Isoniazid BP (INH)

*Generic and additional names:* isonicotinic acid hydrazide; isonicotinoylhydrazine; isonicotinylhydrazine; INH; rimitsid; tubazid

*CAS name:* pyridine-4-carbohydrazide

*CAS registry number:* 54-85-3

*Molecular formula:* \( \text{C}_6\text{H}_7\text{N}_3\text{O} \)

*Molecular weight:* 137.14

*Structure:*

![Isoniazid Structure](image)


*Brand names:* Cotinazin (Pfizer); Dinacrin (Winthrop); Ditubin (Schering); Hycozid (Takeda); Iscotin (Daiichi); Isobicina (Maggioni); Isocid (CID); Isolyn (Abbott); Isonex (Dumex); Isonizida (Bial); Isozid (Fatol); Laniazid (Lannett); Mybasan (Antigen); Neoteben (Bayer); Nicizina (Pfizer); Niconyl (Parke-Davis); Nicotibina (Lapetit); Nydrazid (Bristol-Myers Squibb); Pycazide (Smith & Nephew); Pyricidin (Nepera); Rimifon (Roche); Tabinide (Ferrosan); Tubilysin (Orion)

*Derivatives:* Isoniazid 4-aminosalicylate Isoniazid 4-pyridinecarboxylic acid 2-(sulfomethyl) Isoniazid methanesulfonate sodium (derivative)

*Description:* Antibacterial agent used primarily as a tuberculostatic. It remains the treatment of choice for tuberculosis
Properties:

State: Solid

Melting point: 171.4°C

Solubility: Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride

Polarity: Log P -0.64

Acidity/basicity: pH of a 1% aqueous solution 5.5 to 6.5.

pKa: 1.82 (at 20°C)

Spectrum of activity: INH is a bactericidal agent active against organisms of the genus *Mycobacterium*, specifically *M. tuberculosis*, *M. bovis* and *M. kansasii*. INH is bactericidal to rapidly-dividing mycobacteria, but is bacteriostatic if the mycobacterium is slow-growing. INH is highly specific, being active against only a subset of the mycobacteria and largely ineffective against other microorganisms; this is in part due to several unusual aspects of metabolism, exemplified in *M. tuberculosis*, including unusually high KatG activity and a defective drug efflux mechanism.

In-vitro potency against MTB: MIC value of about 0.025 mcg/ml against M. tuberculosis H37Rv.

Optimal human dosage: 5 mg/kg for adults, 10-20 mg/kg for children. Adult dosing generally 300 mg capsule administered orally, once daily; or 15 mg/kg up to 900 mg/day, two or three times/week, ideally dose administered one hour before or two hours after a meal. Concomitant administration of pyridoxine (B6) recommended for malnourished patients, adolescents, and those predisposed to neuropathy (e.g. diabetic). It can also be given intramuscularly or intravenously.

Pharmacology

Mechanism of action: INH is a prodrug activated by catalase-peroxidase hemoprotein, KatG. INH inhibits InhA, a nicotinamide adenine dinucleotide
Drug Profile: Isoniazid

(NADH)-specific enoyl-acyl carrier protein (ACP) reductase involved in fatty acid synthesis.

**Indication:** For the treatment of all forms of tuberculosis in which organisms are susceptible.

**Pharmacodynamics:** Isoniazid is a bactericidal agent active against organisms of the genus *Mycobacterium*, specifically *M. tuberculosis*, *M. bovis* and *M. kansasii*. It is a highly specific agent, ineffective against other microorganisms. Isoniazid is bactericidal to rapidly-dividing mycobacteria, but is bacteriostatic if the *mycobacterium* is slow-growing.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Species</th>
<th>Half-life (h)</th>
<th>AUC (mg·h/l)</th>
<th>Cmax (µg/ml)</th>
<th>PK methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>1.7 ± 0.17</td>
<td>52.2 ± 2.2</td>
<td>28.2 ± 3.8</td>
<td>Single oral dose of 25 mg/kg</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>3.5 ± 0.7</td>
<td>10.9 ± 1.8</td>
<td>1.7 ± 0.3</td>
<td>Single oral dose of 10 mg/kg</td>
</tr>
<tr>
<td>Human</td>
<td>FA: 1.54 ±0.3</td>
<td>FA: 19 ± 6.1</td>
<td>FA:5.4 ± 20</td>
<td>Single oral dose of 6.2 mg/kg</td>
</tr>
<tr>
<td></td>
<td>SA: 3.68 ±0.59</td>
<td>SA: 48.2 ±1.5</td>
<td>SA: 7.1 ± 1.9</td>
<td></td>
</tr>
</tbody>
</table>

*FA: Fast acetylators; SA: Slow acetylators*

**Absorption:** Readily absorbed following oral administration; however, may undergo significant first pass metabolism. Absorption and bioavailability are reduced when isoniazid is administered with food.

**Distribution:** INH is found widely distributed in all body fluids (cerebrospinal, pleural, ascitic), tissues, organs, and excreta (saliva, sputum, faeces); it passes through the placental barrier and into milk.

**Metabolism:** INH is acetylated by N-acetyl transferase to give N-acetylisoniazid, then biotransformed to isonicotinic acid and monoacetylyhydrzone. Monoacetylyhydrzone is associated with hepatotoxicity via formation of a reactive intermediate metabolite when N-hydroxylated by the cytochrome P450 mixed oxidase system. The rate of acetylation is genetically determined (50% of blacks and whites are slow acetylators).
[SA], 85% of Eskimos and Asians are fast acetylators [FA]). Slow acetylators are characterized by a relative lack of hepatic N-acetyltransferase.

**Route of elimination:** Excretion is primarily renal. 50 to 70% of a dose of isoniazid is excreted in the urine within 24 hours.

**Half-life:** Fast acetylators: 0.5 to 1.6 h. Slow acetylators: 2 to 5 h

**Safety and Tolerability**

*Animal drug-drug interactions:* Antagonism between INH, RIF and PZA can be observed in mice under specific circumstances even though these drugs are used in combination in humans. In the initial phase of infection (first 2 months) INH/RIF was as efficacious as INH/RIF/PZA but less active than RIF/PZA. At the end of the continuation phase (6 months treatment) with INH/RIF or INH/RIF/PZA or RIF/PZA all animals were apparently sterilized. After 6 months (drug free) more animals relapsed in the INH/RIF or INH/RIF/PZA group compared with the RIF/PZA group, suggesting antagonism between INH and RIF/PZA. The cause of the apparent antagonism is most likely to be the effect of INH on the RIF AUC and Cmax, both of which were decreased in the presence of INH. Such antagonism may not be apparent in humans because the generally accepted experimental use level of INH is higher in mice compared with the standard human dose.

**Animal toxicity**

*Acute toxicity:* LD50 in mice (mg/kg), 151 i.p., 149 i.v.

*Hepatotoxicity:* INH administered in encapsulated form once or twice a week was as effective as free drug and showed less liver toxicity as measured by ALT, alkaline phosphatase and bilirubin levels. Favorable results were achieved with an INH-Schiff base analog to block *in vivo* acetylation by arylamine N-acetyltransferase (NAT). The acetylated drug is inactive. The Schiff-base analog demonstrated an increase in mouse LD50 to ~1000 mg/kg from ~150 mg/kg for INH and may be less toxic *in vivo*. INH and RIF dosed simultaneously in rabbits caused an elevation in phospholipids and a reduction in phosphatidylcholine, cardiolipin and inorganic phosphates, possibly via a choline deficiency, which may lead to the observed liver toxicity. INH has been
shown to induce pulmonary tumors in a number of mouse strains. INH has not been shown to be carcinogenic in humans

**Reproductive toxicology:** INH has embryocidal effects in rats and rabbits when administered orally during pregnancy, but no congenital anomalies were found in reproduction studies in mammalian species (mice, rats and rabbits).

**Mutagenecity:** INH has been found to be weakly mutagenic in strains TA 100 and TA 1535 of Salmonella typhimurium (Ames assay) without metabolic activation.

**Animal safety pharmacology:** Convulsions were induced in chicks with INH and a corresponding rise in GABA was observed, however coadministration of pyridoxine reversed the effects. INH binds to pyridoxal-5-phosphate, the active form of pyridoxine (vitamin B6), to form INH-pyridoxal hydrazones. Pyridoxal-5-phosphate is a cofactor for glutamic acid decarboxylase and GABA transaminase in the GABA synthetic pathway. INH overdose results in decreased pyridoxal-5-phosphate, decreased GABA synthesis, increased cerebral excitability, and seizures

**Human drug-drug interactions:** INH interacts with the cytochrome P450 system, especially CYP2E1, where it shows a biphasic inhibition induction; it causes increases in serum concentrations of various drugs, especially phenytoin and carbamazepine, increases the effects of warfarin and theophylline, inhibits metabolism of benzodiazepines, and inhibits monoamine oxidase and histaminase. It should not be administered with food, as studies have shown that this significantly reduces its bioavailability.

**Human potential toxicity**

**Hepatitis:** Risk of developing severe and sometimes fatal hepatitis is associated with INH usage, and risk increases with age and with daily alcohol consumption. The drug is acetylated in vivo and slow acetylators generally experience higher blood levels and a potential for increase in toxicity. Acetyl hydrazine is released from acetylated INH and may be at least one of the toxic components.

**CNS:** Peripheral neuropathy: chronic use of INH can produce peripheral neuropathy but this can be prevented by the concurrent administration of pyridoxine.
**Human adverse reactions**

*CNS effects:* Peripheral neuropathy is the most common CNS-related toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paraesthesias of the feet and hands. The incidence is higher in “slow acetylators”. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

**Hepatitis:** Liver toxicity and hepatitis risks are increased with concomitant use of carbamazepine, phenobarbital, RIF, and alcohol abuse. Elevated serum transaminase (SGOT SGPT), bilirubinaemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis can occur with normal dosing regimens. The common prodromal symptoms of hepatitis are anorexia nausea, vomiting, fatigue, malaise, and weakness. Mild hepatic dysfunction, evidenced by mild and transient elevation of serum transaminase levels, occurs in 10-20% of patients taking INH. This abnormality usually appears in the first 1-3 months of treatment but can occur at any time during therapy. In most instances enzyme levels return to normal, and generally there is no necessity to discontinue medication during the period of mild serum transaminase elevation. The frequency of progressive liver damage increases with age.

**Gastrointestinal:** effects such as nausea, vomiting, epigastric distress and dark urine can occur but are rare.

**Haematological effects:** Agranulocytosis; hemolytic, sideroblastic, or aplastic anaemia, thrombocytopenia; and eosinophilia can occur.

**Endocrine and metabolic:** Pyridoxine deficiency, pellagra, hyperglycaemia, acidosis and gynecomastia can occur.

**Hypersensitivity:** Fever, skin rashes, lymphadenopathy and vasculitis can occur.