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## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

**UKUZID 300 mg,** tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg isoniazid.

UKUZID 300 mg tablets are sugar free.

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablet.

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

UKUZID is used in the prophylaxis and treatment of tuberculosis. It is administered with other antituberculosis medicines.

### 4.2 Posology and method of administration

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**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**: UKUZID is to be taken in combination with other anti-tuberculosis 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 central nervous system (CNS) tuberculosis and multidrug- resistant tuberculosis.

***Paediatric population***

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

**Treatment**: UKUZID is to be taken in combination with other anti-tuberculosis medicines, as 10 mg to 20 mg per kg of body weight up to 300 mg, once a day.
Higher doses are used for CNS tuberculosis and multidrug- resistant tuberculosis

***Special populations***

**Slow acetylators**

The rate of acetylation is determined genetically.The mean half-life in fast acetylators is approximately 70 minutes, and about 2 - 5 hours is characteristic of slow acetylators. Patients who are slow acetylators may be more prone to adverse effects and may require lower than usual doses.

**Elderly (65 years of age and older):**

No dosage reduction is required 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, and therefore UKUZID should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4).

**Renal impairment:**

No dosage reduction of UKUZID is required 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.

**Paediatrics**

The age/youth of the patient influences the rate of medicine metabolism: 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 blood levels that are considered effective to produce bactericidal activity.

**Method of administration**

For oral use.

UKUZID should ideally be taken on an empty stomach (i.e. at least 30 minutes before a meal or 2 hours after a meal).

UKUZID may be taken with meals if gastrointestinal irritation occurs, but oral absorption may be reduced.

The absorption of isoniazid may be delayed or decreased by aluminium-containing antacids. UKUZID 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.**

UKUZID is contraindicated in:

- hypersensitivity to isoniazid, ethionamide, pyrazinamide, niacin, other chemically-

related medicines or to any of the inactive ingredients of UKUZID (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 UKUZID 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*

Severe and sometimes fatal hepatitis in patients of advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extra-pulmonary tuberculosis may occur with UKUZID therapy. If signs and symptoms of hepatotoxicity occur, treatment should be promptly discontinued.

All patients should have baseline liver function tests performed and repeated at regular intervals for the duration of treatment. If serum ALT rises to more than three times normal, or if there is any increase in bilirubin, treatment with UKUZID should be withdrawn. Special precautions will be required in patients with impaired liver function. Any deterioration in liver function in these patients is an indication for discontinuing treatment.

UKUZID should not be given to patients who have experienced severe adverse reactions including medicine-induced liver disease. Care should be taken in giving UKUZID to patients suffering from convulsive disorders, diabetes mellitus, chronic alcoholism, or impaired liver or kidney function or to patients taking other potentially hepatoxic medicines. If symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea develop, UKUZID should be discontinued immediately.

*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 (see section 4.8). Patients should be advised of these signs and symptoms and should be 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.
The treatment with UKUZID 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 treatment (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 without an evident rash. If such signs or symptoms are present, the patient should be advised to consult their doctor immediately.
Treatment with UKUZID should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Isoniazid, as in UKUZID, should be given with caution in patients suffering from convulsive disorders and diabetes mellitus, and patients with a history of psychosis.

Isoniazid, as in UKUZID, 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 worsen in these patients, UKUZID 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.

The usual dose of 10 - 15 mg daily, with a maximum of 30 mg/day of pyridoxine during treatment with UKUZID should be prescribed to patients at risk of neuropathy or pyridoxine deficiency, including those in the above-mentioned high risk groups.

Periodic eye examinations during UKUZID therapy is recommended.
Isoniazid in combination with other anti-tuberculosis medicines causes optic neuritis which may lead to optic atrophy and blindness (see section 4.8).

**4.5 Interaction with other medicines and other forms of interaction**

*Inhibition of CYP450*

Adverse reactions, including increased toxicity (as the active ingredient isoniazid can inhibit the hepatic metabolism of a number of medicines), have occurred when isoniazid as in UKUZID has been given with anti-epileptics such as phenytoin, primidone, carbamazepine, and ethosuximide, with benzodiazepines, such as diazepam or triazolam and other medicines such as chlorzoxazone, warfarin and theophylline.

Concomitant benzodiazepine (diazepam/carbemazepine) and isoniazid, as in UKUZID, therapy has been reported to result in an increased risk of benzodiazepine toxicity (sedation, respiratory depression, etc).

Isoniazid as in UKUZID has been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity at isoniazid doses of 200 mg daily or more. The concurrent use is not recommended unless the effects

can be closely monitored and suitable downward dosage adjustments made (a reduction between one-half or one-third was reported effective).

*Other interactions*

Concurrent administration of UKUZID and rifampicin may lead to a higher incidence of hepatotoxicity.

Increased central nervous system adverse effects have occurred when UKUZID is given with cycloserine or disulfiram. Hepatotoxic reactions

have been reported when paracetamol is given concurrently with Isoniazid as in UKUZID, while chronic alcoholism increases the risk of

isoniazid induced hepatitis.

When isoniazid is given to patients who inactivate it slowly or to patients receiving paraminosalicyclic acid concurrently, plasma concentrations may be enhanced, and adverse effects are more likely to occur.

Prednisolone may increase hepatic metabolism and/or excretion of isoniazid, as in UKUZID.

The absorption and blood concentrations of isoniazid may be delayed or decreased by aluminium-containing antacids. UKUZID should therefore be taken/administered at least 1 hour before taking antacids (see section 4.2).

UKUZID may reduce the therapeutic effects of levodopa.

Co-administration of isoniazid, as in UKUZID, with itraconazole or ketoconazole may result in significant decreases in either medicine's serum concentrations and will result in therapeutic failure. Co-administration should be well monitored, and dosage increased may be required.

Because the clearance of isoniazid (as in UKUZID) was found doubled when zalcitabine was given in HIV-positive patients, co-administration of UKUZID and zalcitabine should be monitored to ensure isoniazid effectiveness.
There may be an increased risk of distal sensory neuropathy when isoniazid, as in UKUZID, is used in patients taking stavudine (d4T).

*Interactions with food*
Isoniazid, the active ingredient in UKUZID, is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), and can therefore reduce tyramine and histamine metabolism, causing symptoms such as headache, conjunctival irritation, sweating, palpitations, severe flushing, tachycardia, tachypnoea, and hypotension.

Patients should be advised to avoid ingesting foods rich in tyramine and/or histamine during treatment with UKUZID, 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**

Women of child-bearing potential should be advised to avoid becoming pregnant while on treatment with UKUZID. Use of isoniazid, as in UKUZID, 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.

**Pregnancy**

Isoniazid, as in UKUZID, crosses the placenta. The safe use of UKUZID 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**

Isoniazid, as in UKUZID, should be avoided during lactation (see section 4.3), as it passes into breast milk. The safety of infants receiving breast milk of mothers on treatment with UKUZID 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:**

UKUZID may affect the ability to drive or use machinery.

Since adverse reactions such as convulsions have been reported in patients receiving isoniazid, as in UKUZID, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that UKUZID does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

## 4.8 Undesirable effects

### a). Tabulated summary of adverse reactions

| System Organ Class | Frequency | Side effects |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent<br>Frequency unknown | Blood dyscrasias<br>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 mood |
| Nervous system disorders | Frequent<br>Less frequent<br>Frequency unknown | Peripheral neuritis<br>Neurotoxicity<br>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 pancreatitis acute, vomiting and other gastrointestinal effects |
| Hepato-biliary disorders | Frequent<br><br><br><br><br><br>Less frequent<br>Frequency unknown | Hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness), hepatitis<br><br>Hepatitis<br>Acute hepatic failure, liver injury, jaundice |
| Skin and subcutaneous tissue disorders | Less frequent<br><br>Frequency unknown | Toxic epidermal necrolysis, eosinophilia systemic symptoms<br>Erythema multiforme, Stevens-Johnson syndrome |
| Musculoskeletal, connective tissue and bone 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 | Hepatic enzyme increased |

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

**b) Description of selected adverse reactions**

*Ear and labyrinth disorders*

There have been reports of deafness, tinnitus, vertigo 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 adverse 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 linked to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

*Nervous system disorders*

Hyperreflexia may be troublesome with an isoniazid dosage 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 with isoniazid.

*Miscellaneous*

On the cessation of treatment, withdrawal symptoms such as include headache, insomnia, excessive dreaming, irritability and nervousness may occur.

**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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

## 4.9 OVERDOSE

**Signs and symptoms:**

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

**Management of overdose:**

Treatment for significant overdosage 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

Pharmacological classification: A.20.2.3. Tuberculostatics

Pharmacotherapeutic Group: Anti-Infective For Systemic Use

ATC Code: J04AC01

**Mechanism of action**

Isoniazid is a synthetic, bactericidal antitubercular medicine, which is active against many mycobacteria, 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 and completely 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. Isoniazid is widely distributed to all fluids and tissues, including cerebrospinal fluid (CSF), pleural and ascitic fluids, skin, sputum, saliva, lungs, muscle, and caseous tissue. It crosses the placenta and is excreted in the breast milk (see section 4.6).

**Biotransformation**

The primary metabolic route is acetylation.

**Metabolic reactions:**

Acetylation, hydrolysis and glycine conjugation, hydrazone formation, and n-methylation; acetylation is polymorphic and two groups of acetylators have been identified, rapid and

slow acetylators. The rate of hydrolysis is more rapid in the rapid acetylators than in the slow ones. The metabolites formed include acetyl isoniazid, isonicotinic acid, isonicotinuric acid, isonicotinoyl-hydrazones of pyruvic and glutaric acids, and n-methylisoniazid.

**Elimination:**

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

### 5.3 Preclinical safety data

Not applicable.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Colloidal Silicon Dioxide

Copovidone

Crospovidone

Microcrystalline Cellulose

Polyethylene glycol 6000

Povidone (K-30/BASF)

Stearic acid

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store at a temperature below 30 °C. Protected from light and moisture.

### 6.5 Nature and contents of container

Amber PVC/PVDC blister strips of 10 tablets. 10 or 28 blister strips per printed outer carton.

Not all packs may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House, Steenberg Office Park

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7945, South Africa

## 8. REGISTRATION NUMBER

A57/20.2.3/0155

## 9. DATE OF FIRST AUTHORISATION

18 April 2023

## 10. DATE OF REVISION OF THE TEXT