ISONIAZID PYRIDOXINE HCl

200 mg/12 mg per 5 mL Syrup
(Pediatric Dose)

COMPRILEX®

Antituberculosis

FORMULATION
Each 5 mL (1 tsp) contains:
Isoniazid.....200 mg
Pyridoxine HCl (Vitamin B_6).....12 mg

MECHANISM OF ACTION
Isoniazid
Isoniazid kills actively growing tubercle bacilli by inhibiting the biosynthesis of mycolic acids which are the major components of the bacterial cell wall of *Mycobacterium tuberculosis*.

Pyridoxine hydrochloride
Pyridoxine hydrochloride is converted to its active forms, pyridoxal phosphate and pyridoxamine phosphate, required in the metabolism of proteins, carbohydrates and fats. It enables body tissues to obtain energy from metabolism of carbohydrates, fats, and proteins by functioning as coenzymes for various metabolic and biochemical reactions.

PHARMACOLOGY
Isoniazid
Isoniazid is rapidly and completely absorbed orally and produces peak blood levels within 1 to 2 hours. It readily diffuses into all body fluids including cerebrospinal, pleural and ascitic, tissues, organs and excreta (saliva, sputum and feces). Isoniazid is not substantially bound to plasma proteins. It also passes through the placental barrier and into breast milk in concentrations comparable to those in plasma.

The plasma half-life of Isoniazid in patients with normal renal and hepatic function ranges from 1 to 4 hours, depending on the rate of metabolism. Isoniazid is primarily acetylated by the liver; this process is genetically determined. Fast acetylators metabolize the drug 5 to 6 times faster than the slow acetylators. Several minor metabolites have been identified, one or more of which may be "reactive", and responsible for the liver damage. Approximately 50% of African, Americans and Caucasians are "slow acetylators" and the rest are "rapid acetylators"; majority of Orientals and Eskimos are "rapid acetylators". The rate of acetylation does not significantly alter the effectiveness of Isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus to an increase in toxic reactions.

Approximately 50 to 70% of a dose of Isoniazid is excreted as unchanged drug and metabolites by the kidneys in 24 hours. Elimination is largely independent of renal function.

Pyridoxine hydrochloride
Pyridoxine hydrochloride is readily absorbed from the gastrointestinal tract. It is also widely distributed in body tissues. Excretion is through the urine as metabolites or in the original form. Excessively high doses which exceed the binding capacity of tissues is excreted through the urine.

INDICATIONS
Prevention and treatment of pulmonary and extrapulmonary tuberculosis in children in conjunction with at least one other antituberculous drug. (*See table* for recommended regimens in pediatric tuberculosis*)

DOSAGE/ADMINISTRATION
Once a day. Use in conjunction with at least one other antituberculous drug. (*See table* for recommended regimens in pediatric tuberculosis*)

Pediatric dose: 5 to 10 mg/kg/day

Age Group	Dosage
Infants	0.5 to 1.5 mL
1 to 2 years	1.5 to 2.5 mL
3 to 6 years	2.5 to 5 mL
7 to 12 years	5 to 7.5 mL

Or as prescribed by the physician.

*INITIAL TREATMENT OF TUBERCULOSIS DOSAGE RECOMMENDATION FOR CHILDREN

(adapted from the Philippine Coalition against Tuberculosis, the Philippine Infectious Disease Society of the Philippines and the Philippine Pediatric Society Joint Recommendations, 1997)

DRUGS	DOSAGE (mg/kg)			
	DAILY		2 - 3X/week (DOT)**	
	≤12 y.o.	>12 y.o.	≤12 y.o.	>12 y.o.
Isoniazid (INH)	5-10 (max 300 mg)	5 (max 300 mg)	20-40 (max 900 mg)	15 (max 900 mg)
Rifampicin (Rif)	10-15 (max 600 mg)	10 (max 600 mg)	10-20 (max 600 mg)	10 (max 600 mg)
Pyrazinamide (PZA)	15-30 (max 2 g)	15-30 (max 2 g)	50-70 (max 4 g)	50-70 (max 4 g)
Ethambutol HCl (E)***	15-25 first 2 mos, then 15 (max 2.5 g)	15-25 (max 2.5 g)	30 (3x/week) 50 (2x/week) (max 2.5 g)	30 (3x/week) 50 (2x/week) (max 2.5 g)
Streptomycin sulfate (S)****	20-30 (max 1 g)	15 (max 1 g)	25-30 (max 1.5 g; 2x/week) (max 1 g; 3x/week)	25-30 (max 1.5 g; 2x/week) (max 1 g; 3x/week)

* Currently recommended 6-month regimen for drug-susceptible tuberculosis consists of INH, Rif & PZA for 2 months, followed by 4 months of INH & Rifampicin.
** Directly-observed therapy.
*** Not recommended for children < 6 years old due to potential ocular complications. Only an "add-on" drug if quadruple therapy is required.
**** Used as a 4th drug in children < 6 years old where E is not recommended. Used also in more severe types of TB such as TB meningitis & miliary TB.

Patient Information
Take on an empty stomach, at least 1 hour before or 2 hours after meals; it may be taken with food to decrease GI upset.

Take medication as directed, avoid missing doses. Do not discontinue therapy except on advice of physician.

Avoid certain foods (i.e., fish-skipjack, tuna, and perhaps tyramine-containing products).

Notify physician if weakness, fatigue, loss of appetite, nausea and vomiting, yellowing of skin or eyes, darkening of urine, or numbness or tingling in hands and feet occurs.

CONTRAINDICATIONS
Patients with previous isoniazid-associated hepatic injury or other severe adverse reactions to Isoniazid (i.e., drug fever, chills, arthritis, acute liver disease of any etiology).

WARNING
Hypersensitivity: Stop all drugs and evaluate at the first sign of a hypersensitivity reaction. If Isoniazid must be reinstituted, give only after symptoms have cleared. Restart the drug in very small and gradually increasing doses and withdraw immediately if there is any indication of recurrent hypersensitivity reaction.

Hepatic and renal function impairment: Monitor patients with active chronic liver disease or severe renal dysfunction.

PRECAUTIONS
Periodic ophthalmologic examinations during Isoniazid therapy are recommended even when visual symptoms do not occur.

Pyridoxine administration is recommended in individuals likely to develop peripheral neuropathies secondary to Isoniazid therapy. Prophylactic doses of 6 to 50 mg of Pyridoxine daily have been recommended.

Carcinogenesis: Isoniazid induces pulmonary tumors in a number of strains of mice.

Pregnancy: Isoniazid exerts an embryocidal effect in both rats and rabbits, but no Isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, and rabbits). Prescribe during pregnancy only when therapeutically necessary. Weigh the benefit of preventive therapy against a possible risk to the fetus. Start preventive treatment generally after delivery because of the increased risk of tuberculosis for new mothers.

Lactation: Since Isoniazid appears in breast milk, observe breastfed infants of Isoniazid-treated mothers for any evidence of adverse effects.

ADVERSE EFFECTS
Toxic effects are usually encountered with higher doses of Isoniazid; the most frequent are those affecting the nervous system and the liver.

CNS: Most common toxic effect is peripheral neuropathy, characterized by symmetrical numbness and tingling of the extremities. Other neurotoxic effects uncommon with conventional doses include convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

GI: Nausea, vomiting and epigastric discomfort.

Hepatic: Commonly, elevated serum transaminase levels, bilirubinemia, bilirubinuria, and jaundice. Occasionally, severe and sometimes fatal hepatitis.

Hematologic: Agranulocytosis; hemolytic, sideroblastic or aplastic anemia; thrombocytopenia; and eosinophilia.

Hypersensitivity: Fever, skin eruptions (morbilliform, maculopapular, purpuric or exfoliative), lymphadenopathy, and vasculitis.

Metabolic/Endocrine: Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia. Isoniazid may cause hypocalcemia and hypophosphatemia due to alterations of vitamin D metabolism.

Miscellaneous: Rheumatic syndrome and systemic lupus erythematosus-like syndrome.

DRUG INTERACTIONS
Isoniazid inhibits the metabolism of the following drugs: anticonvulsants (i.e. Carbamazepine, phenytoin, primidone, and valproic acid), benzodiazepines, haloperidol, ketoconazole, theophylline, and warfarin.

Concomitant antacid administration may reduce the absorption of Isoniazid.

Corticosteroids may decrease the serum concentration of Isoniazid by increasing acetylation rate and/or renal clearance. Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of Isoniazid by competition of acetylating enzymes.

The CNS effects of Meperidine (drowsiness), cycloserine (dizziness, drowsiness) and disulfiram (acute behavioral and coordination changes) may be exaggerated when concomitantly administered with Isoniazid. Concurrent administration with Levodopa may produce symptoms of excess catecholamine stimulation (agitation, flushing and palpitations) or lack of levodopa effect.

Isoniazid may produce hypoglycemia and lead to loss of glucose control in patients on oral hypoglycemics.

Fast acetylation of Isoniazid may produce high concentrations of Hydrazine which facilitate defluorination of Enflurane.

Pyridoxine hydrochloride reverses the therapeutic effects of Levodopa by accelerating peripheral metabolism of levodopa. It may also decrease serum concentrations of phenobarbital and phenytoin.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY: In amber bottles of 10 mL (Physician's Sample), 120 mL and 250 mL.

ALWAYS KEEP CONTAINER TIGHTLY CLOSED.
STORE AT TEMPERATURES NOT EXCEEDING 30°C.

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