PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AFARIS PAED 75/50 (dispersible tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AFARIS PAED 75/50

Each dispersible tablet contains rifampicin 75 mg and isoniazid 50 mg.

Sugar free

Contains sweetener – aspartame 3,13 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AFARIS PAED 75/50

Brick red mottled, 9,5 mm circular, uncoated biconvex tablets having deep score on one side and plain surface on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AFARIS PAED 75/50 is indicated for pulmonary tuberculosis in children.

4.2 Posology and method of administration

Posology

AFARIS PAED 75/50 is recommended in the continuation phase of the treatment of pulmonary tuberculosis. During this phase **AFARIS PAED 75/50** should be administered on a continuous daily basis.

The total dosage requirement is as follows:

	Daily	Maximum daily dose
Rifampicin	15 mg/kg (10 to 20)	600 mg
Isoniazid	10 mg/kg (7 to 15)	300 mg

The daily dosage is calculated from the recommended daily requirement given above and to closely regulate dosage according to body mass.

Table 1: Dosage calculation	
Number of tablets	**For infants/children with body mass (kg)**
1 tablet	4-7
2 tablets	8-11
3 tablets	12-15
4 tablets	16-24
Adult dosages recommended	25 +

Method of administration

Oral use

The tablets can either be dispersed in as little as 5 ml of water, or chewed, and should preferably be taken on an empty stomach as a single dosage.

AFARIS PAED 75/50 should be taken at least 1 hour before aluminium containing antacids are used.

4.3 Contraindications

- **AFARIS PAED 75/50** is contra-indicated in patients with a history of hypersensitivity to rifamycins or isoniazid and other chemically related medicines or to any of the excipients of **AFARIS PAED 75/50** listed in Section 6.1.
- It is contra-indicated in the presence of jaundice or in patients with hepatic impairment.
- **AFARIS PAED 75/50** is contra-indicated in patients with impaired renal or liver function, diabetes mellitus, chronic alcoholism, a history of gout, patients suffering from convulsive disorders and porphyria.

- The concomitant use of **AFARIS PAED 75/50** and nevirapine is contra-indicated.
- **AFARIS PAED 75/50 i**s contra-indicated when given concurrently with the combination of saquinavir/ritonavir (see Section 4.5).
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Rifampicin:

- Patients with impaired liver function should not be given **AFARIS PAED 75/50**. Should **AFARIS PAED 75/50** be the only treatment option in these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase ALT and serum glutamic oxaloacetic transaminase AST, should be carried out prior to therapy and repeated every two to four weeks during therapy. If signs of hepatocellular damage occur, **AFARIS PAED 75/50** should be withdrawn (see section 4.3). A report showing a moderate rise in bilirubin and/or transaminase level in itself is not an indication for interruption of treatment. This decision should rather be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.
- Liver function should be checked before and during treatment with **AFARIS PAED 75/50** and special care should be taken in alcoholic patients or those with pre-existing liver disease should **AFARIS PAED 75/50** be the only treatment option (see Section 4.3). Dosage adjustment is necessary where there is evidence of hepatic function impairment and treatment may need to be changed where there is more serious liver toxicity. Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders (see section 4.3). If other serious complications arise e.g. renal failure or haemolytic anaemia, **AFARIS PAED 75/50** should be stopped and never restarted.
- Because of the possibility of immunological reactions including anaphylaxis occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens since these reactions may occur.
- Patients should be advised that discolouration of the urine, faeces, saliva, sputum, sweat and tears may occur. Patients should be further advised that soft contact lenses may be permanently stained.
- Rifampicin has enzyme induction properties that can enhance the metabolism of endogeneous substrates including adrenal hormones, thyroid hormones and vitamin D.

Isoniazid:

- Use of isoniazid as contained in **AFARIS PAED 75/50** is contra-indicated in patients with chronic liver disease or renal dysfunction. Should **AFARIS PAED 75/50** be the only treatment option, these patients should be carefully monitored. Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may even develop after many months of treatment. The risk of developing hepatitis is age related. Patients should be monitored for prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, treatment should be discontinued promptly. Continued use of **AFARIS PAED 75/50** in these cases may cause a more severe form of liver damage and may exacerbate convulsive disorders (see Section 4.3).
- Liver function should be checked before and during treatment with **AFARIS PAED 75/50** and special care should be taken in alcoholic patients or those with pre-existing liver disease should **AFARIS PAED 75/50** be the only treatment option (see Section 4.3). Periodic eye examinations during **AFARIS PAED 75/50** treatment have been suggested.
- Vitamin B6 in a dose of 15 to 50 mg per day should be administered with isoniazid therapy to minimise adverse reactions in malnourished patients and those predisposed to neuropathy.
- Use of isoniazid should be carefully monitored in patients with slow acetylators status (see section 5.2), history of psychosis, history of peripheral neuropathy and HIV infection.

Excipients

AFARIS PAED 75/50 contains 3,13 mg aspartame in each tablet.

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction~~s~~ with other medicines and other forms of interaction

Rifampicin

The concomitant use of **AFARIS PAED 75/50** and nevirapine is contraindicated.

When **AFARIS PAED 75/50** is given concomitantly with the combination of saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of **AFARIS PAED 75/50** with saquinavir/ritonavir is contraindicated.

Halogenated inhalation anaesthetics, when given concomitantly with rifampicin has been reported to increase the hepatotoxicity of both rifampicin and isoniazid.

Ketaconazole has been reported to diminish the serum concentrations of both medicines when given concomitantly.

Rifampicin has liver-enzyme inducing properties and may reduce the activity of azathioprine, chloramphenicol, cimetidine, clofibrate, corticosteroids, coumarin anticoagulants, ciclosporin, dapsone, diazepam, doxycycline, fluconazole, haloperidol, hexobarbitone, itraconazole, ketoconazole, methadone, oral hypoglycaemic medicines, phenytoin, quinine, sulphasalazine, thyroid hormones, theophylline, zidovudine, and several cardiovascular medicines including beta-adrenoceptor blocking medicines, digoxin, and antidysrhythmic medicines such as disopyramide, lorcainide, mexiletine, propafenone, quinidine, tocainide, and verapamil and other calcium-channel blocking medicines, oral contraceptives, narcotics, analgesics and barbiturates.

It may be necessary to adjust the dosage of these medicines if they are given concurrently with **AFARIS PAED 75/50.** Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during therapy with **AFARIS PAED 75/50**.

Magnesium trisilicate, aluminium hydroxide or sodium bicarbonate reduce the bioavailability of **AFARIS PAED 75/50**.

Alcohol

Concurrent daily consumption of alcohol may increase the risk of rifampicin-induced hepatotoxicity and increased metabolism of rifampicin. Dosage adjustments of rifampicin may be necessary and patients should be monitored closely for signs of hepatotoxicity.

Corticosteroids

Concurrent use with rifampicin may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a decrease in corticosteroid plasma concentration. Dosage adjustment of the corticosteroid may be required.

Anti-retroviral medicines

Rifampicin as contained in **AFARIS PAED 75/50** can induce the metabolism of zidovudine, the NNRTI's delavirdine, efavirenz and nevirapine (see section 4.3) and the HIV-protease inhibitors, resulting in subtherapeutic plasma concentrations. Furthermore, HIV-protease inhibitors inhibit the metabolism of rifampicin resulting in elevated plasma-rifampicin concentrations and an increased incidence of adverse effects.

Rifampicin as contained in **AFARIS PAED 75/50** decreases the concentration of efavirenz and it is recommended that the dose of efavirenz be increased in patients weighing more than 60 kg; no dose modification is required for rifampicin as contained in **AFARIS PAED 75/50**.

Isoniazid:

Isoniazid is known to inhibit and rifampicin to induce certain cytochrome P-450 enzymes. In general, the impact of the competing effects of rifampicin and isoniazid on the metabolism of medicines that undergo biotransformation through the affected pathways is unknown. Therefore, caution should be used when prescribing **AFARIS PAED 75/50** with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, the dosages of these medicines metabolised by these enzymes may require adjustment when starting or stopping **AFARIS PAED 75/50**.

As isoniazid is an inhibitor of hepatic metabolism of medicines it may therefore enhance the effects of some medicines taken concomitantly.

Adverse reactions have occurred when isoniazid has been given with phenytoin, primidone, carbamazepine, ethosuximide, benzodiazepines such as diazepam or triazolamand warfarin. Appropriate adjustments of the doses of the anticonvulsants should be made.

Theophylline plasma concentrations can be increased.

Increased central nervous system adverse effects have occurred when isoniazid is given with cycloserine and disulfiram.

Isoniazid can be affected by compounds such as alcohol, alfentanil, aminosalicylic acid, corticosteroids, ketoconazole, propranolol and large doses of pyridoxine.

Oral absorption of isoniazid as contained in **AFARIS PAED 75/50** is reduced by aluminium-containing antacids; **AFARIS PAED 75/50** should be given at least 1 hour before the antacid.

Concurrent use of **AFARIS PAED 75/50** with chronically used paracetamol, alcohol and other hepatotoxic medicines may increase the potential for isoniazid induced hepatotoxicity.

Anti-retroviral medicines

The clearance of isoniazid is approximately doubled when given concomitantly with zalcitabine.

AFARIS PAED 75/50 should be used with caution with stavudine and zalcitabine as stavudine, zalcitabine and isoniazid have been associated with causing peripheral neuropathy. The use of **AFARIS PAED 75/50** with stavudine has been reported to increase the incidence of peripheral neuropathy.

Food interactions:

Due to some monoamine oxidase inhibiting activity of isoniazid, 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). Tyramine- and histamine-containing foods should be avoided by patients receiving **AFARIS PAED 75/50**.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy has not been established (see section 4.3).

Breastfeeding

Safety and efficacy in lactation has not been established (see section 4.3).

Rifampicin and isoniazid cross the placenta and both are excreted in breastmilk.

Fertility

No data is available on the effect on fertility

4.7 Effects on ability to drive and use machines

AFARIS PAED 75/50 may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Rifampicin

MedDRA System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Blood dyscrasias, unusual bleeding or bruising, thrombocytopenia, purpura, haemolysis, eosinophilia, leucopenia, haemolytic anaemia.
Immune system disorders	Less frequent	Anaphylaxis and shock.
Nervous system disorders	Less frequent	Confusion, drowsiness, headache, ataxia, dizziness, peripheral neuropathy and generalised numbness.
Eye disorders	Less frequent	Blurred vision, eye irritation.
Ear and labyrinth disorders	Less frequent	Transient hearing loss
Respiratory, thoracic and mediastinal disorders	Unknown	Pulmonary fibrosis, pneumonitis, shortness of breath and wheezing.
Gastrointestinal disorders	Frequent	Nausea, vomiting, anorexia, diarrhoea and epigastric distress.
	Less frequent	Pseudomembranous colitis.
	Unknown	Ulcerative colitis, gastrointestinal bleeding,
Hepatobiliary disorders	Less frequent	Hepatitis (which may be fatal), hepatitis prodromal symptoms which include loss of appetite, nausea or vomiting, unusual tiredness or weakness. A rise in serum transaminase levels.
Skin and subcutaneous tissue disorders	Frequent	Cutaneous reactions, which typically consist of flushing and itching, with or without a rash.
	Less frequent	More serious hypersensitivity cutaneous reactions, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme including Stevens-Johnson syndrome and vasculitis, drug reaction with eosinophilia and system symptoms

		(DRESS).
Musculoskeletal and connective tissue disorders	Frequent	Muscle weakness and myopathy.
Renal and urinary disorders	Less frequent	Interstitial nephritis, renal failure.
Reproductive system and breast disorders	Less frequent	Disturbances of the menstrual cycle, reduction of effectiveness of oral contraceptives.
General disorders and administration site conditions	Frequent	Reddish-orange to reddish-brown discolouration of the urine, faeces, saliva, sputum, sweat and tears. Soft contact lenses may be permanently stained.
	Less frequent	Intermittent, interrupted or repeated treatment of rifampicin may increase the chance of a patient developing flu syndrome, a febrile reaction with influenza-like symptoms, fungal overgrowth i.e. sore mouth or tongue.
	Unknown	Oedema

Isoniazid

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Various haematological disturbances including eosinophilia, agranulocytosis, thrombocytopenia and various anaemias
Immune system disorders	Less frequent	Hypersensitivity reactions including various skin eruptions, fever, lymphadenopathy and

		vasculitis, lupus-like reactions.
Metabolism and nutritional disorders	Less frequent	Hyperglycaemia, metabolic acidosis
Psychiatric disorders	Less frequent	Psychotic reactions (characterised by delusions, hallucinations and confusion), memory impairment.
Nervous system disorders	Frequent	Peripheral neuropathy.
	Less frequent	Polyneuritis associated with paraesthesia, muscle weakness, loss of tendon reflexes, convulsions, increase in frequency of fits in epileptic patients, ataxia.
Eye disorders	Less frequent	Optic neuritis (blurred vision or loss of vision, with or without eye pain).
Ear and labyrinth disorders	Less frequent	Vertigo
Gastrointestinal disorders	Frequent	Diarrhoea, nausea and vomiting, stomach pain, constipation, dry mouth, pancreatitis.
Hepatobiliary disorders	Frequent	Hepatitis (sometimes fatal), hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness). Transient increases in liver enzymes.
Skin and subcutaneous tissue disorders	Less frequent	Skin reactions, acne, pellagra, Stevens-Johnsons syndrome, exfoliative dermatitis.
	Unknown	alopecia, urticaria
Musculoskeletal and connective tissue disorders	Unknown	A rheumatic syndrome, hyperreflexia
Renal and urinary disorders	Less frequent	Urinary retention
Reproductive system and breast disorders:	Less frequent	Gynaecomastia

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose

Rifampicin: Acute overdosage with rifampicin has produced a characteristic bright-red discolouration of the skin and mucous membranes, sometimes referred to as "the red-man syndrome", mental obtundation, periorbital or facial oedema and generalised pruritus.

Isoniazid: Symptoms are more likely to be related to isoniazid. These include hyperglycaemia and metabolic acidosis, slurred speech, convulsions, coma, hallucinations, respiratory distress, central nervous system depression; fatalities can occur.

Treatment of overdose

General: In cases of overdosage with **AFARIS PAED 75/50** activated charcoal slurry into the stomach may help absorb any remaining medicine from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Intensive supportive measures should be instituted and individual symptoms treated as they arise. Further treatment is symptomatic and supportive.

If acute overdose is suspected, even in asymptomatic patients, the administration of intravenous pyridoxine (vitamin B6) should be considered. In patients with seizures not controlled with pyridoxine, anticonvulsant therapy should be administered. Sodium bicarbonate should be given to control metabolic acidosis. Haemodialysis is advised for refractory cases: if this is not available, peritoneal dialysis can be used along with forced diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.3 Tuberculostatic

Antimicrobial medicine

Rifampicin and isoniazid are bactericidal antituberculosis medicines which both act against tuberculosis. Isoniazid is bactericidal for rapidly dividing micro-organisms and bacteriostatic for resting bacilli.

Rifampicin

Rifampicin inhibits the growth of *Mycobacterium tuberculosis.* Rifampicin binds to the β subunit of DNA-dependent RNA polymerase (rpoB) to form a stable medicine-enzyme complex. Rifampicin binding suppresses chain formation in RNA synthesis.

Isoniazid

Isoniazid is bactericidal and the mechanism of action is by entering the bacilli through passive diffusion. Isoniazid then inhibits the biosynthesis of mycolic acids which are essential components of the cell wall of *Mycobacterium tuberculosis*, leading to bacterial cell death.

5.2 Pharmacokinetic properties

Rifampicin

Absorption

Rifampicin is readily absorbed from the gastrointestinal tract with an oral bioavailability of 68 % for a 150 mg dose; Cmax of 2,1 µg/mL and tmax of 1,5 – 2,0 hours. Absorption of rifampicin is reduced by about 30 % when ingested with food.

Distribution

Rifampicin is widely distributed throughout the body and has good penetration into many tissues, but levels in CNS reach only approximately 5 % of those in plasma. Rifampicin is about 85 % protein bound.

Metabolism

Rifampicin is metabolised by microsomal β-esterases and cholinesterases that remove the acetyl group at position 25, resulting in 25-O-desacetyl rifampicin. Rifampicin is also metabolised by hydrolysis to 3-

formyl rifampicin. A major pathway for rifampicin elimination is CYP3A. Due to autoinduction, rifampicin reduces its own area under concentration-time curve (AUC) with repeated administration.

Elimination

The half-life of rifampicin ranges from 2 – 5 hours. Rifampicin and its metabolites are excreted by bile and eliminated via faeces, with urine elimination accounting for one–third and less of metabolites.

Isoniazid

Absorption

Isoniazid is readily absorbed from the gastrointestinal tract with an oral bioavailability of 100 % for a 300 mg dose; Cmax of 3,4 – 7,4 µg/mℓ for rapid acetylators and C_{max} of 5,2 – 9 µg/mℓ for slow acetylators; t_{max} of 1,1 ± 0,5 hours for rapid acetylators and 1,1 ± 0,6 hours for slow acetylators. Absorption of isoniazid is decreased by food and antacids.

Distribution

The ratio of isoniazid in the epithelial lining fluid to that in plasma is 1 – 2 and for CSF is 0,9. Approximately 10 % of isoniazid is protein bound.

Metabolism

Isoniazid is metabolised by hepatic arylamine N-acetyltransferase type 2 (NAT2). Isoniazid is N-acetylated to N-acetylisoniazid in reactions that uses acetyl-coA. Acetylisoniazid is excreted by the kidney; acetylisoniazid can also be converted to acetylhydrazine and then to hepatoxic metabolites by CYP2E1. Alternatively, acetylhydrazine may be further acetylated by NAT2 to diacetylhydrazine, which is non-toxic. Isoniazid clearance in patients is classified as one of two phenotypic groups: “slow” acetylators and “fast” acetylators. Rapid acetylators will remove acetylhydrazine while slower acetylators or induction of CYP2E1 will lead to more toxic metabolites.

Elimination

The half-life of isoniazid ranges from 1,1 ± 0,1 hours for rapid acetylators and 3,1 ± 1,1 for slow acetylators. From 75 – 95 % of a dose of isoniazid is excreted in the urine within 24 hours, mostly as acetylisoniazid and isonicotinic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, raspberry flavour, magnesium stearate.

Contains aspartame.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

AFARIS PAED 75/50: 24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture and light.

Keep the aluminium sachet in the HDPE container until required for use.

Keep the blister in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE Container:

Tablets are packed in a transparent, self-sealing LDPE polybag and further packed in a silver coloured triple laminated aluminium sachet (LDP/PET/AL), kept in a white plastic container (HDPE), which is sealed at the mouth with an aluminium tagger and is closed with a white HDPE screw-on lid. Pack sizes include 100 tablets.

Alu-alu strip pack:

Tablets are packed in silver-metallic coloured aluminium foil (soft tempered) laminated with low density polyethylene film as the lidding and forming material. The blister is packed in a pre-printed carton. Pack sizes include 28, 56, 84 and 100 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd.

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Bassonia Estate Office Park (East)

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Alberton

Gauteng

8. REGISTRATION NUMBER:

51/20.2.3/0852

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2018

10. DATE OF REVISION OF THE TEXT

26 July 2024