SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ISONIAZID 300 mg ADCO, 300 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of **ISONIAZID 300 mg ADCO** contains 300 mg isoniazid.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off white, circular flat faced beveled edged, uncoated tablet with score line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISONIAZID 300 mg ADCO is indicated for the prophylaxis and treatment of tuberculosis in conjunction with other antituberculosis medicines.

4.2 Posology and method of administration

Prescribers should also consult the National Anti-tuberculosis Guidelines in regard to dosages of isoniazid.

Adults and adolescents

Prophylaxis:

5 mg/kg (maximum 300 mg) once daily

It may be used in combination with rifampicin for prophylaxis against multidrug-resistant tuberculosis.

Treatment (in combination with other antituberculosis medicines):
5 to 15 mg/kg, once daily or in divided doses (maximum 900 mg per day), based on the type of tuberculosis and sensitivity pattern. Higher doses are used for CNS tuberculosis and multidrug- resistant tuberculosis.

Children
Prophylaxis:
10 mg per kg of body weight, up to 300 mg, once daily

Treatment (in combination with other antituberculosis medicines):
10 to 20 mg per kg of body weight, up to 300 mg, once daily

Higher doses are used for CNS tuberculosis and multidrug- resistant tuberculosis.

Special populations
Slow or fast acetylators
The rate of acetylation is determined genetically.

The mean half-life in fast acetylators is approximately 70 minutes, whereas 2 to 5 hours is characteristic of slow acetylators.

Patients who are slow acetylators may be more prone to adverse effects and may require lower doses than usual.

Paediatrics
The rate of medicine metabolism is influenced by the youth/age of the patient: a particular dose of isoniazid in mg/kg when given to a young child (under 5 years) may not reach the same blood levels as when given to an older child or adult.

Higher mg/kg dosages are therefore required in younger children to achieve levels that are considered effective to produce bactericidal activity.

Elderly (65 years of age and older)
No dosage reduction is necessary in the elderly, but caution should be exercised due to the possible decrease in renal and hepatic function.

Hepatic impairment
The half-life of isoniazid may be prolonged in the presence of hepatic insufficiency.

ISONIAZID 300 mg ADCO should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4).
Renal impairment
No dosage reduction of isoniazid is necessary when given to patients with mild renal failure.

Patients with severe renal failure (glomerular filtration rate of less than 10 ml/minute) (creatinine clearance < 30 ml/min) and slow acetylator status might require a dose reduction of about 100 mg to maintain trough plasma levels at less than 1 mcg/ml.

Method of administration
For oral administration.

ISONIAZID 300 mg ADCO tablets should preferably be taken on an empty stomach, i.e. at least 30 minutes before a meal or 2 hours after a meal.

ISONIAZID 300 mg ADCO may be taken with meals if gastrointestinal irritation occurs, but oral absorption may be reduced.

Aluminium-containing antacids may delay and decrease absorption and serum concentrations of isoniazid. **ISONIAZID 300 mg ADCO** should therefore be taken/administered at least 1 hour before taking antacids.

4.3 Contraindications
The contraindications of all other anti-tuberculosis medicines to be used in combination with isoniazid should be consulted and adhered to, in addition to that of isoniazid.

ISONIAZID 300 mg ADCO is contraindicated in:

- Patients hypersensitive to isoniazid, ethionamide, pyrazinamide, niacin, or other chemically-related compounds or to any of the excipients in **ISONIAZID 300 mg ADCO** (see section 6.1).
- Alcoholism.
- Hepatic impairment and medicine induced liver disease.
- Severe renal failure.
- Patients with uncontrolled seizures.
- Isoniazid in combination with other antituberculosis medicines can lead to optic neuritis. Use of **ISONIAZID 300 mg ADCO** in pregnancy should take into account the woman and/or her developing foetus where these need to be used (see section 4.6).

4.4 Special warnings and precautions for use

Hepatotoxicity

ISONIAZID 300 mg ADCO may cause severe and sometimes fatal hepatitis. Advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extra-pulmonary tuberculosis were identified as risk factors for isoniazid-induced hepatotoxicity.

All patients should have baseline liver function tests performed and repeated at regular intervals during treatment. If serum ALT rises to more than three times normal, or there is any increase in bilirubin, treatment should be withdrawn.

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Cases of severe cutaneous reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with fatal outcome, have been reported with the use of isoniazid, as in **ISONIAZID 300 mg ADCO** (see section 4.8). Patients should be advised of these signs and symptoms and closely monitored for skin reactions. The patient should be advised that if signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develop, they should consult their doctor immediately.

ISONIAZID 300 mg ADCO should be permanently discontinued if an alternative etiology for these signs and symptoms cannot be established.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during antituberculosis therapy (see section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult their doctor immediately.

ISONIAZID 300 mg ADCO should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

ISONIAZID 300 mg ADCO should be given with caution in patients suffering from convulsive disorders and diabetes mellitus, and patients with a history of psychosis.

ISONIAZID 300 mg ADCO should be used with caution in patients with mild to moderate hepatic or renal impairment (see section 4.2) or patients taking other potentially hepatotoxic medicines.

If symptoms of hepatitis deteriorate in these patients, **ISONIAZID 300 mg ADCO** should be discontinued immediately.

Pyridoxine

The administration of pyridoxine daily is recommended to prevent or minimise symptoms of peripheral neuritis in high-risk groups such as in patients who are diabetic, alcoholic, malnourished, uraemic, pregnant or infected with HIV.

Patients who are at risk of neuropathy or pyridoxine deficiency including those in the abovementioned high-risk groups should receive pyridoxine usually in a dose of 10 to 15 mg daily, with a maximum of 30 mg/day during treatment with **ISONIAZID 300 mg ADCO**.

Periodic eye examinations during treatment are recommended.

ISONIAZID 300 mg ADCO in combination with other anti-tuberculosis medicines causes optic neuritis which can lead to optic atrophy and blindness (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Inhibition of CYP450

Isoniazid, as in **ISONIAZID 300 mg ADCO**, can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, and others such as warfarin and theophylline.

Concomitant administration of benzodiazepines (diazepam/carbamazepine) and isoniazid, as in **ISONIAZID 300 mg ADCO**, has been reported to result in benzodiazepine toxicity (sedation, respiratory depression, etc.).

Other interactions

Concurrent administration of **ISONIAZID 300 mg ADCO** and rifampicin may lead to a higher risk of hepatotoxicity, while increased central nervous system adverse effects have occurred when **ISONIAZID 300 mg ADCO** is given with potentially neurotoxic medicines such as cycloserine or disulfiram. Hepatotoxic reactions have been reported when paracetamol is given concurrently with **ISONIAZID 300 mg ADCO**, while chronic alcoholism increases the risk of isoniazid induced hepatitis.

When isoniazid, as in **ISONIAZID 300 mg ADCO** is given to patients receiving paraminosalicyclic acid concurrently, the plasma concentrations of isoniazid may be increased, and adverse effects are more likely to occur.

Prednisolone may increase hepatic metabolism and/or excretion of **ISONIAZID 300 mg ADCO**.

Aluminium-containing antacids may delay and decrease absorption and serum concentrations of isoniazid. It is therefore recommended that **ISONIAZID 300 mg ADCO** be administered at least 1 hour before taking antacids (see section 4.2).

Isoniazid, as in **ISONIAZID 300 mg ADCO** may reduce the therapeutic effects of levodopa.

Concomitant administration of **ISONIAZID 300 mg ADCO**, with itraconazole or ketoconazole may result in significant decreases in either medicine's serum concentrations, and thus

therapeutic failure. Concurrent use should be well monitored, and dosage increases made if necessary.

Because the clearance of isoniazid, as in **ISONIAZID 300 mg ADCO**, was found to be doubled when zalcitabine was given in HIV-positive patients, concurrent use of **ISONIAZID 300 mg ADCO** and zalcitabine should be monitored to ensure isoniazid effectiveness.

Interactions with food

Isoniazid, as in **ISONIAZID 300 mg ADCO**, is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), can therefore reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, conjunctival irritation, tachycardia, tachypnoea and hypotension.

Patients should be advised against ingesting foods rich in tyramine and/or histamine during treatment with isoniazid, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).

4.6 Fertility, pregnancy and lactation

Use of **ISONIAZID 300 mg ADCO** in pregnancy should take into account the safety of other anti-tuberculosis medicines in pregnancy, and the risk to the pregnant woman and/or her embryo/developing foetus where these medicines are to be used in combination with isoniazid.

Women of childbearing potential

Women of child-bearing potential should be advised to avoid becoming pregnant while on treatment with **ISONIAZID 300 mg ADCO**.

Pregnancy

Isoniazid, as in **ISONIAZID 300 mg ADCO**, crosses the placenta.

The safe use of isoniazid in pregnancy has not been established, and harm to the embryo/developing foetus cannot be excluded (see section 4.3).

Pyridoxine supplementation is recommended (see section 4.4).

Breastfeeding

Women on treatment with **ISONIAZID 300 mg ADCO** should not breastfeed their infants.

The safety of infants receiving breast milk of mothers on treatment with **ISONIAZID 300 mg ADCO** has not been established.

Fertility

No data on the effect of isoniazid on fertility is available.

4.7 Effects on ability to drive and use machines

ISONIAZID 300 mg ADCO may influence the ability to drive and use machines. Since adverse reactions such as convulsions have been reported in patients receiving isoniazid, as in **ISONIAZID 300 mg ADCO**, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **ISONIAZID 300 MG ADCO** does not adversely affect their ability to do so (see sections 4.4 and 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse Reactions
Blood and the lymphatic system disorders	Less frequent	Blood dyscrasias
	Frequency unknown	Agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders	Less frequent	Hypersensitivity reactions (fever, skin rashes, joint pain)
Metabolism and nutrition disorders	Frequency unknown	Hyperglycaemia, metabolic acidosis, hypoglycaemia, nicotinic acid deficiency
Psychiatric disorders	Frequency unknown	Psychotic reactions/ disorders, elevated moods
Nervous system disorders	Frequent	Peripheral neuritis
	Less frequent	Neurotoxicity
	Frequency unknown	Convulsions, peripheral neuropathy, hyperreflexia
Eye disorders	Frequency unknown	Optic neuritis which can lead to optic atrophy and blindness*
Ear and labyrinth disorders	Frequency unknown	Deafness, tinnitus, vertigo

Vascular disorders	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Interstitial lung disease
Gastrointestinal disorders	Frequency unknown	Gastrointestinal irritation, nausea, pellagra, constipation, dry mouth acute pancreatitis, vomiting, other gastrointestinal effects
Hepato-biliary disorders	Frequent	Hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness)
	Less frequent	Hepatitis
	Frequency unknown	Acute hepatic failure, liver injury, jaundice
Skin and subcutaneous tissue disorders	Less frequent	Toxic epidermal necrolysis, eosinophilia systemic symptoms
	Frequency unknown	Erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequency unknown	Lupus-like syndrome, rheumatoid syndrome, systemic lupus erythematosus
Renal and urinary disorders	Frequency unknown	Urinary retention, dysuria
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia
General disorders and administrative site conditions	Frequency unknown	Pyrexia
Investigations	Frequency unknown	Increased hepatic enzymes

* When isoniazid is taken in combination with other anti-tuberculosis medicines.

Description of selected adverse reactions

Ear and labyrinth disorders

Deafness, tinnitus, vertigo have been reported in patients with end stage renal impairment/failure. Vertigo may be troublesome with doses of 10 mg per kg body weight.

Eye disorders
Isoniazid causes optic neuritis which in combination with other anti-tuberculosis medicines, can lead to optic atrophy and blindness.

Hepato-biliary disorders
The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.

Metabolism and nutrition disorders
Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

Nervous system disorders
Hyperreflexia may be troublesome with doses of 10 mg per kg body weight.

Psychiatric disorders
Mood elevation and mental disturbances, ranging from minor personality changes to major mental derangement have been reported.

Miscellaneous
Withdrawal symptoms, which may occur on the cessation of the treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
Symptoms of isoniazid overdose includes slurred speech, metabolic acidosis, hyperglycaemia, hallucinations, respiratory and CNS depression, convulsions and coma.

Treatment consists of symptomatic and supportive therapy. This includes use of large doses of pyridoxine (1:1) to prevent and/or control convulsions, and sodium bicarbonate for metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.3 Tuberculostatics
Anti-infective for systemic use, ATC code: J04AC01

Isoniazid is a synthetic bactericidal antituberculosis medicine, that is active against many mycobacteria, and primarily those that are actively dividing. Its exact mechanism of action is not known, but it may relate to inhibition of mycolic acid synthesis and disruption of the cell wall in susceptible organisms.

5.2 Pharmacokinetic properties

Absorption

Isoniazid is readily absorbed from the gastrointestinal tract following oral administration. Absorption and bio-availability are reduced when administered with food.

Distribution

The plasma half-life for isoniazid ranges from about 1 to 4 hours. It is widely distributed to all fluids and tissues, including cerebrospinal fluid (CSF), pleural and ascitic fluids, skin, sputum, saliva, lungs, muscle, and caseous tissue. Isoniazid crosses the placenta and is excreted in the breast milk (see section 4.6).

Biotransformation

The primary metabolic route is acetylation.

Elimination

Approximately 75 to 95 % is excreted by the kidneys within 24 hours, mainly as metabolites. Small amounts are excreted in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Copovidone
Crospovidone
Microcrystalline cellulose
Polyethylene glycol
Povidone
Stearic acid

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
No special requirements.

6.5 Nature and contents of container
10 tablets shall be packed per blister using amber PVC/PVdC foil as a base material and hard tampered heat seal lacquer coated printed aluminium foil as a lidding material. 10 blisters packs are packed in a carton.

28 tablets shall be packed per blister using amber PVC/PVDC foil as a base material and hard tampered heat seal lacquer coated printed aluminium foil as a lidding material. 24 blisters packs are packed in a carton.

Not all packs and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Store at or below 30 °C.
Protect from light and moisture.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT