SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AKuriT*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Rifampicin 150 mg
Isoniazid 75 mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Brick-red coloured, capsule shaped, biconvex, film coated tablets with break-line on one side and plain on the other side.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

AKuriT is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis,* according to the guidelines of WHO (Treatment of Tuberculosis: guideline 4th edition, WHO, available at:
http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf
and

Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd edition, 2014 available at:

http://www.who.int/tb/publications/childtb_guidelines/en/

4.2 Posology and method of administration

Oral use

In patients weighing 25-35 kg the daily dose is 2 tablets administered as a single dose.

In patients weighing 36-55kg the daily dose is 3 tablets administered as a single dose.

In patients weighing more than 55 kg the daily dose is 4 tablets administered as a single dose.

AKuriT should not be used for intermittent treatment regimens.

AKuriT should be taken on an empty stomach (at least one hour prior to or two hours after a meal). If taken with food to improve gastrointestinal tolerance bioavailability may be impaired.

For situations where discontinuation of therapy with one of the active agents of this medicine, or dose reduction is necessary, separate preparations of rifampicin and/or isoniazid should be used.

It is important not to miss a dose of AKuriT. If you miss a dose of AKuriT, take it as soon as you can, and then take your next dose at its regular time.

* Trade names are not prequalified by WHO. This is national medicines regulatory authority's (NMRA) responsiblity. Throughout this WHOPAR the proprietary name is given as an example only.

However, if your next dose is due within 6 hours, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.
If you vomit within 1 hour after taking AKuriT, take another tablet. You do not need to take another tablet if you were sick more than 1 hour after taking AKuriT.

Special populations

Renal impairment:
No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to 2/3 of the normal daily dose may be considered in slow acetylators with severe renal impairment (ClCr <25 ml/min) or in those with signs of isoniazid toxicity. If so, separate preparations of rifampicin and isoniazid should be administered (see section 4.4 and 5.2).

Hepatic impairment:
Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. AKuriT must not be used in patients with severe liver disease (see section 4.3).

Children and adolescents / patients with a body weight < 25 kg
AKuriT is not recommended for patients with a body weight below 25 kg, since appropriate dose adjustments cannot be made.
For these patients formulations containing less rifampicin and isoniazid are available (see general references below).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Acute liver disease, icterus or severe liver impairment.

Co-administration of AKuriT with voriconazole, any HIV protease inhibitor, elvitegravir/cobicistat or several HCV-antivirals is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Liver toxicity: Rifampicin and isoniazid may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of AKuriT should be avoided in patients with preexisting hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with AKuriT. Patient groups especially at risk for developing hepatitis include:

- age > 35 years,
- daily users of alcohol (see section 4.5),
- patients with active chronic liver disease
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients
- HIV positive patients.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesiae of the hands and feet, persistent fatigue and/or weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, AKuriT should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with AKuriT and periodically throughout treatment.

Increased liver function tests are common during therapy with AKuriT. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin or isoniazid. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of AKuriT should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until symptoms and laboratory abnormalities have subsided. In case of rechallenge, AKuriT should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents should be used.

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 should immediately be discontinued. Such patients should not be rechallenged 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 should not be used.

Cross-sensitivity: Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.

Peripheral neuropathy: This is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely with AKuriT at doses of 5 to 10 mg per day to prevent and at doses 10 to 20 mg 2 or 3 times daily to treat peripheral neuropathy.

Epilepsy and psychotic disorders: AKuriT should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

Haematological toxicity: Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with AKuriT. In case of severe haematological disturbances **AKuriT** must be discontinued.

Renal impairment: 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 above) should be given to avoid neurotoxicity.

Nephrotoxicity: AKuriT should be discontinued in case of clinical signs of nephrotoxicity.

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

Drug interactions: Rifampicin is a strong inducer of hepatic drug metabolism. Therefore AKuriT may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

Contraception: Oral contraceptives do not provide adequate protection against conception when co-administered with AKuriT. This probably also pertains to other forms of hormonal contraceptives (e.g. patches, transdermal implants). Barrier or other non-hormonal methods of contraception should be used.

Treatment with corticosteroids: AKuriT may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria: AKuriT should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids: AKuriT may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears. This is due to rifampicin, and does not require medical attention.

Laboratory monitoring: Full blood count and liver function should be monitored prior to and at regular intervals during treatment with AKuriT.

4.5 Interactions with other medicinal products and other forms of interaction

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 drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of coadministered drugs. 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 taken into account when cotreating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the concomitant administration of AKuriT.

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. However, when co-treating with rifampicin, as when using AKuriT, 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 drug clearance will be an increase due to rifampicin rather than a decrease due to isoniazid.
Concurrent use of isoniazid with other hepatotoxic or neurotoxic medications may increase the hepatotoxicity and neurotoxicity of isoniazid, and should be avoided.

Mainly due to rifampicin, AKuriT may interact with a very large number of other drugs, primarily by reducing the exposure to coadministered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic agents, no interaction data with rifampicin are available. However, clinically significant reductions in drug exposure may occur. Whenever co-prescribing any drug together with AKuriT, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with AKuriT 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.

Use of isoniazid should be carefully monitored with patients with current chronic liver disease. Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment.

Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
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. Co-administration 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 DF / 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 analogues **Efavirenz** / rifampicin	Efavirenz AUC ↓ 26%	When co-treating with AKuriT, it may be considered to increase the efavirenz dose to 800 mg q.d.
Nevirapine / rifampicin	nevirapine: 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 and nevirapine is not recommended.
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of AKuriT and etravirine should be avoided.

Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
Protease inhibitors **Fosamprenavir /** rifampicin **Saquinavir** **Indinavir** **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir**	Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to compensate for this by increasing doses of the PIs, or an increase in ritonavir-boosting, have been ill-tolerated with a high rate of hepatotoxicity.	AKuriT must not be co-administered with HIV protease inhibitors (see section 4.3).
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 coadministered with AKuriT 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. Rifampin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect,	Coadministration is contraindicated.
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/Pibrentasvir** **Ledipasvir/Sofosbuvir** **Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)** **Simeprevir** **Sofosbuvir** **(with or without velpatasvir with or without voxilaprevir)/** Rifampicin Isoniazid	<u>Rifampicin</u>: Coadministration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifampicin and hence to reduce their therapeutic effect. <u>Isoniazid:</u> Coadministration has not been studied .Patients with	Coadministration of AKuriT with these antivirals is not recommended or even contraindicated (for further details see Summary of product characteristics of the drugs for therapy of HCV. -.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	current chronic liver disease should be carefully monitored. Severe and sometimes fatal 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	Fluconazol 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 chloramphenicol exposure.	Co-administration should be avoided.
Ciprofloxacin / rifampicin	No significant interaction	No dose adjustment required.
Doxycyclin / rifampicin	Doxycyclin AUC ↓ 50-60%	If co-treatment is considered necessary, the dose of doxycyclin should be doubled.
Metronidazole / rifampicin	Metronidazole AUC i.v.↓ 33%	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-

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		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. Co-administration 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 DRUGS		
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 may increase the	Co-administration of AKuriT

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
/ rifampicin / isoniazid	glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive.Concurrent use with isoniazid may increase hepatotoxicity.	and acetaminophen (paracetamol) should be avoided.
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 and carbamazepine should be avoided.
Phenobarbital / rifampicin / isoniazid	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isonazid may increase the risk of hepatotoxicity.	Co-administration of AKuriT and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin / rifampicin isoniazid	Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and AKuriT 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		
Cyclosporine / 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 cyclosporine should be monitored and doses adapted

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		accordingly (3-5 fold increases in cyclosporine dose have been required).
Tacrolimus / rifampicin	Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 68-70% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of Rifampicin/Isoniazid 150 mg/75 mg film-coated Tablets 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 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 with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine. / rifampicin	Lidocaine CLi.v. ↑ 15%	No dose adjustment required
Amlodipine / rifampicin	Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating 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.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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 drugs or antacids that do not contain aluminium hydroxide should be used, if co-treatment with AKuriT 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 isoniazid may impair the metabolism of isoniazid.	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity.
Haloperidol / rifampicin	Haloperidol clearance is substantially increased by rifampicin.	If co-treatment of AKuriT 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 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

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		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-adminstration with AKuriT may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.
Norethindrone / rifampicin	Norethindrone AUC ↓ 51%	Co-administration with AKuriT 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 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.
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 with enflurane should be avoided.

Interactions with food and drink:

Alcohol: concurrent daily use of alcohol may result in an increased incidence of isoniazid induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages (see section 4.4).

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.

Interactions with laboratory tests:

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

4.6 Pregnancy and lactation

Pregnancy:
No adverse effects of isoniazid on the foetus have been reported. Use of rifampicin in the third trimester has been associated with postnatal haemorrhages in the mother and infant.
AKuriT should be used in pregnancy only if the benefits are considered to outweigh the risks. If AKuriT is used in the last weeks of pregnancy, the mother and neonate should be substituted with vitamin K.

Lactation:
Rifampicin and isoniazid are excreted into the breast milk of lactating mothers. However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants. No adverse effects in the baby have been reported.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of AKuriT, especially the potential neurotoxicity of isoniazid, should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most important adverse reactions of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinaemia 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. The majority of cases have occurred within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

Adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomized controlled trials, but on published literature data, generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Nervous system disorders
Very common: Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4),
Uncommon: headache, lethargia, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy,
Not known: tremor, vertigo, insomnia, hyperreflexia.

Psychiatric disorders
Uncommon: memory impairment, toxic psychosis,
Not known: confusion, disorientation, hallucination.

Gastrointestinal disorders
Common: Diarrhoea, abdominal pain, nausea, anorexia, vomiting,

Rare: Erosive gastritis, pseudomembranous colitis,
Not known: dry mouth, flatulence, constipation.

Hepatobiliary disorders:
Very common: Transient increases of serum transaminases,
Uncommon: Increases of serum bilirubin and alkaline phosphatases, hepatitis.

Renal and urinary disorders
Rare: acute renal failure, interstitial nephritis,
Not known: urinary retention.

Metabolic and nutrition disorders
Very rare: aggravated porphyria,
Not known: hyperglycaemia, metabolic acidosis, pellagra.

General disorders
Very common: Flushing,
Common: Reddish discolouration of body fluids and –secretions, such as urine, sputum, tears, saliva and sweat,
Not known: allergic reactions with skin manifestations, pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome, hypotension, shock.

Blood and lymphatic systems disorders
Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis.

Musculoskeletal disorders
Not known: Arthralgia, myalgia.

Skin and subcutaneous tissue disorders:
Common: Erythema, exanthema, pruritus with or without rash, urticaria.
Rare: photosensitivity reaction, exfoliative dermatitis, pemphigoid reactions, purpura.
Not known: Lyell's Syndrome, Stevens-Johnson Syndrome.

Eye disorders:
Common: Ocular redness, permanent discolouration of soft contact lenses,
Rare: Exudative conjunctivitis,
Not known: Optic atrophy or neuritis.

Reproductive system and breast disorders
Common: Disturbances of the menstrual cycle.

4.9 Overdose

Symptoms:
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances have occurred within 30 minutes to 3 hours after ingestion of isoniazid. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

When overdosed, rifampicin may cause a reddish-orange discoloration of the skin ('red man syndrome'). Further symptoms include facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14 g has caused cardiopulmonary arrest.

Treatment:
Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram per gram basis, equal to the isoniazid dose, if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring/support of ventilation and correction of metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis
ATC Code: J04AM02.

Mechanism of action
In vitro, rifampicin is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. The mode of action is by inhibition of DNA-dependent RNA polymerase, inhibiting transcription. In tuberculosis, rifampicin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance may occur, and is a result of alterations in the target enzyme (RNA polymerase).

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids, which are unique constituents of the mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

5.2 Pharmacokinetic properties

Rifampicin

Absorption:
Rifampicin is rapidly absorbed from the gastrointestinal tract. Its bioavailability is 90-95% in adults, but may be lower in children. Concomitant intake of food delays absorption and reduces the peak concentration, but does not decrease bioavailability.

Following single dose administration of 4 x AKuriT 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 12232 ng/ml (± 3129), and the corresponding value for AUC was 89786 ng.h/ml (± 22019). The mean (± SD) rifampicin t_{max} value was 3.60 (± 0.93) hours.

Distribution
Rifampicin is 60-90% bound to plasma proteins and has a volume of distribution of approximately 0.9 l/kg. CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Rifampicin readily crosses the placenta.

Metabolism:
Rifampicin is metabolized by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetylrifampicin. Rifampicin induces its own metabolism; after repeat doses bioavailability is reduced to approximately 70% and apparent clearance is increased.

Excretion:
The half-life of rifampicin after a single dose is approximately three hours. After repeat doses this is reduced to approximately 1-2 hours. Rifampicin and its metabolites are mainly excreted in bile, and rifampicin undergoes enterohepatic recirculation. Approximately 25% of a dose is excreted in the urine.

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

Isoniazid

Absorption:

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first pass) metabolism in the wall of small intestine and liver.

Following single dose of 4 x AKuriT administration in healthy volunteers, the mean (± SD) isoniazid Cmax value was 4649 ng/ml (± 1713), and the corresponding value for AUC was 14547 ng.h/ml (± 7408). The mean (± SD) isoniazid tmax value was 0.68 ± 0.55 hours.

Distribution:

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/kg. Protein binding is very low (0-10%).

Metabolism:
Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolising enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators.

Excretion:
Up to 95% of the ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

Pharmacokinetics in 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.

5.3 Preclinical safety data

Rifampicin

After oral administration of 100 mg/kg bodyweight (bw) rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg bw swelling and hydropic degeneration of the liver were observed.
In monkeys, vomiting, anorexia and weight loss were observed at chronic doses of 105 mg/kg bw/day.

Because of only limited evidence available for the carcinogenicity of rifampicin in mice and the absence of epidemiological studies, no evaluation of the carcinogenicity of rifampicin to humans can be made.

The available studies on mutagenicity indicate an absence of a mutagenic effect.

Rifampicin concentrations in cord blood reach 12-33% of maternal blood concentrations.
Teratogenic effects were noted in rodents treated with high doses. 100 to 150 mg/kg bw daily in rodents have been reported to cause cleft palate and spina bifida.
In rats neither fertility nor peri- or postnatal development was impaired.
Malformation and death in infants born to mothers exposed to rifampicin, were reported at the same frequency as in the general population.

Isoniazid

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Microcrystalline cellulose
Crospovidone
Pregelatinized starch
Ascorbic acid
Colloidal silicon dioxide
Magnesium stearate

Film coat:

Hypromellose
Polyethylene glycol
Talc
Titanium dioxide
Colour iron oxide red
simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, protected from excessive humidity. Protect from light.

6.5 Nature and contents of container

Blister packs
The primary packs are blister cards of 6 tablets (comprised of orange PVC/PVDC foil sealed with aluminium foi1 lid). Such 15 blister cards are packed in a carton with one pack insert.
Pack size: 15 x 6 Tablets.

The primary packs are blister cards of 28 tablets (comprised of green PVC/PVDC foil sealed with aluminium foil lid). Such 24 interlocked blister cards are packed in a carton with one partition after 12 cards and one insert in each partition.
Pack size: 24 x 28 Tablets.

Cold form Alu-Alu blister pack of 28 tablets. Such 24 blisters kept in a carton.
Pack size: 24 x 28 Tablets

Bottle pack
Tablets are packed in a sealed polypropylene bag, which is packed inside a white HDPE container together with one, a 1 gram silica gel bag. with foam on top of the bag and the container is sealed with aluminium tagger. An insert is placed above the container and is shrink wrapped.
Pack size: 1000 Tablets.

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
Mumbai 400055
India

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

TB068

9. DATE OF FIRST PREQUALIFICATION

19 December 2003

10. DATE OF REVISION OF THE TEXT

September 2017
Section 6 updated: February 2018

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/

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