



## TUBOZID (tablets)

Isoniazid (300, 100) mg

Composition: each tablet contains 100 or 300 mg Isoniazid

excipients: anhydrous lactose- calcium stearate-colloidal silicon dioxide- microcrystalline cellulose- and stearic acid.

Mechanism of Action

Isoniazid inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall. At therapeutic levels isoniazid is bactericidal against actively growing intracellular and extracellular Mycobacterium tuberculosis organisms.

### INDICATIONS AND USAGE:

Isoniazid tablets, are recommended for all forms of tuberculosis in which organisms are susceptible. However, active tuberculosis must be treated with multiple concomitant anti-tuberculosis medications to prevent the emergence of drug resistance. Single-drug treatment of active tuberculosis with isoniazid or any other medication, is inadequate therapy.

Isoniazid tablets, are recommended as preventive therapy for the following groups, regardless of age:

1. Persons with human immunodeficiency virus (HIV) infection and persons with risk factors for HIV infection whose HIV infection status is unknown but who are suspected of having HIV infection. Preventive therapy may be considered for HIV infected persons who are tuberculin-negative but belong to groups in which the prevalence of tuberculosis infection is high. Candidates for preventive therapy who have HIV infection should have a minimum of 12 months of therapy.

2. Close contacts of persons with newly diagnosed infectious tuberculosis. In addition, tuberculin-negative children and adolescents who have been close contacts of infectious persons within the past 3 months are candidates for preventive therapy until a repeat tuberculin skin test is done 12 weeks after contact with the infectious source. If the repeat skin test is positive, therapy should be continued.

3. Recent converters, as indicated by a tuberculin skin test (greater than or equal to 10 mm increase within a -2year period for those less than 35 years old; greater than or equal to 15 mm increase for those greater than or equal to 35 years of age). All infants and children younger than 4 years of age with a greater than 10 mm skin test are included in this category.

4. Persons with abnormal chest radiographs that show fibrotic lesions likely to represent old healed tuberculosis (greater than or equal to 5 mm). Candidates for preventive therapy who have fibrotic pulmonary lesions consistent with healed tuberculosis or who have pulmonary silicosis should have 12 months of isoniazid or 4 months of isoniazid and rifampin, concomitantly.

5. Intravenous drug users known to be HIV-seronegative (greater than 10 mm).

6. Persons with the following medical conditions that have been reported to increase the risk of tuberculosis (greater than or equal to 10 mm): silicosis; diabetes mellitus; prolonged therapy with adrenocorticosteroids; immunosuppressive therapy; some hematologic and reticuloendothelial diseases, such as leukemia or Hodgkin's disease; end-stage renal disease; clinical situations associated with substantial rapid weight loss or chronic undernutrition (including: intestinal bypass surgery for obesity, the postgastrectomy state [with or without weight loss], chronic peptic ulcer disease, chronic malabsorption syndromes and carcinomas of the oropharynx and upper gastrointestinal tract that prevent adequate nutritional intake). Candidates for preventive therapy who have fibrotic pulmonary lesions consistent with healed tuberculosis or who have pulmonary silicosis should have 12 months of isoniazid or 4 months of isoniazid and rifampin, concomitantly.

### CONTRAINDICATIONS:

Isoniazid is contraindicated in patients who develop severe hypersensitivity reactions, including drug-induced hepatitis; previous isoniazid-associated hepatic injury; severe adverse reactions to isoniazid such as drug fever, chills, arthritis; and acute liver disease of any etiology.

### PRECAUTIONS:

#### General:

All drugs should be stopped and an evaluation made at the first sign of a hypersensitivity reaction. If isoniazid therapy must be reinstated, the drug should be given only after symptoms have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

- Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of + isoniazid hepatitis.
- Patients with active chronic liver disease or severe renal dysfunction.
- Age greater than 35.
- Concurrent use of any chronically administered medication.
- History of previous discontinuation of isoniazid.
- Existence of peripheral neuropathy or conditions predisposing to neuropathy.
- Pregnancy.
- Injection drug use.
- Women belonging to minority groups, particularly in the postpartum period.
- HIV seropositive patients.

### WARNINGS:

Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported and may occur or may develop even after many months of treatment.

The risk of developing hepatitis is age related. Approximate case rates by age are:

less than 1 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20 to 34 year age group, 12 per 1,000 for persons in the 35 to 49 year age group, 23 per 1,000 for persons in the 50 to 64 year age group and 8 per 1,000 for persons over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a U.S. Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis.

Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. For persons 35 and older, in addition to monthly symptom reviews, hepatic enzymes (specifically, AST and ALT (formerly SGOT and SGT, respectively)) should be measured prior to starting isoniazid therapy and periodically throughout treatment.

Isoniazid-associated hepatitis usually occurs

during the first three months of treatment. Usually, enzyme levels return to normal despite continuance of drug, but in some cases progressive liver dysfunction occurs. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease and injection drug use.

Patients with tuberculosis who have hepatitis attributed to isoniazid should be given appropriate treatment with alternative drugs. If isoniazid must be reinstated, it should be reinstated only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement.

Preventive treatment should be deferred in persons with acute hepatic diseases.

Drug Interactions:

#### Food:

Isoniazid should not be administered with food. Studies have shown that the bioavailability of isoniazid is reduced significantly when administered with food. Tyramineand histamine-containing foods should be avoided in patients receiving isoniazid. Because isoniazid has some monoamine oxidase inhibiting activity, an interaction with tyramine-containing foods (cheese, red wine) may occur. Diamine oxidase may also be inhibited, causing exaggerated response (e.g., headache, sweating, palpitations, flushing, hypotension) to foods containing histamine (e.g., skipjack, tuna, other tropical fish).

Acetaminophen

A report of severe acetaminophen toxicity was reported in a patient receiving isoniazid.

### Carbamazepine:

Isoniazid is known to slow the metabolism of carbamazepine and increase its serum levels. Carbamazepine levels should be determined prior to concurrent administration

with isoniazid, signs and symptoms of carbamazepine toxicity should be monitored closely and appropriate dosage adjustment of the anticonvulsant should be made .

#### Ketoconazole:

Potential interaction of ketoconazole and isoniazid may exist. When ketoconazole is given in combination with isoniazid and rifampin the AUC of ketoconazole is decreased by as much as 88 percent after 5 months of concurrent isoniazid and rifampin therapy .

#### Phenytoin:

Isoniazid may increase serum levels of phenytoin. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant should be made. Theophylline:

A recent study has shown that concomitant administration of isoniazid and theophylline may cause elevated plasma levels of theophylline and in some instances a slight decrease in the elimination of isoniazid. Since the therapeutic range of theophylline is narrow, theophylline serum levels should be monitored closely and appropriate dosage adjustments of theophylline should be made .

#### Valproate:

A recent case study has shown a possible increase in the plasma level of valproate when co-administered with isoniazid. Plasma valproate concentration should be monitored

when isoniazid and valproate are co-administered and appropriate dosage adjustments of valproate should be made .

#### Carcinogenesis and Mutagenesis:

Isoniazid has been shown to induce pulmonary tumors in a number of strains of mice.

Isoniazid has not been shown to be carcinogenic in humans.

#### Pregnancy:

Pregnancy Category C

Isoniazid has been shown to have an embryocidal effect in rats and rabbits when given orally during pregnancy Isoniazid should be used as a treatment for active tuberculosis during pregnancy because the benefit justifies the potential risk to the fetus. The benefit of preventive therapy also should be weighed against a possible risk to the fetus. Preventive therapy generally should be started after delivery to prevent putting the fetus at risk of exposure; the low levels of isoniazid in breast milk do not threaten the neonate. Since isoniazid is known to cross the placental barrier, neonates of isoniazid treated mothers should be carefully observed for any evidence of adverse effects.

#### Nursing Mothers:

The small concentrations of isoniazid in breast milk do not produce toxicity in the nursing newborn; therefore, breast feeding should not be discouraged. However, because levels of isoniazid are so low in breast milk, they cannot be relied upon for prophylaxis or therapy of nursing infants.

#### ADVERSE REACTIONS:

The most frequent reactions are those affecting the nervous system and the liver.

#### Nervous System Reactions

Peripheral neuropathy is the most common 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 paresthesias of the feet and hands.

Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

#### Hepatic Reactions:

Elevated serum transaminase (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice and occasionally severe and sometimes fatal hepatitis.

#### Gastrointestinal Reactions:

Nausea, vomiting, epigastric distress, and pancreatitis.

#### Hematologic Reactions

Agranulocytosis; hemolytic, aplastic anemia, thrombocytopenia; and eosinophilia.

#### Hypersensitivity Reactions:

Fever, skin eruptions (morbilliform, maculopapular, purpuric or exfoliative),lymphadenopathy, vasculitis, toxic epidermal necrolysis, and drug reaction with eosinophilia syndrome (DRESS).

#### Metabolic and Endocrine Reactions

Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis and gynecomastia.

#### Miscellaneous Reactions

Rheumatic syndrome and systemic lupus erythematosus-like syndrome.

### DOSAGE AND ADMINISTRATION:

#### For Treatment of Tuberculosis:

Isoniazid is used in conjunction with other effective anti-tuberculous agents. Drug susceptibility testing should be performed on the organisms initially isolated from all patients with newly diagnosed tuberculosis. If the bacilli becomes resistant, therapy must be changed to agents to which the bacilli are susceptible.

Usual Oral Dosage (depending on the regimen used):

#### Adults:

5 mg/kg up to 300 mg daily in a single dose; or 15 mg/kg up to 900 mg/day, two or three times/week.

#### Children:

10 mg/kg to 15 mg/kg up to 300 mg daily in a single dose; or 20 mg/kg to 40 mg/kg up to 900 mg/day, two or three times/week

#### Patients with Pulmonary Tuberculosis Without HIV Infection:

There are 3 regimen options for the initial treatment of tuberculosis in children and adults:

Option 1

Daily isoniazid, rifampin and pyrazinamide for 8 weeks followed by 16 weeks of isoniazid and rifampin daily or 2 to 3 times weekly. Ethambutol or streptomycin should be added to the initial regimen until sensitivity to isoniazid and rifampin is demonstrated. The addition of a fourth drug is optional if the relative prevalence of isoniazid-resistant Mycobacterium tuberculosis isolates in the community is less than or equal to four percent.

Option 2

Daily isoniazid, rifampin, pyrazinamide and streptomycin or ethambutol for 2 weeks followed by twice weekly administration of the same drugs for 6 weeks, subsequently twice weekly isoniazid and rifampin for 16 weeks.

Option 3

Three times weekly with isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin for 6 months.

\*All regimens given twice weekly or 3 times weekly should be administered by directly observed therapy [see also Directly Observed Therapy (DOT)].

The above treatment guidelines apply only when the disease is caused by organisms that are susceptible to the standard antituberculous agents. Because of the impact of resistance to isoniazid and rifampin on the response to therapy, it is essential that physicians initiating therapy for tuberculosis be familiar with the prevalence of drug resistance in their communities. It is suggested that ethambutol not be used in children whose visual acuity cannot be monitored.

#### Patients with Pulmonary Tuberculosis and HIV Infection

The response of the immunologically impaired host to treatment may not be as satisfactory as that of a person with normal host responsiveness. For this reason, therapeutic decisions for the impaired host must be individualized. Since patients coinfectd with HIV may have problems with malabsorption, screening of antimycobacterial drug levels, especially in patients with advanced HIV disease, may be necessary to prevent the emergence of MDRTB.

Patients with Extra Pulmonary Tuberculosis:

The basic principles that underlie the treatment of pulmonary tuberculosis also apply to extra pulmonary forms of the disease. Although there have not been the same kinds of carefully conducted controlled trials of treatment of extra pulmonary tuberculosis as for pulmonary disease, increasing clinical experience indicates that a 6 to 9 month short course regimen is effective. Because of the insufficient data, milary tuberculosis,

bone/joint tuberculosis and tuberculous meningitis in infants and children should receive 12 month therapy. Bacteriologic evaluation of extra pulmonary tuberculosis may be limited by the relative inaccessibility of the sites of disease. Thus, response to treatment often must be judged on the basis of clinical and radiographic findings.

The use of adjunctive therapies such as surgery and corticosteroids is more commonly required in extra pulmonary tuberculosis than in pulmonary disease. Surgery may be necessary to obtain specimens for diagnosis and to treat such processes as constrictive pericarditis and spinal cord compression from Pott's disease.

Corticosteroids have been shown to be of benefit in preventing cardiac constriction from tuberculous pericarditis and in decreasing the neurologic sequelae of all stages of tuberculous meningitis, especially when administered early in the course of the disease.

#### Pregnant Women with Tuberculosis:

The options listed above must be adjusted for the pregnant patient. Streptomycin interferes with in utero development of the ear and may cause congenital deafness.

Routine use of pyrazinamide is also not recommended in pregnancy because of inadequate teratogenicity data. The initial treatment regimen should consist of isoniazid and rifampin. Ethambutol should be included unless primary isoniazid resistance is unlikely (isoniazid resistance rate documented to be less than %4).

#### Treatment of Patients with Multi-Drug Resistant Tuberculosis (MDRTB):

Multiple-drug resistant tuberculosis (i.e., resistance to at least isoniazid and rifampin) presents difficult treatment problems. Treatment must be individualized and based on susceptibility studies. In such cases, consultation with an expert in tuberculosis is recommended.

#### Directly Observed Therapy (DOT):

A major cause of drug-resistant tuberculosis is patient noncompliance with treatment.

The use of DOT can help assure patient compliance with drug therapy. DOT is the observation of the patient by a health care provider or other responsible person as the patient ingests anti-tuberculosis medications. DOT can be achieved with daily, twice weekly or thrice weekly regimens and is recommended for all patients.

#### For Preventative Therapy of Tuberculosis:

Before isoniazid preventive therapy is initiated, bacteriologically positive or radiographically progressive tuberculosis must be excluded. Appropriate evaluations should be performed if extra pulmonary tuberculosis is suspected.

**Adults over 30 kg:** 300 mg per day in a single dose.

**Infants and Children:** 10 mg/kg (up to 300 mg daily) in a single dose. In situations where adherence with daily preventative therapy cannot be assured, 20 mg/kg to 30 mg/kg (not to exceed 900 mg) twice weekly under the direct observation of a health care worker at the time of administration .

Continuous administration of isoniazid for a sufficient period is an essential part of the regimen because relapse rates are higher if chemotherapy is stopped prematurely. In the treatment of tuberculosis, resistant organisms may multiply and the emergence of resistant organisms during the treatment may necessitate a change in the regimen.

For following patient compliance: the Potts-Cozart test , a simple colorimetric method of checking for isoniazid in the urine, is a useful tool for assuring patient compliance, which is essential for effective tuberculosis control. Additionally, isoniazid test strips are also available to check patient compliance.

Concomitant administration of pyridoxine (B ) is recommended in the malnourished and in those predisposed to neuropathy (e.g., alcoholics and diabetics).

### OVERDOSAGE:

#### Signs and Symptoms:

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations (including bright colors and strange designs) are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycemia are typical laboratory findings.

#### Treatment:

##### General:

Obtain blood samples for immediate determination of gases, electrolytes, BUN, glucose, etc.; type and cross-match blood in preparation for possible hemodialysis.

Rapid Control of Metabolic Acidosis:

Patients with this degree of INH intoxication are likely to have hypoventilation. The administration of sodium bicarbonate under these circumstances can cause exacerbation of hypercarbia. Ventilation must be monitored carefully, by measuring blood carbon dioxide levels and supported mechanically, if there is respiratory insufficiency.

#### Dialysis:

Both peritoneal and hemodialysis have been used in the management of isoniazid overdosage. These procedures are probably not required if control of seizures and acidosis is achieved with pyridoxine, diazepam and bicarbonate.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, utilize meticulous respiratory and other intensive care to protect against hypoxia, hypotension, aspiration, pneumonitis, etc.

#### Storage conditions:

Keep at 25-20 c0, protect from light and moisture.

Keep out of the reach of children.

**Packaging:** 3 blisters, each blisters contains 10 tablets/ carton box.

THIS IS MEDICATION
<ul style="list-style-type: none"><li>- A medicine is a product that affects your health, and its consumption contrary to instructions will expose you to danger.</li><li>- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold it to you.</li><li>- The doctor and the pharmacist are the experts in medicine. Its benefits and harms.</li><li>- Do not interrupt the prescribed treatment period on your own.</li><li>- Do not repeat the medication without a prescription.</li><li>- Keep the medicine out of the reach of children.</li></ul>
(Instructions of the Council of Arab Health Ministers and the Union of Arab Pharmacists)

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