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

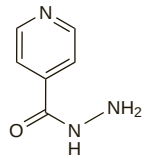
Proprietary Preparations (details are given in Part 3)
Austria: Isepacin†; ***Belg.:*** Isepacine†; ***Cz.:*** Isepacin†; ***Fr.:*** Isepalline†; ***Ital.:*** Isepacin†; ***Mex.:*** Isepacin†; ***Turk.:*** Isepacine.

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%