PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AKURIT KID 75/50 ODT, dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each AKURIT KID 75/50 ODT dispersible tablet contains 75 mg rifampicin and 50 mg isoniazid.

AKURIT KID 75/50 ODT dispersible tablets are sugar free. Contains sweetener, aspartame 2,0 mg and Saccharin Sodium 2,0 mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablets.

AKURIT KID 75/50 ODT dispersible tablets are brick red coloured, flat faced bevelled edged, mottled, circular uncoated tablet plain on both sides with characteristic flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AKURIT KID 75/50 ODT is indicated for pulmonary tuberculosis in children.

4.2 Posology and method of administration

Posology

AKURIT KID 75/50 ODT is recommended in the continuation phase of the treatment of pulmonary tuberculosis. During this phase AKURIT KID 75/50 ODT 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 dispersible tablets	**For infants/children with body mass (kg)**
1 dispersible tablet	4-7
2 dispersible tablets	8-11
3 dispersible tablets	12-15
4 dispersible tablets	16-24
Adult dosages recommended	25 +

Method of administration

The dispersible 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, orally.

AKURIT KID 75/50 ODT should be taken at least 1 hour before aluminium containing antacids are used (see section 4.5).

For missed doses, the missing dose can be taken as soon as possible, and then take the next dose at its regular time. However, if the next dose is due within 6 hours, do not take the missed dose. Wait and take the next dose at the regular time. A double dose should not be taken to make up for a forgotten tablet.

4.3 Contraindications

- Hypersensitivity or a history of hypersensitivity to rifampicin, other rifampicins, isoniazid or to any of the ingredients of AKURIT KID 75/50 ODT
- The presence of jaundice or in patients with hepatic impairment
- In patients with moderate to severe renal or hepatic impairment, diabetes mellitus, chronic alcoholism, a history of gout, patients suffering from convulsive disorders and porphyria
- Concomitant use of AKURIT KID 75/50 ODT and nevirapine is contraindicated (see section 4.5)
- 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:

Hepatic impairment

Patients with impaired liver function should not be given AKURIT KID 75/50 ODT. Should AKURIT KID 75/50 ODT 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, AKURIT KID 75/50 ODT 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 AKURIT KID 75/50 ODT and special care should be taken in alcoholic patients or those with pre-existing liver disease should AKURIT KID 75/50 ODT 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).

Discoloration of bodily fluids

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.

Other

If other serious complications arise e.g. renal failure or haemolytic anaemia (see haematological toxicity), AKURIT KID 75/50 ODT should be stopped and never restarted.

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D.

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.

Hypersensitivity

Rifampicin may cause a hypersensitivity syndrome including ‘flu-like’ symptoms and/or organ manifestation. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity do appear (e.g.

thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure). AKURIT KID 75/50 ODT dispersible tablets should immediately be discontinued. Such patients should not be re-challenged with rifampicin. If rifampicin therapy is temporarily discontinued, rifampicin should be restarted carefully at a reduced dose, and with close monitoring. In this situation, AKURIT KID 75/50 ODT dispersible tablets should not be used.

Haematological toxicity

Since rifampicin treatment has been associated with haemolytic anaemia, leukopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with AKURIT KID 75/50 ODT dispersible tablets. In case of severe haematological disturbances AKURIT KID 75/50 ODT dispersible tablets must be discontinued.

Medicine interactions

Rifampicin is a strong inducer of hepatic medicine metabolism, as a result, AKURIT KID 75/50 ODT dispersible tablets may reduce exposure and efficacy of many therapeutic medicines, including antiretrovirals, antiepileptic medicines, immunosuppressants and warfarin (see section 4.5).

Porphyria

AKURIT KID 75/50 ODT dispersible tablets should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Isoniazid:

Hepatic and renal impairment

Use of isoniazid as contained in AKURIT KID 75/50 ODT is contraindicated in patients with chronic liver disease or renal dysfunction. Should AKURIT KID 75/50 ODT 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 AKURIT KID 75/50 ODT in these cases may cause a more severe form of liver damage (see section 4.3).

Liver function should be checked before and during treatment with AKURIT KID 75/50 ODT and special care should be taken in alcoholic patients or those with pre-existing liver disease, should AKURIT KID 75/50 ODT be the only treatment option (see section 4.3).

Patients with renal impairment, particularly those who are slow acetylators (see sections 4.2 and 5.2) may be at increased risk for isoniazid adverse effects such as peripheral neuropathy and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see below) should be given to avoid neurotoxicity.

Use of isoniazid should be carefully monitored in patients with a history of psychosis, history of peripheral neuropathy and HIV infection.

Peripheral neuropathy

Periodic eye examinations during AKURIT KID 75/50 ODT treatment have been suggested as isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on antiretroviral therapy (ART), Vitamin B_6 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.

Cross-sensitivity

Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medicines may also be hypersensitive to isoniazid.

Diabetes Mellitus

Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

Rifampicin/Isoniazid combination:

Epilepsy and psychotic disorders

AKURIT KID 75/50 ODT dispersible tablets should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

Nephrotoxicity

AKURIT KID 75/50 ODT dispersible tablets should be discontinued in case of clinical signs of nephrotoxicity.

Treatment with corticosteroids

AKURIT KID 75/50 ODT dispersible tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Laboratory monitoring

Full blood count and liver function should be monitored prior to and at regular intervals during treatment with AKURIT KID 75/50 ODT dispersible tablets.

Aspartame

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 with other medicines and other forms of interaction

Rifampicin

The concomitant use of AKURIT KID 75/50 ODT and nevirapine is contraindicated (see section 4.3).

When AKURIT KID 75/50 ODT is given concomitantly with the combination of saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant

use of AKURIT KID 75/50 ODT with saquinavir/ritonavir is contraindicated (see section 4.3).

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

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

Rifampicin is a very potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as of glucuronidation and the P-glycoprotein transport system. Administration of rifampicin with medicines that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered medicines. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be considered when co-treating with other medicines. To maintain optimum therapeutic blood levels, dosages of medicines metabolised by these enzymes may require adjustment when starting or stopping the concomitant administration of AKURIT KID 75/50 ODT dispersible tablets.

As rifampicin has liver-enzyme inducing properties and may reduce the activity of azathioprine, chloramphenicol, cimetidine, clofibrate, corticosteroids, warfarin, 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. Thus, it may be necessary to adjust the dosage of these medicines if they are given concurrently with AKURIT KID 75/50 ODT.

Oral contraceptives

Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during therapy with AKURIT KID 75/50 ODT.

Minerals

Magnesium trisilicate, aluminium hydroxide or sodium bicarbonate reduce the bioavailability of AKURIT KID 75/50 ODT.

Alcohol

Concurrent daily consumption of alcohol may increase the risk of rifampicin-induced hepatotoxicity and increased the 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 AKURIT KID 75/50 ODT 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 AKURIT KID 75/50 ODT 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 AKURIT KID 75/50 ODT.

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 AKURIT KID 75/50 ODT 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 AKURIT KID 75/50 ODT.

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 triazolam and 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.

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

Antacids

Oral absorption of isoniazid as contained in AKURIT KID 75/50 ODT is reduced by aluminium-containing antacids; AKURIT KID 75/50 ODT should be given at least 1 hour

before the antacid.

Anti-retroviral medicines

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

AKURIT KID 75/50 ODT should be used with caution with stavudine and zalcitabine as stavudine, zalcitabine and isoniazid have been associated with causing peripheral neuropathy. The use of AKURIT KID 75/50 ODT 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 histamine- or tyramine-containing foods (cheese, FISH, red wine) may occur. Diamine oxidase may also be inhibited, causing exaggerated response (e.g. headache, sweating, palpitations, flushing, hypotension) to foods containing histamine. Tyramine- and histamine-containing foods should be avoided by patients receiving AKURIT KID 75/50 ODT.

Combination Rifampicin/Isoniazid

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Therefore, it may increase exposure to medicines mainly eliminated through either of these pathways. However, when co-treating with rifampicin, as when using AKURIT KID 75/50 ODT

dispersible tablets, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. Insofar as it has been investigated, the net effect of rifampicin and isoniazid on medicine clearance will be an increase due to rifampicin rather than a decrease due to isoniazid. Concurrent use of isoniazid with other hepatotoxic or neurotoxic medicines may increase the hepatotoxicity and neurotoxicity of isoniazid and should be avoided.

Mainly due to rifampicin, AKURIT KID 75/50 ODT dispersible tablets may interact with a very large number of other medicines, primarily by reducing the exposure to co-administered medicines, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic medicines, no interaction data with rifampicin are available. However, clinically significant reductions in medicine exposure may occur. Whenever co-prescribing any medicine together with AKURIT KID 75/50 ODT dispersible tablets, the possibility of a medicine-medicine interaction should be considered. The following list of medicine interactions with AKURIT KID 75/50 ODT dispersible tablets is not exhaustive but is a selection of interactions of putative importance. The scope of the table is largely based on the WHO Essential Medicines List.

Medicines by Therapeutic Area	**Interaction**	**Recommendations concerning coadministration**
INFECTION *Antiretrovirals*		
Nucleoside analogues Zidovudine / rifampicin	Zidovudine AUC ↓ 47 %	The clinical significance of the

		lowered zidovudine exposure is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.
Stavudine Didanosine Lamivudine Emtricitabine	No interaction expected	No dose adjustment required.
Tenofovir alafenamide/ emtricitabine/ rifampicin	Interaction not studied. Coadministration of rifampicin, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Coadministration is not recommended.
Tenofovir disoproxil fumarate / rifampicin	Tenofovir AUC ↓ 13 %	No dose adjustment required.
Abacavir / rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.
Non-nucleoside	Efavirenz AUC ↓ 26 %	When co-treating

analogues Efavirenz / rifampicin		with AKURIT KID 75/50 ODT dispersible tablets, it may be considered to increase the efavirenz dose to 800 mg q.d.
Nevirapine / rifampicin	AUC ↓ 58 %	Neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established. Concomitant use of AKURIT KID 75/50 ODT dispersible tablets and nevirapine is not recommended.
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of AKURIT KID 75/50 ODT dispersible tablets and etravirine should be avoided.
Protease inhibitors (PI) Rifampicin/ Fosamprenavir Saquinavir Indinavir Ritonavir Lopinavir	Protease inhibitor (PI) exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to compensate for by	AKURIT KID 75/50 ODT dispersible tablets must not be co-administered with HIV protease inhibitors (see section 4.3).

Atazanavir Tipranavir Darunavir	increasing doses of the PIs, or an increase in ritonavir boosting, have been ill tolerated with a high rate of hepatotoxicity.	
Others:		
Integrase inhibitors Raltegravir / rifampicin	Raltegravir AUC ↓ 40 %	Co-treatment should be avoided. If deemed necessary, consider an increase of the raltegravir dose to 600 mg b.i.d.
Dolutegravir / rifampicin	Dolutegravir AUC ↓ 54 %	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with AKURIT KID 75/50 ODT dispersible tablets in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
Elvitegravir/cobicistat/ rifampicin	Coadministration has not been studied. Rifampicin is a potent inducer of CYP450 metabolism and may	Coadministration is contraindicated.

	cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect.	
Maraviroc / rifampicin	Maraviroc AUC ↓ 63 %	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d.
Antivirals Hepatitis C-infection		
Daclatasvir Elbasvir/granzoprevir Glecaprevir/ P=pibrentasvir Ledipasvir/sofosbuvir Ombitasvir/paritaprevir /ritonavir (with or without dasabuvir) Simeprevir Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/ Rifampicin Isoniazid	Rifampicin: Coadministration has not been studied but is expected to decrease concentrations of these Hepatitis C virus(HCV)-antivirals due to induction of CYP3A4 by rifampicin and hence to reduce their therapeutic effect. Isoniazid: Coadministration has not been studied. Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal	Coadministration of AKURIT KID 75/50 ODT dispersible tablets with these antivirals is not recommended or even contraindicated (for further details see professional information of the medicines for therapy of HCV.

	hepatitis associated with isoniazid therapy may develop even after many months of treatment.	
Antifungals		
Ketoconazole / rifampicin	Ketoconazole AUC ↓ 80%	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Fluconazole / rifampicin	Fluconazole AUC ↓ 23	Efficacy should be monitored. An increased dose of fluconazole may be required.
Itraconazole / rifampicin	Itraconazole AUC ↓ >64-88 %	Co-administration should be avoided.
Voriconazole / rifampicin	Voriconazole AUC ↓ 96 %	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
ANTIBACTERIALS/ANTITUBERCULOTICS		
Clarithromycin / rifampicin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
Chloramphenicol / rifampicin	Case reports indicate >60-80 % reduction of	Co-administration should be avoided.

	chloramphenicol exposure.	
Ciprofloxacin / rifampicin	No significant interaction.	No dose adjustment required.
Doxycycline / rifampicin	Doxycycline AUC ↓ 50-60 %	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole / rifampicin	Metronidazole AUC i.v. ↓ 33 %. The clinical relevance of the interaction is unknown.	The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Efficacy should be monitored.
Sulfamethoxazole / rifampicin	Sulfamethoxazole AUC ↓ 23 %	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
Trimethoprim / rifampicin	Trimethoprim AUC ↓ 47 %	A dose increase of trimethoprim may be required. Efficacy should be monitored.
Ethionamide / rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
ANTIMALARIALS		

Chloroquine / rifampicin		Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Coadministration should be avoided.
Atovaquone / rifampicin	Atovaquone AUC ↓ 50 % Rifampicin AUC ↑ 30 %	Co-administration should be avoided.
Mefloquine / rifampicin	Mefloquine AUC ↓ 68 %	Co-administration should be avoided.
Amodiaquine / rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Co-administration should be avoided.
Quinine / rifampicin	Quinine AUC ↓ ≈ 80 %. This has been associated with significantly higher recrudescence rates.	Co-administration should be avoided. If co-administration is deemed necessary, an increased dose of quinine should be considered.
Lumefantrine / rifampicin	Lumefantrine AUC ↓ 68 %	Co-administration should be avoided.

Artemisinin and its derivatives / rifampicin	Artemether AUC ↓ 89 % Dihydroartemisinin AUC ↓ 85 %	Co-administration should be avoided.
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES		
Morphine / rifampicin	Morphine AUC p.o. ↓ 30 % loss of analgesic effect	Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased.
Codeine / rifampicin	Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary.
Methadone / rifampicin	Methadone AUC ↓ 33-66 %	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3-fold).
Acetaminophen (paracetamol) / rifampicin / isoniazid	Rifampicin may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of	Co-administration of AKURIT KID 75/50 ODT and acetaminophen (paracetamol) should be avoided.

	hepatotoxicity on coadministration, but data are inconclusive. Concurrent use with isoniazid may increase hepatotoxicity.	
ANTICONVULSANTS		
Carbamazepine / rifampicin / isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine. Isoniazid appears to have an increased risk of hepatotoxicity when co-treating with carbamazepine.	Co-administration of AKURIT KID 75/50 ODT and carbamazepine should be avoided.
Phenobarbitone / rifampicin / isoniazid	Phenobarbitone and rifampicin are both strong hepatic enzyme inducers, and each medicine may lower the plasma concentrations of the other. Also, co-treatment with phenobarbitone and isoniazid may increase the risk of hepatotoxicity.	Co-administration of AKURIT KID 75/50 ODT and phenobarbitone should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma medicine concentrations.
Phenytoin / rifampicin / isoniazid	Phenytoin AUC i.v. ↓ 42 % Co-treatment with phenytoin and	Co-treatment with phenytoin and AKURIT KID 75/50

	isoniazid may result in an increased risk of hepatotoxicity.	ODT should be avoided.
Valproic acid / rifampicin	Interaction studies are lacking. Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, reduced plasma levels of valproic acid are likely with concomitant use.	Co-treatment should be avoided. If deemed necessary, efficacy and, if possible, also plasma concentrations of valproic acid, should be carefully monitored.
Lamotrigine / rifampicin	Lamotrigine AUC ↓ 45 %	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
IMMUNOSUPPRESSIVES		
Ciclosporin/ rifampicin	Several studies and case reports have shown substantially increased cyclosporine clearance when co-administered with rifampicin.	Co-administration should be avoided. If deemed necessary, plasma concentrations of ciclosporin should be monitored and doses adapted accordingly (3-5-fold increases in ciclosporin dose have been required).
Tacrolimus / rifampicin	Tacrolimus AUC i.v. ↓	Co-administration of

	35 %; AUC p.o ↓ 68-70 % Sirolimus AUC ↓ 82 % Everolimus AUC ↓ 63 %	AKURIT KID 75/50 ODT and tacrolimus should be avoided. If deemed necessary, plasma drug concentrations of tacrolimus should be monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Warfarin / rifampicin /isoniazid	Warfarin AUC ↓ 85 % Isoniazid may inhibit hepatic metabolism of warfarin	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifampicin treatment.
Atenolol / rifampicin	Atenolol AUC ↓ 19 %	No dose adjustment required.
Verapamil / rifampicin	S-verapamil p.o. CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	AKURIT KID 75/50 ODT and verapamil per-orally should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required.
Digoxin / rifampicin	AUC p.o ↓ 30 %	When co-administering AKURIT KID 75/50 ODT with digoxin, the

		efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine / rifampicin	Lidocaine CL i.v. ↑ 15 %	No dose adjustment required
Amlodipine / rifampicin	Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when cotreating with rifampicin.	Efficacy should be monitored.
Enalapril / rifampicin	No interaction expected	No dose adjustment required.
Simvastatin / rifampicin	Simvastatin AUC ↓ 87 % Simvastatin acid AUC ↓ 93 %	Co-administration is not recommended.
Atorvastatin / rifampicin	Atorvastatin AUC ↓ 80 %	Co-administration is not recommended.
GASTROINTESTINAL MEDICINES		
Ranitidine / rifampicin	Ranitidine AUC ↓ 52 %	Efficacy should be monitored, and ranitidine dose increased if necessary.

Antacids / isoniazid/ rifampicin	Antacids may reduce the bioavailability of rifampicin by up to one third. Aluminium hydroxide impairs the absorption of isoniazid.	The clinical importance is unknown. Acid-suppressing medicines or antacids that do not contain aluminium hydroxide should be used, if co-treatment with AKURIT KID 75/50 ODT is necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam / rifampicin / isoniazid Midazolam Triazolam Alprazolam Nitrazepam	Diazepam AUC ↓ >70 % Midazolam AUC ↓ 98 % Triazolam AUC ↓ 95 % Alprazolam AUC ↓ 88 % Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended.
Zolpidem / rifampicin Zopiclone /rifampicin	Zolpidem AUC ↓73 % Zopiclone AUC ↓82 %	Co-administration should be avoided.
Chlorpromazine / rifampicin / isoniazid	Rifampicin may reduce chlorpromazine exposure. Also, concomitant use of chlorpromazine with	Co-administration should be avoided. If considered necessary, patients should be carefully

	isoniazid may impair the metabolism of isoniazid	monitored for isoniazid toxicity.
Haloperidol / rifampicin	Haloperidol clearance is substantially increased by rifampicin.	If co-treatment of AKURIT KID 75/50 ODT with haloperidol is deemed necessary, efficacy of haloperidol should be monitored. A dose increase may be required.
Amitriptyline / rifampicin Nortriptyline	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases clearance of tricyclic antidepressants.	Co-treatment should be avoided. If necessary, monitor for clinical response, side effects, and, if possible, plasma concentrations.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone / rifampicin and other systemically administered corticosteroids	Prednisolone AUC ↓ 66 % Also, for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of AKURIT KID 75/50 ODT with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as

		needed.
Glibenclamide / rifampicin	Glibenclamide AUC ↓ 34 %	Blood glucose levels should be closely monitored. A dose increase of glibenclamide may be required.
Insulin	No interaction expected.	No dose adjustment required.
Levothyroxine / rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored.
Ethinylestradiol / rifampicin	Ethinylestradiol AUC ↓ 66 %	Co-administration with AKURIT KID 75/50 ODT may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.
Norethisterone / rifampicin	Norethisterone AUC ↓ 51 %	Co-administration with AKURIT KID 75/50 ODT may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should

		be used.
OTHERS		
Praziquantel / rifampicin	Praziquantel AUC ↓ 80-99 %	Co-treatment with AKURIT KID 75/50 ODT should be avoided.
Disulfiram / isoniazid	Concurrent use of disulfiram together with isoniazid may result in increased incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with AKURIT KID 75/50 ODT
Theophylline / Isoniazid / Rifampicin	Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of combination are unknown	Theophylline dose adjustment may be needed.
Enflurane / Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Coadministration of AKURIT KID 75/50 ODT with enflurane should be avoided.

Interactions with laboratory tests:

Isoniazid may cause a false positive response to copper sulphate glucose tests; enzymatic glucose tests are not affected.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established

Breastfeeding

Safety during lactation has not been established. Rifampicin and isoniazid cross the placenta, and both are excreted in breastmilk.

4.7 Effects on ability to drive and use machines

AKURIT KID 75/50 ODT 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

Summary of the safety profile

The most important adverse reactions of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinemia or jaundice without hepatocellular damage, but occasionally causes hepatocellular injury. It can also potentiate the hepatotoxicity of the other anti-tuberculosis medications.

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects, and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. Most cases have occurred within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

Tabulated list of adverse effects

Side effects for AKURIT KID 75/50 ODT dispersible tablets:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leukopenia, neutropenia with eosinophilia, agranulocytosis
Immune system disorders	Frequency unknown	Allergic reactions with skin manifestations, pruritus, fever, leukopenia, anaphylaxis, allergic pneumonitis, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome, hypotension, shock
Metabolism and nutrition disorders	Less frequent Frequency unknown	Aggravated porphyria Hyperglycaemia, metabolic acidosis, pellagra

Psychiatric disorders	Less frequent Frequency unknown	Memory impairment, toxic psychosis Confusion, disorientation, hallucination
Nervous system disorders	Frequent Less frequent Frequency unknown	Peripheral neuropathy, usually preceded by paraesthesia of feet and hands Headache, lethargy, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy Tremor, vertigo, insomnia, hyperreflexia, cerebral haemorrhage
Eye disorders	Frequent Less frequent Frequency unknown	Ocular redness, permanent discolouration of soft contact lenses Exudative conjunctivitis Optic atrophy or neuritis

Gastrointestinal disorders	Frequent	Diarrhoea, abdominal pain, nausea, anorexia, vomiting
	Less frequent	Erosive gastritis, pseudomembranous colitis, pancreatitis
	Frequency unknown	Dry mouth, flatulence, constipation
Hepato-biliary disorders	Frequent	Transient increases of serum transaminases
	Less frequent	Increases of serum bilirubin and alkaline phosphatases, hepatitis
Skin and subcutaneous tissue disorders	Frequent	Erythema, exanthema, pruritus with or without rash, urticaria
	Less frequent	Photosensitivity reaction, exfoliative dermatitis, pemphigoid reactions, purpura
	Frequency unknown	Lyell's Syndrome, Stevens-Johnson Syndrome
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia, myalgia
Renal and urinary disorders	Less frequent	Acute renal failure, interstitial nephritis
	Frequency unknown	Urinary retention

Reproductive system and breast disorders	Frequent	Disturbances of the menstrual cycle
General disorders and administrative site conditions	Frequent	Flushing, reddish discolouration of body fluids and –secretions, such as urine, sputum, tears, saliva and sweat, decrease in blood pressure, shock

Side effects for Rifampicin:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Blood dyscrasias, unusual bleeding or bruising, thrombocytopenia, purpura, haemolysis, eosinophilia, leukopenia, haemolytic anaemia Disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, decreased haemoglobin
Immune system disorders	Frequency unknown	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	Frequency unknown	Pulmonary fibrosis, pneumonitis, shortness of breath and wheezing
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting, anorexia, diarrhoea and epigastric distress Pseudomembranous colitis. Ulcerative colitis, gastrointestinal bleeding.
Hepato-biliary 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 Less frequent	Cutaneous reactions, which typically consist of flushing and itching, with or without a rash 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, connective tissue and bone disorders	Frequent	Muscle weakness and myopathy

Renal and urinary disorders	Less frequent	Interstitial nephritis, renal failure.
Reproductive system and breast disorders	Frequent	Disturbances of the menstrual cycle, reduction of effectiveness of oral contraceptives
General disorders and administrative 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
	Frequency unknown	Oedema

Side effects for Isoniazid:

System Organ Class	**Frequency**	**Side effects**
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 nutrition disorders	Less frequent	Hyperglycaemia, metabolic acidosis
Psychiatric disorders	Less frequent	Psychotic reactions (characterised by delusions, hallucinations and confusion), memory impairment
Nervous system disorders	Frequent Less frequent	Peripheral neuropathy 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
Hepato-biliary 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 Frequency unknown	Skin reactions, pellagra, acne, Stevens-Johnsons syndrome, exfoliative dermatitis Alopecia, urticaria
Musculoskeletal and connective tissue disorders	Frequency unknown	Rheumatic syndrome, hyperreflexia
Renal and urinary disorders	Less frequent	Urinary retention
Reproductive system and breast disorders	Less frequent	Gynecomastia

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

4.9 Overdose

Signs and symptoms:

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.

Management of overdose:

In cases of overdosage with AKURIT KID 75/50 ODT 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

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis

ATC code: J04AM02

Pharmacological classification: A.20.2.3 Tuberculostatics

PHARMACOLOGICAL ACTION

Antimicrobial medicine.

5.1 Pharmacodynamic properties

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; C_{max} of 2,1 µg/mL and t_{max} of 1,5 – 2,0 hours. Absorption of rifampicin is reduced by about 30 % when ingested with food.

Following single dose administration of 2 x Rifampicin/Isoniazid 75 mg/50 mg dispersible tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) rifampicin C_{max} value 2160 ng/mL (± 516), and the corresponding value for AUC was 10495 ng.h/mL (± 2153). The mean (± SD) rifampicin t_{max} value was 1,20 (± 0,50) hours.

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.

Biotransformation:

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.

Pharmacokinetics in special patient groups

The half-life of rifampicin has been reported to be prolonged in patients with liver impairment or biliary obstruction.

Isoniazid:

Absorption:

Isoniazid is readily absorbed from the gastrointestinal tract with an oral bioavailability of 100 % for a 300 mg dose; C_{max} 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.

Following single dose of 2 x Rifampicin/Isoniazid 75 mg/50 mg dispersible tablets administration in healthy volunteers, the mean (± SD) isoniazid C_{max} value was 2043 ng/mL (± 739), and the corresponding value for AUC was 7348 ng.h/mL (± 3733). The

mean (± SD) isoniazid t_{max} value was 0,57 ± 0,34 hours.

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.

Biotransformation:

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.

Pharmacokinetics in special patient groups

Renal impairment:

The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged, and exposure is increased, in slow acetylators. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic Acid

Aspartame

Colloidal silicon dioxide

Colour Ponceau 4R Supra D

Crospovidone NF

Dry Flavour Trusil Raspberry Special LD

Dry Flavour Trusil Strawberry Select LD

Magnesium stearate

Microcrystalline cellulose

Pregelatinized starch

Saccharin sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture and light.

6.5 Nature and contents of container

Aluminium Strip packs:

10 dispersible tablets shall be packed per strip using plain strip aluminium foil 0,03 mm as a base material and plain strip aluminium strip pack 0,03 mm aluminium foil as a lidding material. 10 strip packs will be packed into a printed outer carton.

6 dispersible tablets shall be packed per strip using plain strip aluminium foil 0,03 mm as a base material and plain strip aluminium strip pack 0,03 mm aluminium foil as a lidding material. 14 strip packs will be packed into a printed outer carton.

Aluminium Blister pack:

5 dispersible tablets shall be packed per blister using plain aluminium foil 25 micron as a lidding material and cold forming Alu-Alu foil base material. 18 blisters shall be packed

into a printed outer carton

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

A54/20.2.3/0648

9. DATE OF FIRST AUTHORISATION

To be allocated.

10. DATE OF REVISION OF THE TEXT

14 December 2021