SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

NEORIFAN 300 mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg rifapentine.
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Reddish brown colored, round shaped, beveled edge, biconvex, film coated tablets debossed with "J" and "37" separated by break-line on one side and plain on other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEORIFAN 300 is indicated in combination with isoniazid, moxifloxacin and pyrazinamide for the treatment of tuberculosis due to *Mycobacterium tuberculosis* in adult patients.

NEORIFAN 300 is also indicated for the treatment of latent tuberculosis infection caused by *Mycobacterium tuberculosis* in adults who are at high risk of progression to tuberculosis disease (including those in close contact with active tuberculosis patients with culture confirmed TB disease who were TST positive, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on radiograph). Active tuberculosis disease should be ruled out before initiating treatment for latent tuberculosis infection. NEORIFAN 300 must always be used in combination with isoniazid as a 12-week once weekly regimen for the treatment of latent tuberculosis infection.

4.2 Posology and method of administration

Use of NEORIFAN 300 should be initiated and monitored by a health care provider experienced in the management and prevention of Mycobacterium tuberculosis infection.
Patients should be advised to take NEORIFAN 300 exactly as prescribed and to complete the full course.

Posology

Treatment

For the treatment of drug-susceptible tuberculosis, NEORIFAN 300 should be given to adult patients once daily for a period of 4 months, as part of a regimen with isoniazid, moxifloxacin and pyrazinamide.
The daily dose of NEORIFAN 300 is 1,200 mg (4 tablets) once daily.

Treatment of Latent Tuberculosis Infection

Patients aged 2-14 years may be given NEORIFAN 300 with isoniazid once weekly for a period of 3 months, i.e., 12 doses, as follows:

Body weight	Number of tablets	Dose of rifapentine
10 to less than 16 kg	1	300 mg
16 to less than 24 kg	1½	450 mg
24 to less than 31 kg	2	600 mg
31 kg and over	2½	750 mg

Patients aged over 14 years and weighing at least 30 kg may be given 3 tablets of NEORIFAN 300

(rifapentine 900 mg) weekly with isoniazid for 3 months.

Missed doses and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed.

If the patient forgets to take a daily dose and there are more than 6 hours till their next dose, they should take the missed dose as soon as possible. Then they should continue their treatment as before. If there are less than 6 hours till their next dose, the missed dose should be skipped. A double dose should not be taken to make up for a missed dose.

If a weekly dose is missed but it is remembered within the next 2 days, the patient can take the dose immediately and continue the schedule as originally planned. If the missed dose is remembered more than 2 days later, the person can take the missed dose immediately and change the schedule for weekly intake to the day the missed dose was taken until treatment completion.

If 4 or more weekly doses are missed, consideration should be given to restarting the full preventive treatment.

If a patient vomits within 1 hour of taking NEORIFAN 300, the dose should be repeated.

Method of Administration

NEORIFAN 300 should be taken orally with a meal.

For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

- Hypersensitivity to rifapentine or any of the other rifamycins (rifampicin and rifabutin), or to any of the tablet excipients listed in section 6.1.
- Acute liver disease, icterus or severe liver impairment.
- History of liver damage or other severe side effects such as drug fever or chills that is linked to rifapentine.
- Co-administration of NEORIFAN 300 with HIV protease inhibitors, elvitegravir/cobicistat, nevirapine, rilpivirine, etravirine, doravirine, bictegravir/emtricitabine/tenofovir alafenamide, artemisinin & its derivatives, or direct-acting antivirals for chronic Hepatitis C (see section 4.4).
- Patients with porphyria. Based on experience with rifampicin, it may be assumed that rifapentine can also induce delta aminolevulinic acid synthetase and therefore cause an acute attack of porphyria.

4.4 Special warnings and precautions for use

Hypersensitivity

Rifamycins such as rifapentine 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 rifapentine hypersensitivity do appear (e.g., thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure), then NEORIFAN 300 should immediately be discontinued. Such patients should not be rechallenged with rifapentine.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in some patients taking rifapentine. NEORIFAN 300 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hepatotoxicity

NEORIFAN 300 may cause hepatotoxicity (see section 4.8). Therefore, patients should be carefully monitored at monthly intervals. In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with NEORIFAN 300 and periodically throughout treatment.
NEORIFAN 300 can also cause cholestasis and elevated transaminases. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even with continued therapy.
If abnormalities of liver function exceed 3 to 5 times the upper limit of normal, discontinuation of NEORIFAN 300 should be strongly considered.
Particular care may be needed in patients with pre-existing liver disease. The contribution of other potentially hepatotoxic medicines used with NEORIFAN 300 in combination TB regimens should be taken into consideration.
Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. If these appear, NEORIFAN 300 should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

Hyperbilirubinaemia
A rifapentine-induced, moderate rise in bilirubin is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Drug interactions
Rifapentine is an inducer of CYP3A4 and CYP2C8/9. Concomitant use of rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception may cause a significant decrease in plasma concentrations and loss of therapeutic effect. Rifapentine has also been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (a P-gp substrate with narrow therapeutic index). Appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with rifapentine (see Section 4.5).
For the effect of rifapentine on oral contraceptives and corticosteroids, see also under the headings 'Contraception' and 'Addison's disease' below.

Haematological toxicity
Rifapentine may be associated with haemolytic anaemia, leucopenia and thrombocytopenia; full blood count should be monitored regularly throughout therapy with NEORIFAN 300. In case of severe haematological disturbances, NEORIFAN 300 must be discontinued.

Clostridium difficile-Associated Diarrhea
Pseudomembranous colitis has been reported to occur with various antibiotics, including other rifamycins. Diarrhea, particularly if severe and/or persistent,occurring during treatment or in the initial weeks following treatment may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, rifapentine should be stopped immediately and the patient treated appropriately without delay. Medications inhibiting the peristalsis are contraindicated in this clinical situation.

Contraception
Oral contraceptives do not provide adequate protection against conception when co-administered with NEORIFAN 300. 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.

Addison's disease

NEORIFAN 300 may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria

Porphyria has been reported in patients receiving rifampin, attributed to induction of delta amino levulinic acid synthetase. Because rifapentine may have similar enzyme induction properties, avoid the use of rifapentine in patients with porphyria.

Discolouration of body fluids

NEORIFAN 300 may cause a reddish-orange discolouration of body fluids and/or fluids, e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid. This is due to rifapentine, and does not require medical attention. In addition, contact lenses or dentures may be permanently stained red-orange.

4.5 Interaction with other medicinal products and other forms of interaction

Like other rifamycins, rifapentine is a potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as of glucuronidation and the P-glycoprotein transport system. In vitro and in vivo enzyme induction studies have suggested rifapentine induction potential may be less than rifampicin but more potent than rifabutin.

Administration of rifapentine with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping administration of NEORIFAN 300. This must be taken into account when giving NEORIFAN 300 with other medicines.

The effects of rifapentine on biotransformation approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. The magnitude of enzyme induction by rifapentine is dependent on dose and dosing frequency; less enzyme induction occurred with rifapentine doses of 600 mg every 72 hours versus the same dose daily.

The following list of drug interactions with NEORIFAN 300, based largely on what is known of the properties of rifapentine and experience with other rifamycins such as rifampicin, 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.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside/nucleotide reverse transcriptase inhibitors **Didanosine** **Lamivudine** **Emtricitabine** **Stavudine** **Zidovudine**	No interaction expected.	No dose adjustment required.
Abacavir	Empirical data are lacking, but rifapentine may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Tenofovir alafenamide	Co-administration with rifapentine, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Additional monitoring, alteration of tenofovir drug dosage or timing of administration may be required.
Bictegravir/ Emtricitabine/Tenofovir alafenamide	Interaction not studied. Co-administration of rifapentine, a P-gp inducer, may decrease bictegravir and tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration with NEORIFAN 300 is contraindicated.
Non-nucleoside reverse transcriptase inhibitors **Doravirine**	Significant decrease in doravirine concentration.	Co-treatment of NEORIFAN 300 and doravirine is contraindicated.
Efavirenz	Potential interaction likely to be of weak intensity.	Additional action/monitoring or dosage adjustment is unlikely to be required.
Etravirine	Rifapentine significantly reduces exposure to etravirine.	Co-treatment of NEORIFAN 300 and etravirine is contraindicated.
Nevirapine	Rifapentine will decrease the level or effect of nevirapine by altering drug metabolism	Co-administration of NEORIFAN 300 with nevirapine is contraindicated.
Rilpivirine	Significant decrease in rilpivirine concentration	Co-treatment of NEORIFAN 300 and rilpivirine is contraindicated.
Protease inhibitors **Atazanivir** **Darunavir** **Fosamprenavir** **Lopinavir** **Ritonavir** **Tipranavir**	Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifapentine. Attempts to dose adjust by increased doses, or an increase in ritonavir-boosting, have been ineffective or ill- tolerated with a high rate of hepatotoxicity.	Co-administration with NEORIFAN 300 is contraindicated.
Integrase inhibitors **Dolutegravir**	Dolutegravir AUC ↓	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with NEORIFAN 300 in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
Elvitegravir/Cobicistat	Co-administration has not been studied. Rifapentine is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of	Co-administration is contraindicated.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	therapeutic effect.	
Raltegravir	Raltegravir AUC ↑	Once weekly rifapentine can be used with raltegravir without dose adjustment. However, a dosing strategy of daily rifapentine (for treatment of active TB) is still under clinical investigation.
CCR5 inhibitors **Maraviroc**	Maraviroc AUC ↓	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d.
Fixed dose combination of **Efavirenz/Emtricitabine/ Tenofovir**	Once-weekly co-administration of 900 mg rifapentine with the antiretroviral fixed dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxyl fumarate 300 mg in HIV-infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir. No clinically significant change in CD4 cell counts or viral loads were noted.	No need for dose adjustment of fixed dose combination of Efavirenz, Emtricitabine and Tenofovir, if co-administered with rifapentine 900 mg once weekly.
Antivirals Hepatitis C-infection		
Daclatasvir **Elbasvir/Grazoprevir** **Glecaprevir/Pibrentasvir** **Ledipasvir/Sofosbuvir** **Ombitasvir/Paritaprevir/ Ritonavir (with or without dasabuvir)** **Sofosbuvir (with or without velpatasvir with or without voxilaprevir)**	Co-administration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifapentine and hence to reduce their therapeutic effect. Rifapentine will decrease the level or effect of sofosbuvir, ledipasvir / sofosbuvir by affecting how the drug is eliminated via what is known as the P-glycoprotein [MDR1] transporter)	Co-administration of NEORIFAN 300 with these antivirals is contraindicated.
Antifungals		
Fluconazole	Fluconazole AUC ↓	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Itraconazole	Itraconazole AUC ↓	Co-administration should be avoided.
Ketoconazole	Ketoconazole AUC ↓	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Voriconazole	Based on interaction data from rifabutin and rifampicin, it is expected for	Concomitant use of NEORIFAN 300 and voriconazole should be

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	expected for voriconazole plasma concentrations to significantly decrease.	avoided.
Antibacterials/TB medicines		
Bedaquiline	Co-administration with rifamycins, including rifapentine, significantly reduces concentrations of bedaquiline (<50%).	Co-administer with caution and dose adjustment of bedaquiline.
Chloramphenicol	Reduction of chloramphenicol exposure.	Co-administration should be avoided.
Clarithromycin	Clarithromycin mean serum concentration ↓. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
Dapsone	Co-administration has not been studied, but based on experience with rifampicin, exposure to dapsone may be reduced.	Dosage of dapsone may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Doxycycline	Doxycycline AUC ↓	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Ethionamide	Empirical data are not available.	Rifapentine and ethionamide should not be co-administered, due to a possible increased risk of hepatotoxicity.
Fluoroquinolones	Empirical data are not available.	Dosage of fluoroquinolone may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Metronidazole	Metronidazole AUC i.v. ↓	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored.
***p*-aminosalicylic acid**	Co-administration has not been studied, but based on experience with rifampicin, *p*- aminosalicylic acid granules may reduce absorption of rifapentine if given concomitantly.	If *p*-aminosalicylic acid and rifapentine are both included in the treatment regimen, they should be given not less than 8 hours apart to ensure satisfactory blood levels.
Sulfamethoxazole	Sulfamethoxazole AUC may decrease	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
Trimethoprim	Trimethoprim AUC may decrease	A dose increase of trimethoprim may be required. Efficacy should bemonitored.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Antimalarials		
Amodiaquine	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifapentine.	Co-administration should be avoided.
Artemisinin and its derivatives	Artemether AUC ↓ Dihydroarthemisinin AUC ↓	Co-administration is contraindicated.
Atovaquone	Empirical data are not available but based on experience with rifampicin and atovaquone, it is likely that: Atovaquone AUC ↓ Rifapentine AUC ↑	Co-administration should be avoided.
Chloroquine	Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifapentine co-therapy.	Co-administration should be avoided.
Lumefantrine	Empirical data are not available but based on data on rifampicin and lumefantrine, it is likely that: Lumefantrine AUC ↓	Co-administration should be avoided.
Mefloquine	Rifapentine may modify the metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentration.	The clinical consequences of these effects are unknown and a close clinical surveillance is warranted. Co-administration should be avoided.
Quinine	Quinine AUC ↓. 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.
Anthelmintics		
Praziquantel	Therapeutically effective plasma levels of praziquantel may not be achieved when co-administered with rifapentine.	Co-administration should be avoided.
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Codeine	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	Methadone AUC expected to decrease when co-administered with rifapentine.	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
Morphine	Morphine AUC decreased with reduced analgesic effect.	Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		dose may need to be increased.
Paracetamol	Rifapentine may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of hepatotoxicity on co- administration, but data are inconclusive.	Co-administration of NEORIFAN 300 and acetaminophen (paracetamol) should be avoided.
ANTICONVULSANTS		
Carbamazepine	Rifapentine is expected to decrease the serum concentration of carbamazepine. The risk of hepatotoxicity increases when co-treating with carbamazepine.	Co-administration of NEORIFAN 300 and carbamazepine should be avoided.
Lamotrigine	Empirical data are not available but based on data on rifampicin and lamotrigine co- administration, it is likely that: Lamotrigine AUC ↓	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
Phenobarbital	Phenobarbital and rifapentine are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other.	Co-administration of NEORIFAN 300 and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin	Phenytoin AUC ↓	Co-treatment with phenytoin and NEORIFAN 300 should be avoided.
Valproic acid	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, plasma concentrations of valproic acid should be carefully monitored.
IMMUNOSUPPRESSIVES		
Cyclosporine	Substantially increased cyclosporine clearance when co-administered with rifapentine.	Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
Everolimus **Sirolimus** **Tacrolimus**	Everolimus AUC ↓ Sirolimus AUC ↓ Tacrolimus AUC i.v. ↓ AUC p.o ↓	Co-administration of NEORIFAN 300 and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Antiarrhythmics **Diltiazem** **Disopyramide** **Mexiletine** **Propafenone** **Quinidine** **Tocainide**	Interaction studies are mostly lacking but based on rifampicin, an effect on antiarrhythmic exposure might be expected.	Dosage of these drugs may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Warfarin	Warfarin AUC ↓	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifapentine treatment.
Other cardiovascular medicines **Atenolol** **Propranolol**	Atenolol AUC ↓	Dose adjustment may be required.
Amlodipine **Nifedipine**	Amlodipine and nifedipine like other calcium channel blockers, are metabolised by CYP3A; lower exposure is expected when co-treating with rifapentine.	Efficacy should be monitored.
Clofibrate	Rifapentine may increase the metabolism of clofibrate, thus decreasing its activity.	Dosage of clofibrate may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Clopidogrel	Rifapentine may increase active clopidogrel metabolite exposure due to CYP2C19 induction. Increased level of clopidogrel active metabolite and platelet inhibition may potentiate the risk of bleeding.	Concomitant use of clopidogrel and rifapentine is discouraged.
Digoxin **Digitoxin**	AUC p.o.↓	When co-administering NEORIFAN 300 with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Enalapril	No interaction expected. Empirical data are not available but based on data on rifampicin and enalapril, it is likely that enalapril active metabolite AUC ↓	Dosage of enalapril may require adjustment.
Eplerenone	Empirical data are not available but based on data on rifampicin and eplerenone, it is likely that: Eplerenone AUC ↓	Dosage of eplerenone may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Lidocaine	Lidocaine CL i.v. ↑	Dose adjustment may be required.
Statins **Atorvastatin** **Simvastatin**	Atorvastatin AUC ↓ Simvastatin AUC ↓ Simvastatin acid AUC ↓	Co-administration is not recommended.
Verapamil	S-verapamil p.o CL/F ↑. T-With i.v. S-verapamil, CL ↑	NEORIFAN 300 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.
GASTROINTESTINAL MEDICINES		
Antacids	Antacids may reduce the bioavailability of rifapentine.	The clinical importance is unknown.
Ranitidine	Ranitidine AUC ↓	Efficacy should be monitored, and ranitidine dose increased if necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Benzodiazepines **Alprazolam** **Diazepam** **Midazolam** **Nitrazepam** **Triazolam**	Diazepam AUC ↓ Midazolam AUC ↓ Triazolam AUC ↓ Alprazolam AUC ↓ Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals.
Non-benzodiazepine sedative-hypnotics **Zolpidem** **Zopiclone**	Zolpidem AUC ↓ Zopiclone AUC ↓	Co-administration should be avoided.
Antipsychotics **Chlorpromazine**	Rifapentine may reduce chlorpromazine exposure.	Co-administration should be avoided.
Aripiprazole **Clozapine** **Haloperidol**	Haloperidol clearance is substantially increased by rifapentine, theoretical considerations imply that same applies to aripiprazole and clozapine.	If co-treatment of NEORIFAN 300 with aripiprazole, haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Tricyclic antidepressants **Amitriptyline** **Nortriptyline**	Case reports (supported by theoretical considerations) suggest that rifapentine 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		
Corticosteroids **Prednisolone** **Other systemically administered corticosteroids**	Prednisolone AUC ↓ Also, for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifapentine.	Co-administration of NEORIFAN 300 with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		monitored, and corticosteroid doses adjusted as needed.
Oral hypoglycemics *Sulfonylureas* **Glibenclamide** **Gliclazide** **Glimepiride** **Glipizide** **Glyburide, etc** *Other oral antidiabetics* **Repaglinide**	Glibenclamide AUC ↓ Glimepiride AUC ↓ Repaglinide AUC ↓	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
Insulin	No interaction expected.	No dose adjustment required.
Levothyroxine	Case reports indicate that rifapentine may decrease the effect of levothyroxine.	TSH levels should be monitored.
Estrogens **Ethinylestradiol**	Ethinylestradiol AUC ↓	Co-administration with NEORIFAN 300 may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
Progestogens **Levonorgestrel** **Norethindrone**	The metabolism of progestogens may be increased by concomitant administration of rifapentine.	Co-administration with NEORIFAN 300 may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
CHEMOTHERAPEUTICS		
Cytotoxics **Irinotecan** **Imatinib**		Dosage of these drugs may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Hormone antagonist: antiestrogens **Tamoxifen** **Toremifene** **Gestrinone**		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
OTHERS		
Theophylline	Rifapentine may increase the clearance of theophylline.	Theophylline dose adjustment may be needed.
5-HT3 receptor antagonists		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Riluzole	Rifapentine may increase the clearance of riluzole.	Dosages of riluzole may require adjustment when starting or stopping concomitantly administered NEORIFAN 300.
Phosphodiesterase-5 (PDE-5) Inhibitors	Rifapentine may increase clearance of PDE-5 inhibitors such as sildenafil.	Dosage of PDE-5 inhibitor may require adjustment during concomitant administration with NEORIFAN 300.

Interactions with laboratory tests

Therapeutic levels of rifampicin may inhibit standard microbiological assays for serum folate and Vitamin B12. Similar effects may occur with rifapentine. Transient elevation of BSP and serum bilirubin may also occur. Rifapentine may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of NEORIFAN 300.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic (see section 5.3). When administered during the last few weeks of pregnancy, rifampicin, another rifamycin, may increase the risk for maternal postpartum haemorrhage and bleeding in the exposed infant.

Therefore, pregnant women and their infants, who are exposed to rifapentine during the last few weeks of pregnancy, should have appropriate monitoring of clotting parameters. Treatment with vitamin K may be indicated.

NEORIFAN 300 should only be used in pregnant women or in women of child-bearing potential if the potential benefit justifies the potential risk to the fetus. Untreated tuberculosis is considered to represent a far greater hazard to a pregnant woman and her fetus than treatment of the disease.

Lactation

It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-fed infants, a decision should be made whether to discontinue breast-feeding or discontinue NEORIFAN 300, taking into account the importance of NEORIFAN 300 to the mother and the benefits of breast-feeding.

Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

Fertility

There are no data on the effects NEORIFAN 300 on human male or female fertility. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats (see section 5.3).

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 NEORIFAN 300, should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Below is a table showing adverse drug reactions that have occurred when rifapentine was administered as part of a combination regimen (including with isoniazid), and thus the adverse reaction profile reflects the entire regimen.

System Organ Class	Adverse effects with a frequency of ≥ 1%	Adverse effects with a frequency of < 1%
Blood and lymphatic system disorders	Anaemia, lymphopenia, neutropenia, leukocytosis, thrombocytosis, thrombocytopenia, lymphadenopathy	Lymphocytosis, haematoma, purpura, thrombosis, leukopenia
Cardiovascular and vascular disorders		Syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis
Eye disorders	Conjunctivitis	
Gastrointestinal disorders	Dyspepsia, nausea, diarrhoea, vomiting, abdominal pain	Gastritis, oesophagitis, pancreatitis, salivary gland enlargement, constipation, dry mouth, oesophageal irritation
General disorders	Fever	Fatigue, asthenia, chest pain, chills, feeling jittery, facial Oedema
Hepatobiliary disorders	Elevated ALT, elevated AST	Bilirubinaemia, hepatomegaly, jaundice
Immune system disorders	Hypersensitivity disorders	
Investigations	Blood urea increased	
Infections and infestations		Pharyngitis, viral infection, vulvovaginal candidiasis, other fungal infections
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia, gout, hyperkalaemia, hyperlipidaemia, alkaline phosphatase increased
Musculoskeletal and connective tissue disorders	Arthralgia, back pain	Myalgia, myositis, rhabdomyolysis
Nervous system disorders	Headache, dizziness	Somnolence, dysphonia, convulsion, paresthesia, neuropathy peripheral, syncope.
Pregnancy and perinatal conditions		Abortion
Psychiatric disorders		Confusion, depression, anxiety, disorientation, suicidal ideation.
Renal and urinary disorders		Azotemia
Reproductive disorders		Vaginitis, vaginal haemorrhage, leucorrhoea, vulvovaginal pruritus
Respiratory, thoracic and mediastinal disorders	Cough, haemoptysis	Dyspnoea, oropharyngeal pain, asthma, bronchial hyperactivity, epistaxis, pneumonitis, pulmonary fibrosis, asthma, bronchospasm,

System Organ Class	Adverse effects with a frequency of ≥ 1%	Adverse effects with a frequency of < 1%
		laryngeal oedema, laryngitis.
Skin disorders	Rash, hyperhidrosis, pruritus	Urticaria, skin discoloration

The following serious and otherwise important adverse drug reactions are discussed in Section 4.4 'Special warnings and precautions for use'. Their frequencies are unknown.

- Severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS)
- Discoloration of body fluids
- Clostridioides difficile–associated diarrhoea
- Porphyria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorization holder via email (pv@sampharindoretro.com), or to the national reporting system :
National Pharmacovigilance Center / National MESO
Directorate of Drug, Narcotics, Psychotropics, Precursors, and Addictive Substances Safety, Quality, and Import-Export Control
Indonesian Food and Drug Authority
No. 23 Percetakan Negara Street, Central Jakarta - 10560, Indonesia
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR.

4.9 Overdose

Symptoms

When overdosed, rifapentine may cause heartburn, headache and pruritus. There is no experience with the treatment of acute overdose with rifapentine at doses exceeding 1200 mg per dose.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, ATC Code: J04AB05.

Mechanism of action

In vitro, rifapentine 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. Both rifapentine and the 25-desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.
Microbial resistance may occur and is a result of alterations in the target enzyme (RNA polymerase). Development of rifapentine resistance in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpo*β portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine-resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10^7 to 10^8 bacilli.

M. *tuberculosis* organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampicin and rifapentine has been demonstrated. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents.

Clinical efficacy and safety

5.1.1 Pulmonary Tuberculosis

Summary of the Rifapentine-containing Treatment Shortening Regimens for Pulmonary Tuberculosis: A Randomized, Open-Label, Controlled Phase 3 Clinical Trial

Clinical study based on published clinical studies conducted using the innovator product of Rifapentine Tablets 150 mg (n = 2516), by Centers for Disease Control and Prevention).

A randomized, open-label, noninferiority trial of two 4-month rifapentine-containing regimens, as compared with a standard 6-month rifampin-containing regimen, for the treatment of drug-susceptible tuberculosis. 2516 participants 12 years of age or older with newly diagnosed tuberculosis were randomly assigned to a 6-month control regimen, a 4-month regimen in which rifampin was replaced with rifapentine (rifapentine group), or a 4-month regimen in which rifampin was replaced with rifapentine and ethambutol with moxifloxacin (rifapentine-moxifloxacin group).

The primary objectives were to evaluate the efficacy of a rifapentine–containing regimen to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to seventeen weeks the duration of treatment for drug susceptible pulmonary tuberculosis. Also, to evaluate the efficacy of a rifapentine–containing regimen that in addition substitutes moxifloxacin for ethambutol and continues moxifloxacin during the continuation phase to determine whether it is possible to reduce to seventeen weeks the duration of treatment for drug-susceptible pulmonary tuberculosis.

Table 1 – Study treatment doses and durations

Rifapentine Group (2PHZE/2PH)	Rifapentine–moxifloxacin Group (2PHZM/2PHM)	Control Regimen (2RHZE/4RH)
<u>Dosage</u> Rifapentine (P) 1200 mg Isoniazid (H) 300 mg Pyrazinamide (Z): <55 kg: 1000 mg 55-75 kg: 1500 mg >75 kg: 2000 mg Ethambutol (E): <55 kg: 800 mg 55-75 kg: 1200 mg >75 kg: 1600 mg	<u>Dosage</u> Rifapentine (P) 1200 mg Isoniazid (H) 300 mg Pyrazinamide (Z): <55 kg: 1000 mg 55-75 kg: 1500 mg >75 kg: 2000 mg Moxifloxacin (M) 400 mg	<u>Dosage</u> Rifampin (R) 600 mg Isoniazid (H) 300 mg Pyrazinamide (Z): <55 kg: 1000 mg 55-75 kg: 1500 mg >75 kg: 2000 mg Ethambutol (E): <55 kg: 800 mg 55-75 kg: 1200 mg >75 kg: 1600 mg
Duration: A daily regimen of PHZE for 8 weeks, followed by PH for 9 weeks	Duration: A daily regimen of PHZM for 8 weeks, followed by PHM for 9 weeks	Duration: A daily regimen of RHZE for 8 weeks, followed by RH for 18 weeks

The primary endpoints for efficacy was TB disease-free survival at twelve months after study treatment assignment, for safety was proportion of participants with grade 3 or higher adverse events during study drug treatment.

Among 2516 participants who had undergone randomization, 2343 had a culture positive for

Mycobacterium tuberculosis that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine– moxifloxacin group, and 752 in the rifapentine group).

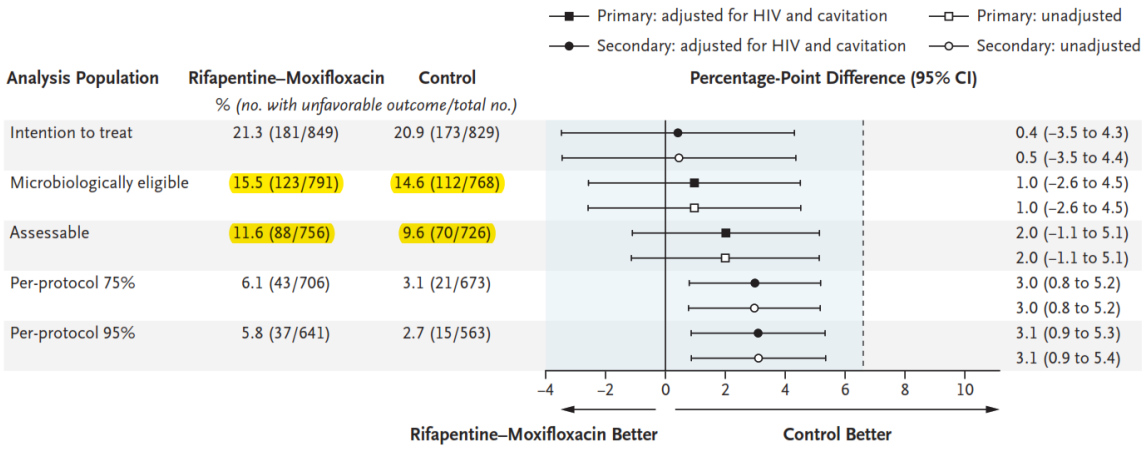

Figure 1 – Primary Efficacy Analysis Rifapentine–Moxifloxacin Regimen vs. Control Regimen

In the comparison between the rifapentine–moxifloxacin group and the control group, noninferiority was confirmed in both analysis populations. Figure 1 above shows that in the microbiologically eligible population, an unfavourable outcome occurred in 15.5% of the participants in the rifapentine–moxifloxacin group and the 14.6% of those in the control group, for an adjusted absolute difference of 1.0 percentage points (90% confidence interval [CI], −2.6 to 4.5). The corresponding values in the assessable population were 11.6% and 9.6%, for an adjusted absolute difference of 2.0 percentage points (95% CI, −1.1 to 5.1).

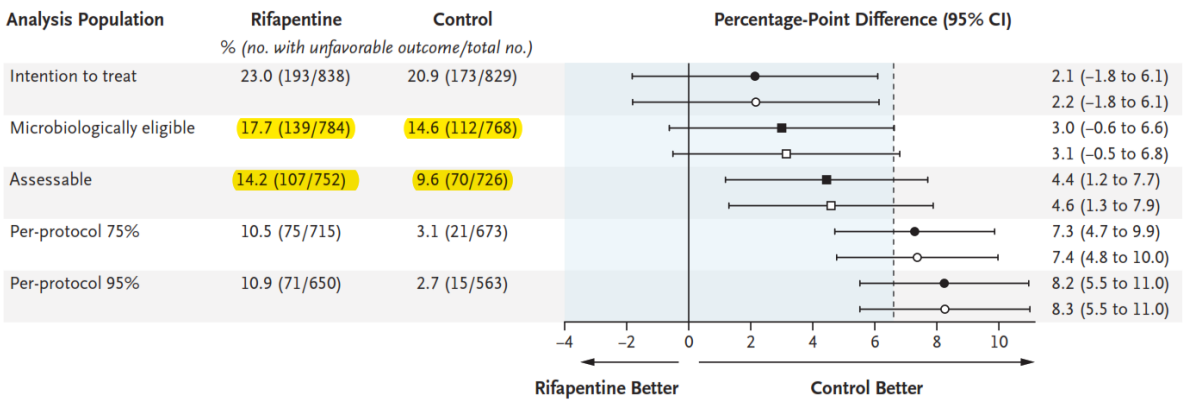

Figure 2 – Primary Efficacy Analysis Rifapentine Regimen vs. Control Regimen

The rifapentine regimen was not shown to be noninferior to the control regimen in either analysis population. Figure 2 above shows that in the microbiologically eligible population, an unfavorable outcome occurred in 17.7% of participants in the rifapentine group and 14.6% of those in the control group, with an adjusted absolute difference of 3.0 percentage points (95% CI], −0.6 to 6.6). The corresponding values in the assessable population were 14.2% and 9.6%, for an adjusted absolute difference of 4.4 percentage points (95% CI, 1.2 to 7.7).

Table 2 – Safety Analysis of Assigned Regimen*

Variable	Control (N=825)	Rifapentine–Moxifloxacin (N=846)	Rifapentine (N=835)	Total (N=2506)
Primary safety outcome				
Grade 3 or higher adverse event — no. (%)	159 (19.3)	159 (18.8)	119 (14.3)	437 (17.4)
Percentage-point difference from control (95% CI)†	NA	−0.6 (−4.3 to 3.2)	−5.1 (−8.7 to −1.5)	NA

Abbreviations:

* The safety analysis population included all the participants who had undergone randomization and received at least one dose of the assigned treatment. Safety was assessed during the on-treatment period (the time during which the participants were receiving the trial medications and up to 14 days after the last dose), unless otherwise specified. Adverse events were graded by the site investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

† The analysis was adjusted for the stratification factors of presence of cavitation on baseline chest radiography at baseline and HIV status.

Table 2 above shows that adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine–moxifloxacin group, and 14.3% in the rifapentine group.

The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. Also has potential benefits over the standard 6-month treatment, indicating that shorter treatment durations with Rifapentine-containing regimens could be effective.

5.1.2 Latent Tuberculosis Infection

Summary of the Treatment for Preventing Tuberculosis in Children and Adolescents: A Randomized Clinical Trial f a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

Clinical studies based on published clinical studies conducted using the innovator product of Rifapentine Tablets 150 mg (n = 1058), by Centers for Disease Control and Prevention

The study is a pediatric cohort nested within a randomized, open-label clinical trial conducted from June 11, 2001, to December 17, 2010, with follow-up through September 5, 2013. It involved children aged 2 to 17 years, who were enrolled from 29 study sites across the United States, Canada, Brazil, Hong Kong (China), and Spain.

Children were enrolled based on their high risk for TB, according to age, tuberculin skin test (TST) results, and TB exposure history. The study protocol was approved by institutional review boards at the Centers for Disease Control and Prevention, the National Institutes of Health, and all study sites. Informed consent was obtained from parents, and assent was provided by children.

The primary objectives were to compare treatment safety and assess noninferiority treatment effectiveness of combination therapy with rifapentine and isoniazid vs 9 months of isoniazid treatment for latent tuberculosis infection in children.

Table 3 – Study treatment doses and durations

Isoniazid (INH) Group	Isoniazid/Rifapentine (RPT/INH) Group
Daily doses of INH for 9 months.	Weekly doses of RPT/INH for 3 months
Dosage: 240 to 270 total doses Isoniazid (H) - Isoniazid (H) 5 mg/kg (rounded up to nearest 50 or 100 mg; 300 mg max) daily x 270 doses (9 months). - For children age 2 - 11, INH 10-15 mg/kg (round up to nearest 50 or 100 mg; 300 mg max) will be given.	Dosage: 11 to 12 total doses Rifapentine (P) - 900 mg once-weekly x 12 doses (3 months) for persons > 50.0 kg. - For persons < 50.0 kg, the following doses will be given (Weight/Dose): 10.0-14.0 kg / 300 mg 14.1-25.0 kg / 450 mg 25.1-32.0 kg / 600 mg 32.1-50.0 kg / 750 mg Isoniazid (H) - INH 15 mg/kg (rounded up to nearest 50 or 100 mg; 900 mg max) once weekly x 12 doses if > 12 years old. - INH 25 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) if 2-11 years old.
Self-administered (without supervision by a healthcare professional)	Directly Observed Therapy (DOT)
Duration of treatment: Duration per participant is approximately 33 months	

The primary endpoint was the comparison of treatment safety between the two study arms, assessing the rates of adverse events (AEs) and treatment discontinuation attributed to AEs. The secondary endpoint was the assessment of treatment effectiveness for noninferiority of the combination therapy compared with the isoniazid-only regimen for TB prevention.

The trial planned to enroll 1058 participants. During the assessment periods, 1335 individuals were assessed for eligibility, and 823 were enrolled, in addition to 235 enrolled during earlier assessment periods. In total, 1058 children were enrolled. In the isoniazid treatment group, 506 participants were assigned, with 493 receiving at least one dose of the intervention. In the combination drug therapy group, 552 participants were assigned, with 539 receiving at least one dose of the intervention. In the isoniazid treatment group, 434 participants were eligible for the modified intention-to-treat population, while 471 participants in the combination therapy group were eligible. Key points regarding patient disposition included:

a. Intention to Treat Population: All 1058 enrolled participants.
b. Modified Intention to Treat Population: 905 participants who were eligible for efficacy analysis.
c. Safety Population: 1032 participants who received at least one dose of the study medication

Of 1058 children enrolled, 905 were eligible for evaluation of effectiveness. Table 7 shows how the noninferiority criterion was met when none of the 471 patients in the combination-therapy arm developed tuberculosis vs 3 of 434 in the isoniazid-only arm (cumulative rate, 0.74%), for a difference of −0.74% and an upper bound of the 97.5% CI of the difference of +0.32%. Per-protocol population effectiveness analysis showed similar results. The difference in cumulative TB disease rate is the rate in the combination-therapy arm minus the rate in the isozanid-only arm. The noninferiority margin was 0.75% for all analyses.

Table 8 shows that of 471 in the combination-therapy group, 415 (88.1%) completed treatment vs 351 of 434 (80.9%) in the isoniazid-only group (P = 0.003). The 95% CI for the difference in rates of

discontinuation attributed to an AE was −2.6 to 0.1, which was within the equivalence range.

Table 4 – Difference in Tuberculosis Disease Rates Between the 2 Treatment Regimens Over Time (MITT Population)

Treatment Arm	No.	TB Cases[a]	TB per 100 Patient-Years	Cumulative TB Rate, %	Difference in Cumulative TB Rates	One-sided 97.5% CI[b]
Isoniazid only	434	3	0.27	0.74	-0.74	0.32
Combination drug therapy	471	0	0.00	0.00		

[a] None had evidence of re-exposure to infectious TB: (1) one 14-year-old female was diagnosed 72 days after the first dose, with 2 cultures positive for Mycobacterium tuberculosis; (2) one 5-year-old male was clinically diagnosed 818 days after the first dose; and (3) one 2-year-old male was clinically diagnosed 839 days after the first dose.

[b] One-sided 97.5% CI for the difference in cumulative TB disease rates (percentage) using a conservative adjustment for a rare binomial event

Table 5 – Tolerability and Reasons for Discontinuation Among Children in the Modified Intention-to-Treat Population

Characteristic	Patients, No. (%)		*P* Value[a]	Difference (95% CI)[b]
	Isoniazid (n = 434)	Rifapentine Plus Isoniazid (n = 471)		
Treatment completion	351 (80.9)	415 (88.1)	.003	−7.2 (−2.0 to −2.5)
Reason for not completing treatment				
All reasons	83 (19.2)	56 (11.9)	.003	7.2 (2.5 to 12.0)
Discontinuation because of AE[c]	2 (0.5)	8 (1.7)	.11	−1.2 (−2.6 to 0.1)
Withdrawal of informed consent	5 (1.2)	4 (0.9)	.74	0.3 (−1.0 to 1.6)
Lost for ≥3 mo during treatment	26 (6.0)	5 (1.1)	<.001	4.9 (2.5 to 7.4)
Physician decision to cancel other than AE	7 (1.6)	3 (0.6)	.21	1.0 (−0.4 to 2.4)
Participant refusal	15 (3.5)	16 (3.4)	>.99	0.1 (−2.3 to 2.4)
Total dose count and/or administration period outside of protocol guidelines[d]	28 (6.5)	20 (4.3)	.18	2.2 (−0.7 to 5.2)

Abbreviation: AE, adverse event

[a] P value based on Fisher exact test.

[b] 95% CI for the difference in proportions using the Wilson Score Interval method.

[c] Combination-therapy group included 3 influenza-like AEs (grade 2), 3 cutaneous (all with pruritic rash [2 were grade 2], 1 with oral blisters and fever [grade 3]), and 2 gastrointestinal reactions (1 was grade 1 and 1 was grade 2). Isoniazid-only group included 1 cutaneous AE (grade 2) and 1 gastrointestinal reaction (grade 3).

[d] Measure of adherence

No serious AEs were attributed to study treatment in either group. Table 9 shows that in the safety population, 3 of 539 participants (0.6%) who took the combination drugs had a grade 3 AE vs 1 of 493 (0.2%) who received isoniazid only. Neither arm had any hepatotoxicity, grade 4 AEs, or treatment-attributed death. One hepatic event occurred in a 3-year-old with newly diagnosed Kawasaki disease, unrelated to study medication. Among five HIV-infected participants aged 12–17 years, no treatment-related AEs were reported.

Table 6 – Safety End Points Among Children Who Received at Least 1 Dose of Study Medication

Characteristic	Patients, No. (%)		*P* Value[a]	Difference (95% CI)[b]
	Isoniazid (n = 493)	Rifapentine Plus Isoniazid (n = 539)		
AEs attributed to treatment				
Grades 1 and 2	5 (1.0)	11 (2.0)	.21	−1.0 (−2.5 to 0.5)
Grade 3	1 (0.2)	3 (0.6)	.63	−0.4 (−1.1 to 0.4)
Grade 4	0	0	NA	NA
Grade 5, death	0	0	NA	NA
Serious AEs	0	0	NA	NA
AEs not attributed to treatment				
Grades 1 and 2	35 (7.1)	25 (4.6)	.11	2.0 (−0.4 to 5.3)
Grade 3	5 (0.2)	3 (0.6)	.49	0.4 (−0.6 to 1.5)
Grade 4	2 (0.4)	1 (0.2)	.61	0.2 (−0.5 to 0.9)
Grade 5, death[c]	2 (0.4)	0	.23	0.4 (−0.2 to 1.0)
Serious AEs[d]	7 (1.4)	0	.01	1.0 (0.4 to 2.5)

Abbreviations: AE, adverse event; NA, not available.

[a] P value based on Fisher exact test.

[b] 95% CI for the difference in proportions using the Wilson Score Interval method.

[c] Death 1 was due to malignant arrhythmia in a 16-year-old girl on day 201 of study treatment; death 2, gunshot injury in a 16-year-old boy at study day 901 (approximately 657 days after the end of the study treatment phase).

[d] Serious AEs include deaths while receiving therapy or within 60 days of the last dose, life-threatening events, hospitalization, disability or permanent damage, and congenital anomaly. For children aged 2 through 16 years, 6 had 1 serious AE and 1 had more than 1 serious AE.

Treatment with the combination of rifapentine and isoniazid was as effective as isoniazid-only treatment for the prevention of tuberculosis in children aged 2 to 17 years. The combination-therapy group had a higher treatment completion rate than did the isoniazid-only group and was safe.

5.2 Pharmacokinetic properties

Absorption of NEORIFAN 300

The absorption characteristics of NEORIFAN 300 have been determined after administration of 300 mg tablets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	Mean value* ± standard deviation
Maximum concentration (C_{max})	10.8 ± 2.4 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	257 ± 68 µg·h/mL
Time to attain maximum concentration (t_{max})	5.39 ± 0.60 h

Pharmacokinetics of Rifapentine

Absorption	
Absolute bioavailability	NA*
Oral bioavailability	>32%
Food effect	High fat meal: AUC ↑ 43%, C_{max} ↑ 44%
Distribution	
Volume of distribution (mean)	70.2 ± 9.1 L
Plasma proteinbinding *in vitro*	Rifapentine 98% 25-desacetyl rifapentine 93%
Tissue distribution	NA*
	hydrolyzed by esterase enzymes and CYP3A4
Active metabolite(s)	25-desacetyl rifapentine
Elimination	
Elimination half life	Rifapentine: 13.2 – 14.1 hours 25-desacetyl rifapentine: 13.3 – 24.3 hours
Mean systemic clearance (Cl/F)	2.0 ± 0.6 L
% of dose excreted in urine	17%
% of dose excreted in faeces	70%
Pharmacokinetic linearity	Linear up to a 600 mg dose; at higher dose less than dose proportional increase
Drug interactions *(in vitro)*	Rifapentine is an inducer of CYP3A4, 2C8 and 2C9 and P-gp Rifapentine is an auto-inducer by CYP3A
Transporters	NA*
Metabolizing enzymes	Esterases and CYP3A4

*Information not available

Special population

Gender

PK profiles in healthy young women and young men did not evidence any gender effect for rifapentine or 25-desacetyl-rifapentine. Gender was also investigated as covariates of population PK model and was not associated with rifapentine PK variability.

Elderly patients

In elderly (≥65 years), following single oral administration of 600 mg, mean rifapentine and 25-desacetyl-rifapentine exposures were increased (41% for rifapentine AUC, 58% for 25-desacetyl-rifapentine) compared to healthy young subjects (historical comparison). However no dose adjustments were recommended for elderly subjects based on safety results in elderly healthy subjects and elderly patients with LTBI.

Pediatric patients

In healthy adolescents, rifapentine and 25-desacetyl-rifapentine PK were not different from those observed in healthy adults.
In pediatrics (younger than 12-years old), a significant correlation was observed between clearance and age: clearance adjusted to body weight increased when decreasing age.
Based on these findings, a weight band dosing was selected for rifapentine in children with LTBI and validated with PK and safety data in this population.
In children (2-12 years of age) receiving doses based on weight, while the mean rifapentine dosages in mg/kg were 2-fold higher than in adults (23 versus 11 mg/kg), exposures were 31% and 41% higher than adults for rifapentine and 25-desacetyl-rifapentine respectively, exposures that in adults have been associated with successful treatment of LTBI. Among children, exposure was about 25% lower in those who could not swallow the whole tablets and received crushed tablets but still higher than in adults. Despite the generally increased exposure observed in children, higher mg/kg rifapentine doses were well tolerated.

Hepatic impairment
Following oral administration of a single 600 mg dose of rifapentine to mild to severe hepatic impaired patients, the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment. In comparison to healthy subjects, rifapentine and 25-desacetyl-rifapentine exposure (AUC) were increased in subjects with hepatic impairment by 19% to 25% and 77% to 99%, respectively.

Renal impairment
The pharmacokinetics of rifapentine have not been evaluated in renal impaired patients. However, the risk of an impact of impaired renal function on PK is considered as minimal only about 17% of an administered dose is excreted via the kidneys. The clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Asymptomatic HIV-Infected Patients
In asymptomatic HIV-infected subjects, rifapentine and 25-desacetyl metabolite PK profiles were not significantly different from those observed in healthy subjects. The safety and PK results indicated that no dose adjustment for rifapentine is necessary for asymptomatic HIV-infected patients.

Bioequivalence
The bioequivalence study demonstrated that one tablet of NEORIFAN 300 is bioequivalent to two tablets of Priftin® 150 mg (Sanofi-aventis U.S. LLC, USA), with geometric mean ratios of 107.60% (90% CI: 101.57%–113.98%) for Cmax and 103.10% (90% CI: 97.29%–109.27%) for AUC_0–t. Therefore, it is concluded that the test formulation, NEORIFAN 300, is bioequivalent to the reference formulation, two 150 mg Priftin® tablets, in healthy adult subjects under fed conditions. Both formulations were safe and well tolerated following single-dose administration.

5.3 Preclinical safety data

Rifapentine
Hepatocellular carcinomas were increased in male mice that were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).
Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in *Aspergillus nidulans*; in vitro gene conversion assay in *Saccharomyces*

cerevisiae; host-mediated (mouse) gene conversion assay with *Saccharomyces cerevisiae*; in vitro Chinese hamster ovary cell/hypoxanthineguaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

The 25-desacetyl metabolite of rifapentine was positive in the in vitro mammalian chromosome aberration test in V79 Chinese hamster cells, but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay.

Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given rifapentine during organogenesis at doses 0.6 times the human dose (based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered to mated female rats late in gestation, at 0.3 times the human dose (based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls.

Increased resorptions and post implantation loss, decreased mean foetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received rifapentine at doses 0.3 to 1.3 times the human dose (based on body surface area), major fetal malformations occurred including: ovarian agenesis, pes varus, arhinia, microphthalmia and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to one-third of the human dose (based on body surface area conversions).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Microcrystalline Cellulose, Pregelatinized Starch, Low substituted Hydroxy propyl cellulose, Sodium Starch Glycolate, Sodium Lauryl Sulfate, Hydroxypropyl Cellulose, Disodium Edetate, Sodium Ascorbate, Colloidal Silicon Dioxide, Calcium Stearate.

Film Coat: Opadry® II 85F565338 Brown (Polyvinyl Alcohol, Polyethylene Glycol/Macrogol, Titanium Dioxide, Talc, Iron Oxide Red).

This medicine contains too little sodium to have any effect, even if patient is on a low-sodium diet.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date or as printed on the packaging. Do not use after the expiry date.

6.4 Special precautions for storage

Store below 30°C. Protect from heat and humidity. Keep out of reach of children.

6.5 Nature and contents of container <Registration Number>

Strip pack of 10 Tablets such 10 Strips in a carton along with pack insert (10 x 10 tablets).

Reg. No.:

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. MANUFACTURER AND MARKETING AUTHORIZATION HOLDER

Manufactured by :

OXALIS LABS - Village Theda, P.O Lodhimajra, Baddi, Dist. Solan (DT), Himachal Pradesh, 174101, India.

Imported by :

PT. SAMPHARINDO RETROVIRAL INDONESIA - Jalan Tambak Aji Timur V No. 50, Semarang, 50185, Indonesia.

8. DATE OF REVISION OF THE TEXT

9. CLASSIFICATION OF DRUG

Obat Keras

10. SPECIAL WARNING

“ON MEDICAL PRESCRIPTION ONLY”

“HARUS DENGAN RESEP DOKTER”