many of these abnormalities were CNS related. Isoniazid is therefore recognised as being suitable for use in regimens for the **treatment** of tuberculosis in pregnant patients.[2,3] Pyridoxine supplementation is recommended[2] (see Treatment of Adverse Effects, above). **Preventive therapy** with isoniazid is generally delayed until after delivery unless other risk factors are present.

1. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122:** 65–79.
2. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)

Interactions

The risk of hepatotoxicity may be increased in patients receiving isoniazid with a rifamycin or other potentially hepatotoxic drugs, including alcohol.

Isoniazid can inhibit the hepatic metabolism of a number of drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine (p.474), ethosuximide (p.480), primidone, and phenytoin (p.498), the benzodiazepines diazepam and triazolam (p.989), chlorzoxazone (p.1895), theophylline (p.1143), and disulfiram. The metabolism of enflurane (see Effects on the Kidneys, p.1782) may be increased in patients receiving isoniazid, resulting in potentially nephrotoxic levels of fluoride. Isoniazid has been associated with increased concentrations and en-

hanced effects or toxicity of clofazimine (p.255), cycloserine (p.260), and warfarin (p.1428).

For interactions affecting isoniazid, see below.

Alcohol. The metabolism of isoniazid may be increased in chronic alcoholics: this may lead to reduced isoniazid effectiveness.[1] These patients may also be at increased risk of developing isoniazid-induced peripheral neuropathies and hepatic damage (see Precautions, above).

1. Anonymous. Interaction of drugs with alcohol. *Med Lett Drugs Ther* 1981; **23:** 33–4.

Antacids. Oral absorption of isoniazid is reduced by aluminium-containing antacids; isoniazid should be given at least 1 hour before the antacid.[1]

1. Hurwitz A, Schluzman DL. Effects of antacids on gastrointestinal absorption of isoniazid in rat and man. *Am Rev Respir Dis* 1974; **109:** 41–7.

Antifungals. Serum concentrations of isoniazid were below the limits of detection in a patient also receiving rifampicin and *ketoconazole*.[1] For the effect of isoniazid on ketoconazole, see p.539.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109:** 844–5. Correction. *ibid.* 1989; **111:** 96.

Antivirals. The clearance of isoniazid was approximately doubled when *zalcitabine* was given to 12 HIV-positive patients.[1] In addition, care is needed since *stavudine* and zalcitabine may also cause peripheral neuropathy; use of isoniazid with stavudine has been reported to increase its incidence.[2]

1. Lee BL, *et al.* The effect of zalcitabine on the pharmacokinetics of isoniazid in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* 1994; **34:** 3(A4).
2. Breen RAM, *et al*. Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. *AIDS* 2000; **14:** 615.

Corticosteroids. Giving *prednisolone* 20 mg to 13 slow acetylators and 13 fast acetylators receiving isoniazid 10 mg/kg reduced plasma concentrations of isoniazid by 25 and 40% respectively.[1] Renal clearance of isoniazid was also enhanced in both acetylator phenotypes and the rate of acetylation increased in slow acetylators only.[1]

The clinical significance of this effect is not established.

1. Sarma GR, *et al.* Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* 1980; **18:** 661–6.

Food. Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea, and sweating have been reported in patients taking isoniazid after ingestion of *cheese*,[1,2] *red wine*,[1] and some *fish*.[3,4] Accumulation of tyramine[1] or histamine[3] has been proposed as the cause of these food-related reactions, and they could be mistaken for anaphylaxis.[4]

1. Toutoungi M, *et al.* Cheese, wine, and isoniazid. *Lancet* 1985; **ii:** 671.
2. Carvalho ACC, *et al.* Reaction to cheese during TB treatment. *Thorax* 2004; **59:** 635.
3. Kottegoda SR. Cheese, wine and isoniazid. *Lancet* 1985; **ii:** 1074.
4. O'Sullivan TL. Drug-food interaction with isoniazid resembling anaphylaxis. *Ann Pharmacother* 1997; **31:** 928.

Opioid analgesics. For a report of an interaction between isoniazid and *pethidine*, attributed to isoniazid's inhibitory actions on monoamine oxidase, see p.114.

Antimicrobial Action

Isoniazid is highly active against *Mycobacterium tuberculosis* and may have activity against some strains of other mycobacteria including *M. kansasii*.

Although it is rapidly bactericidal against actively dividing *M. tuberculosis*, it is considered to be only bacteriostatic against semi-dormant organisms and has less sterilising activity than rifampicin or pyrazinamide.

Resistance of *M. tuberculosis* to isoniazid develops rapidly if it is used alone in the *treatment* of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of isoniazid with other antimycobacterials which appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when isoniazid is used alone in *prophylaxis*, probably because the bacillary load is low.

Mycobacterium avium complex. Synergistic activity of isoniazid plus streptomycin and, to a lesser degree, isoniazid plus clofazimine, against *Mycobacterium avium* complex (MAC) has been demonstrated *in vitro* and *in vivo*.[1]

1. Reddy MV, *et al.* In vitro and in vivo synergistic effect of isoniazid with streptomycin and clofazimine against Mycobacterium avium complex (MAC). *Tubercle Lung Dis* 1994; **75:** 208–12.

Pharmacokinetics

Isoniazid is readily absorbed from the gastrointestinal tract and after intramuscular injection. Peak concentrations of about 3 to 7 micrograms/mL appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of isoniazid is reduced by food. Isoniazid is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy (see below), and is distributed into breast milk (see under Precautions, above).

The plasma half-life for isoniazid ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by *N*-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised isoniazid is conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly. Ethnic groups differ in their proportions of these genetic phenotypes. When isoniazid is given daily or 2 or 3 times weekly, clinical effectiveness is not influenced by acetylator status.

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the faeces. Isoniazid is removed by haemodialysis.

Distribution. Therapeutic concentrations of isoniazid have been detected in CSF[1,2] and synovial fluid[3] several hours after an oral dose. Diffusion into saliva is good and it has been suggested that salivary concentrations could be used in place of serum concentrations in pharmacokinetic studies.[4]

1. Forgan-Smith R, *et al.* Pyrazinamide and other drugs in tuberculous meningitis. *Lancet* 1973; **ii:** 374.
2. Miceli JN, *et al.* Isoniazid (INH) kinetics in children. *Fedn Proc* 1983; **42:** 1140.
3. Mouries D, *et al.* Passage articulaire de l'isoniazide et de l'éthambutol: deux observations de synovite tuberculeuse du genou. *Nouv Presse Med* 1975; **4:** 2734.
4. Gurumurthy P, *et al.* Salivary levels of isoniazid and rifampicin in tuberculous patients. *Tubercle* 1990; **71:** 29–33.

HIV-infected patients. Malabsorption of isoniazid and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p.328.

Pregnancy. Isoniazid crosses the placenta and average fetal concentrations of 61.5 and 72.8% of maternal serum or plasma concentration have been reported.[1] The half-life of isoniazid may be prolonged in neonates.[1]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.

Uses and Administration

Isoniazid is a hydrazide derivative that is the mainstay of the primary treatment of pulmonary and extrapulmonary tuberculosis (p.196). It is used with other antituberculous drugs usually in regimens including rifampicin, ethambutol, and pyrazinamide. Isoniazid is also used in high-risk subjects for the prophylaxis of tuberculosis.

Isoniazid is given in the initial and continuation phases of short-course tuberculosis regimens. The usual adult dose is 5 mg/kg, to a maximum of 300 mg, daily by mouth on an empty stomach. For intermittent therapy, WHO recommends 10 mg/kg three times a week or 15 mg/kg twice a week, while the recommended dose in the UK is 15 mg/kg three times a week and in the USA 15 mg/kg once weekly or two or three times a week is recommended. Caution is required in patients with hepatic impairment and doses may need to be reduced in those with severe renal impairment.

Similar doses to those used orally may be given by intramuscular injection when isoniazid cannot be taken by mouth; it may also be given by intravenous injection. Isoniazid has also been given intrathecally and intrapleurally.

In the treatment of latent tuberculosis, daily doses of 300 mg for 6 months are recommended by WHO and in the UK, while in the USA the preferred treatment regimen is oral isoniazid 5 mg/kg daily or 15 mg/kg twice weekly for 9 months. As an alternative to such regimens, isoniazid may be given with rifampicin for 3 months.

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

Isoniazid aminosalicylate (pasiniazid) and isoniazid sodium glucuronate have also been used in the treatment of tuberculosis.

Fixed-dose combination products containing 2, 3, or 4 drugs have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing isoniazid in various combinations with rifampicin, ethambutol, and pyrazinamide are available in some countries.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) suggests an oral dose of isoniazid 10 to 15 mg/kg daily or 20 to 30 mg/kg twice weekly by mouth, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests oral doses of 5 to 10 mg/kg once daily or 15 mg/kg three times a week; WHO recommends 5 mg/kg once daily, or 10 mg/kg three times a week, or 15 mg/kg twice a week.

For the treatment of *latent* tuberculosis the AAP and the American Thoracic society suggest oral doses of 10 to 20 mg/kg daily or 20 to 40 mg/kg twice weekly for 9 months. For children 1 month and older the *BNFC* suggests a dose of 5 mg/kg once daily for 6 months when used alone or for 3 months when given with rifampicin; WHO recommends 5 mg/kg once daily for 6 months.

For daily dosing regimens the maximum oral dose of isoniazid is 300 mg and for intermittent regimens the maximum dose is 900 mg per dose.

Preparations

BP 2008: Isoniazid Injection; Isoniazid Tablets;
USP 31: Isoniazid Injection; Isoniazid Syrup; Isoniazid Tablets; Rifampin and Isoniazid Capsules; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Isoniac; ***Belg.:*** Nicotibine; ***Canad.:*** Isotamine; ***Cz.:*** Nidrazid; ***Fin.:*** Tubilysin; ***Fr.:*** Rimifon; ***Ger.:*** Isozid; Isozid comp N; tebesium; tebesium-s; ***Gr.:*** Cemidon; Dianicotyl; Isozid†; Nicozid; ***Hung.:*** Isonicid; ***India:*** Isokin; Isonex; Rifacom E-Z; ***Indon.:*** INH-Ciba; INHA; Inoxin; Medinh-OD; Niacifort-6; Nufadoxin; Pulmolin; Pyravit; Pyrifort; Suprazid; TB Vit 6; ***Israel:*** Inazid; ***Ital.:*** Nicizina; Nicozid; ***Jpn:*** Hydra; Hydrazide; ***Mex.:*** Erbazid†; Hidrasix; Valifol; ***Philipp.:*** Comprilex; Curazid (Reformulated); Eurocoxin; Isodexid; Isoxin; Nicetal; Odinah; Techxafort; Terozid; Trisofort; Vamsoxid; ***Port.:*** Hidrazida; ***Spain:*** Cemidon; Cemidon B6; ***Swed.:*** Tibinide; ***Switz.:*** Rimifon; ***Thai.:*** Antimic; Myrin-P; Myrin†; ***Turk.:*** INH; Isovit; ***USA:*** Laniazid; Nydrazid.

Multi-ingredient: ***Arg.:*** Bacifim; Rifinah; Risoniac†; ***Austria:*** Isoprodian; Myambutol-INH; Rifater; Rifoldin INH; ***Braz.:*** Isoniaton; ***Canad.:*** Rifater; ***Denm.:*** Rimactazid; Rimstar; ***Fin.:*** Rimactazid; Rimstar; ***Fr.:*** Rifater; Rifinah; ***Ger.:*** EMB-INH†; Iso-Eremfat; Isoprodian†; Myambutol-INH; Rifater; Rifinah; tebesium Duo; tebesium Trio; ***Gr.:*** Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong:*** Rifater; Rifinah; ***Hung.:*** Rifazid; ***India:*** Akt-3; Akt-4; Arzide; Bicox-E†; Combunex; Coxina-3; Coxina-4; Coxinex; Cx-3; Cx-4; Cx-5; Gocox Compound; Gocox-3; Gocox-4†; Inabutol Forte; Inapas; Ipcacin Kid; Ipcazide; Isokin-300; Isokin-T Forte; Isorifam; Myconex; R-Cinex; R-Cinex Z; RHZ; RHZ-Plus; Rifa; Rifa E; Rifacomb Plus†; Rifacomb†; Rimactazid + Z; Rimpazid; Siticox-INH; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed-2; Xeed-3E; Xeed-4; ***Indon.:*** bacbutINH; Erabutol Plus; Meditam-6; Mycothambin-INH; Niazitol; Pulna; Ramicin-ISO; Rimactazid; Rimcure; Rimstar; Santibi Plus; ***Irl.:*** Rifater; Rifinah; Rimactazid; ***Ital.:*** Etanicozid B6; Miazide B6†; Rifater; Rifinah; ***Malaysia:*** Rimactazid; Rimcure; ***Mex.:*** Arpisen; Finater; Finateramida; Isonid†; Myambutol-INH†; Rifater; Rifinah; ***Neth.:*** Rifinah; ***NZ:*** Rifinah; ***Philipp.:*** 4D; Bifix; CombiKids; CombiPack; Continukit; Continukit Plus; Continupack; Econokit; Econokit-MDR; Econopack; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Kidz Kit 2; Kidz Kit 3; Myrin; Myrin-P; Quadtab; Refam Duo; Refam Pedia Kit; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; Sthamizide; SVM-Polypac-A; Tres; Triofix; Tritab; Viper; ***Pol.:*** Rifamazid; ***Port.:*** Rifater; Rifinah; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Phthizopiram (Фтизопирам); Repin B (Репин В); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс); Rimactazid (Римактазид); Rimecure 3-FDC (Римкур 3-ФДС); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Myrin†; Rifafour; Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore:*** Rimactazid; ***Spain:*** Amiopia; Duplicalcio 150†; Duplicalcio B12; Duplicalcio Hidraz†; Rifater; Rifazida†; Rifinah; Rimactazid; Rimcure; Rimstar; Tisobrif; ***Swed.:*** Rimactazid; Rimcure; Rimstar; ***Switz.:*** Myambutol-INH†; Rifater; Rifinah; ***Thai.:*** Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid; Rimcure 3-FDC; Rimstar; ***UK:*** Rifater; Rifinah; Rimactazid†; ***USA:*** IsonaRif; Rifamate; Rifater; ***Venez.:*** Rimactazid; Rimcure.

Josamycin *(BAN, USAN, rINN)*

EN-141; Josamicina; Josamicinas; Josamycine; Josamycinum; Josamysiini; Jozamicin; Leucomycin A_3. A stereoisomer of 7-(formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′-acetate 4″-isovalerate.

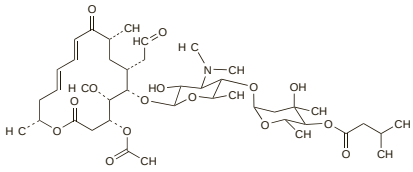
Джозамицин

$C_{42}H_{69}NO_{15}$ = 828.0.

CAS — 16846-24-5; 56689-45-3.

ATC — J01FA07.

ATC Vet — QJ01FA07.



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

Ph. Eur. 6.2 (Josamycin). A macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic powder. It contains a minimum of 900 units/mg calculated with reference to the dried substance. Very slightly soluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Josamycin Propionate *(BANM, rINNM)*

Josamicino propionatas; Josamycine, propionate de; Josamycini propionas; Josamycinpropionat; Josamycin-propionát; Josamysiinipropionaatti; Jozamicin-propionát; Propionato de josamicina; YS-20P. Josamycin 10-propionate.

Джозамицина Пропионат

$C_{45}H_{73}NO_{16}$ = 884.1.

CAS — 56111-35-4; 40922-77-8.

ATC — J01FA07.

ATC Vet — QJ01FA07.

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

Ph. Eur. 6.2 (Josamycin Propionate). It is derived from a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic, crystalline powder. It contains a minimum of 843 units/mg, calculated with reference to the dried substance. Practically insoluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270. Josamycin is reported to produce less gastrointestinal disturbance than erythromycin.

Oedema. A report of josamycin-induced oedema of the foot.[1]

1. Bosch X, *et al.* Josamycin-induced pedal oedema. *BMJ* 1993; **307:** 26.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Josamycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore interact less than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The general absence of an interaction between josamycin and theophylline would appear to support this.

Antimicrobial Action

As for Erythromycin, p.271. Some reports suggest that josamycin may be more active against some strains of anaerobic species such as *Bacteroides fragilis*.

Uses and Administration

Josamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p.272). It is given orally as the base or the propionate but doses are expressed in terms of the base; 1.07 g of josamycin propionate is equivalent to about 1 g of josamycin. Usual doses in the treatment of susceptible infections are the equivalent of 1 to 2 g of josamycin daily in 2 or more divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Josalid; ***Fr.:*** Josacine; ***Ger.:*** Wilprafen†; ***Hung.:*** Wilprafen†; ***Ital.:*** Iosalide; Josaxin†; ***Jpn:*** Josamy; ***Rus.:*** Wilprafen (Вильпрафен); ***Spain:*** Josamina.

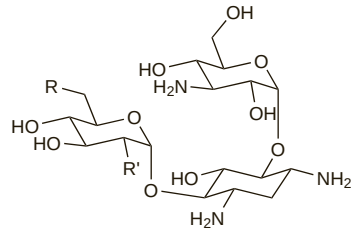
Multi-ingredient: ***Ital.:*** Corti-Fluoral.

Kanamycin Acid Sulfate

Kanamicina, sulfato ácido de; Kanamicino rūgštusis sulfatas; Kanamycin Acid Sulphate *(BANM)*; Kanamycin sulfát kyselý; Kanamycine, sulfate acide de; Kanamycini sulfas acidus; Kanamycinsyrasulfat; Kanamysiinihapposulfaatti; Savanyú kanamicin-szulfát.

ATC — A07AA08; J01GB04; S01AA24.

ATC Vet — QA07AA08; QJ01GB04; QS01AA24.



	R	R'
Kanamycin A	NH_2	OH
Kanamycin B	NH_2	NH_2
Kanamycin C	OH	NH_2

(kanamycin)

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

Ph. Eur. 6.2 (Kanamycin Acid Sulphate). A form of kanamycin sulfate prepared by adding sulfuric acid to a solution of kanamycin sulfate and drying by a suitable method. A white or almost white, hygroscopic powder containing not less than 670 units/mg and 23 to 26% of sulfate, calculated with reference to the dried material. Soluble 1 in about 1 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 5.5 to 7.5.

Kanamycin Sulfate *(rINNM)*

Kanamicin-monoszulfát; Kanamicino monosulfatas; Kanamycin A Sulphate; Kanamycin monosulfát monohydrát; Kanamycin Monosulphate; Kanamycin Sulphate *(BANM)*; Kanamycine, monosulfate de; Kanamycine, Sulfate de; Kanamycini monosulfas; Kanamycini Monosulfas Monohydricus; Kanamycini Sulfas; Kanamycinmonosulfat; Kanamycyny siarczan; Kanamysiinimonosulfaatti; Sulfato de kanamicina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine sulphate monohydrate.

Канамицина Сульфат

$C_{18}H_{36}N_4O_{11},H_2SO_4,H_2O$ = 600.6.

CAS — 59-01-8 (kanamycin); 25389-94-0 (anhydrous kanamycin sulfate).

ATC — A07AA08; J01GB04; S01AA24.

ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

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

Jpn includes the anhydrous substance.

Ph. Eur. 6.2 (Kanamycin Monosulphate; Kanamycin Sulphate BP 2008). The sulfate of an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*. A white or almost white, crystalline powder containing not less than 750 units/mg and 15.0 to 17.0% of sulfate, calculated with reference to the dried material. Soluble 1 in about 8 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 6.5 to 8.5.

USP 31 (Kanamycin Sulfate). A white, odourless crystalline powder. It has a potency equivalent to not less than 750 micrograms of kanamycin per mg, calculated on the dried basis. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides such as kanamycin with beta lactams, see under Gentamicin Sulfate, p.282. Kanamycin is also reported to be incompatible with various other drugs including some other antimicrobials as well as with some electrolytes.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282.

For patients given standard regimens, peak plasma concentrations of kanamycin greater than 30 micrograms/mL, and trough concentrations greater than 10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.

Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.

Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin (p.305), have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.

Breast feeding. Although kanamycin is distributed into breast milk[1] the American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers were receiving kanamycin, and therefore considers[2] that its use is usually compatible with breast feeding.

1. Chyo N, *et al.* Clinical studies of kanamycin applied in the field of obstetrics and gynecology. *Asian Med J* 1962; **5:** 265–75.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. It is active against a similar range of organisms although it is not active against *Pseudomonas* spp. Some strains of *Mycobacterium tuberculosis* are sensitive.

Resistance has been reported in strains of many of the organisms normally sensitive to kanamycin, and at one time was widespread, but a decline in the use of kanamycin has meant that resistance has become somewhat less prevalent. Cross-resistance occurs between kanamycin and neomycin, framycetin, and paromomycin, and partial cross-resistance has been reported between kanamycin and streptomycin.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

Less than 1% of an oral dose is absorbed, although this may be significantly increased if the gastrointestinal mucosa is inflamed or ulcerated.

After intramuscular injection peak plasma concentrations of kanamycin of about 20 and 30 micrograms/mL are attained in about 1 hour following doses of 0.5 and 1 g respectively. A plasma half-life of about 3 hours has been reported. Absorption after intraperitoneal instillation is similar to that from intramuscular doses.

Kanamycin is rapidly excreted by glomerular filtration and most of a parenteral dose appears unchanged in the urine within 24 hours. It has been detected in cord blood and in breast milk.

Uses and Administration

Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin (p.284). It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea (p.191) and neonatal gonococcal eye infections (p.180), although its use has declined in many centres because of the development of resistance. As with gentamicin it may be used with penicillins and with cephalosporins; the injections should be given at separate sites. Kanamycin has also been used as a second-line drug in tuberculosis (p.196), but other, safer drugs are usually preferred.

The sulfate or acid sulfate salts are often used: in the USA, preparations containing the bisulfate ($C_{18}H_{36}N_4O_{11},2H_2SO_4$), but referred to as the sulfate, are available. Doses are expressed in terms of kanamycin base; 1.2 g of kanamycin sulfate, and 1.34 g of kanamycin acid sulfate, are each equivalent to about 1 g of kanamycin. It is usually given by intramuscular injection, and in acute infections adults may be given 15 mg/kg daily, to a maximum of 1.5 g daily, in 2 to 4 divided doses. The same doses may be given by intravenous infusion of a 0.25 to 0.5% solution over 30 to 60 minutes; in the UK, up to 30 mg/kg daily has been given in 2 or 3 divided doses by this route. Similar doses are used in children. Treatment of acute infections should preferably not continue for longer than 7 to 10 days or exceed a cumulative dose of 10 g kanamycin. A dose of 3 to 4 g weekly, given as 1 g on alternate days or as 1 g twice daily on 2 days each week, has been suggested in the UK for chronic bacterial infections, up to a maximum cumulative dose of 50 g, but prolonged use increases the risk of nephrotoxicity and is not generally recommended.

A single intramuscular dose of 2 g of kanamycin has been used in the treatment of penicillin-resistant gonorrhoea. In the treatment and prophylaxis of neonatal gonococcal infections in infants born to mothers with gonorrhoea, 25 mg/kg, up to a maximum of 75 mg, may be given as a single intramuscular dose.

Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284.

Kanamycin has been used orally similarly to neomycin (p.305), for the suppression of intestinal flora. For pre-operative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.

Kanamycin has also been given in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.

Kanamycin tannate has also been used.