SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUOPIC 150/75, 150 mg and 75 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg rifampicin and 75 mg isoniazid.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pulmonary tuberculosis for adults in the continuous phase of treatment.

4.2 Posology and method of administration

Posology

DUOPIC 150/75 tablets are recommended in the continuation phase of the treatment of pulmonary tuberculosis. During this phase, which lasts for 4 months, this medicine should be administered on a continuous daily basis.

The total dosage requirement is as follows:

	Daily (dose range)
Rifampicin	10 mg/kg maximum 600 mg per day (8 mg to 12 mg)
Isoniazid	5 mg/kg maximum 300 mg per day (4 mg to 6 mg)

The daily dosage is as follows:

Patient body mass (kg)	*Amount of tablets (daily)*
30 to 37*	2
38 to 54	3
55 to 70	4
71 and more*	5

* In practice, most patients taking rifampicin containing FDC tablets will receive either 3 or 4 tablets daily. Only a small proportion of adult TB patients will fall into the categories with a body-mass from 30 to 37 kg or body-mass above 70 kg. This might necessitate the maximum dose of rifampicin of 600 mg per day to be exceeded; however, the dose limit of 12 mg/kg will still be observed which does not pose an additional risk.

Method of administration

DUOPIC 150/75 tablets should be taken orally, as a single dose and should be swallowed whole with water.

4.3 Contraindications

DUOPIC 150/75 is contraindicated in:

- Patients with a hypersensitivity to rifamycins or isoniazid or other chemically related medicines such as ethionamide, pyrazinamide, niacin or any of the excipients of DUOPIC 150/75 (see section 6.1).
- Patients with jaundice and acute porphyria (see section 4.4).
- Patients with liver damage.
- Patients with active liver disease of any aetiology.
- Patients with a history of drug-induced liver injury.
- Patients with impaired hepatic function (rifampicin is metabolised in the liver and may also be hepatotoxic. The risk of hepatitis is increased with daily alcohol consumption or existing hepatic impairment).
- Concurrent treatment with:
  - The combination of saquinavir/ritonavir (see section 4.5);
  - Nevirapine (see section 4.5).
  - Lurasidone as it markedly decreases the exposure of lurasidone compared to the use of lurasidone alone (see section 4.5).
- Patients with severe renal failure (CrCl < 30 ml/min).
- Patients with seizure disorders (isoniazid may be neurotoxic and cause seizures).

- Pregnancy and lactation (see section 4.6).
- DUOPIC 150/75 may cause thrombocytopenia and purpura, especially with intermittent tuberculosis regimens. Further administration is contraindicated in such cases (see section 4.8).

4.4 Special warnings and precautions for use

Rifampicin, as in DUOPIC 150/75, should be administered under the supervision of a respiratory or other suitably qualified medical practitioner.

Warnings and precautions associated with rifampicin and isoniazid, alone or in combination

DUOPIC 150/75 a combination of two substances, each of which has been associated with liver dysfunction.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with DUOPIC 150/75 should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count and a platelet count (or estimate).

Patients should be seen at least monthly during therapy and should be questioned specifically about symptoms associated with adverse reactions. If the patient has no evidence of pre-existing liver disease and normal pre-treatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occurs.

All patients with abnormalities should have follow-up, including laboratory testing, if necessary. However, because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 years of age, a transaminase measurement should be obtained at baseline and at least monthly during therapy in this age group. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, intravenous drug use, and being a black or Hispanic woman.

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with Rifampicin or combination products containing Rifampicin, such as DUOPIC 150/75. If laboratory or clinical findings associated with TMA occur in a patient receiving DUOPIC 150/75, treatment should be discontinued and thorough evaluation for TMA performed, including platelet levels, renal function, serum lactate dehydrogenase (LDH) and a blood film for schistocytes (erythrocyte

fragmentation). ADAMTS13 activity and anti-ADAMTS13-antibody determination should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with DUOPIC 150/75 should not be resumed and patients should be treated accordingly (consider plasma exchange).

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (see section 4.8). It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to immediately consult their medical practitioner.

DUOPIC 150/75 should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

A paradoxical drug reaction may be observed due to the treatment with antitubercular agents, including DUOPIC 150/75. If worsening of existing tuberculosis or new onset of tuberculosis symptoms is observed after initiating the treatment, whether to continue administration should be determined on the basis of drug susceptibility tests, etc.

Warnings and precautions associated with rifampicin

Patients with impaired liver function should only be given rifampicin, as in DUOPIC 150/75, in cases of necessity, and then with caution and under close medical supervision. In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should initially be carried out prior to therapy, weekly for two weeks, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

Rifampicin, as in DUOPIC 150/75, should also be withdrawn if clinically significant changes in hepatic function occur. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily.

In patients with impaired liver function, elderly patients, malnourished patients and possibly children

under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with rifampicin.

In some patients, hyperbilirubinemia can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion. An isolated report showing a moderate rise in bilirubin and/or transaminase level 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.

Cases of drug-induced liver injury, including fatal cases (especially when used in combination with other anti-tuberculosis drugs), have been reported in patients treated with rifampicin with an onset of a few days to a few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes, cholestatic jaundice, hepatitis, hepatotoxicity, hepatocellular injury, and mixed liver injury. Most patients recovered on discontinuation of rifampicin treatment; nevertheless, progression to acute liver failure requiring liver transplantation can occur. The mechanism of rifampicin-induced liver injury is not clearly elucidated, but data indicate either an immuno-allergic mechanism or direct toxicity of metabolic products. Patients should be instructed to contact their medical practitioner in case symptoms suggestive of liver injury occur. In such patients, DUOPIC 150/75 should be discontinued, and liver function should be assessed. DUOPIC 150/75 should not be re-introduced in patients with an episode of hepatic injury during treatment with rifampicin for which no other cause of liver injury has been determined.

Because of the possibility of immunological reaction including anaphylaxis (see section 4.8) occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens since these reactions may occur.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with a not known frequency in association with DUOPIC 150/75 treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, DUOPIC 150/75 should be withdrawn immediately and an alternative treatment considered (as appropriate).

Most of these reactions occurred within 2 days to 2 months after treatment initiation; the time to onset can vary depending on the conditions.

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

Rifampicin, as in DUOPIC 150/75, may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained (see section 4.8).

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters and might therefore decrease concomitant drug exposure and efficacy (see Section 4.5). Therefore, potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.

Rifampicin, as in DUOPIC 150/75, may cause vitamin K dependent coagulopathy and severe bleeding (see Section 4.8). Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinaemia).

There have been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving rifampicin for treatment of tuberculosis. ILD/pneumonitis is a potentially fatal disorder. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea accompanied by dry cough) and fever should be performed to confirm the diagnosis of ILD/pneumonitis. If ILD/pneumonitis is diagnosed, DUOPIC 150/75 should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

Warnings and precautions associated with isoniazid

Cerebellar syndrome (including cerebellar ataxia, ataxia, dysdiadochokinesis, balance disorders, nystagmus, dysmetria) has been reported with the use of isoniazid mainly in patients with chronic kidney disease (see section 4.8).

Use of isoniazid, as in DUOPIC 150/75, should be carefully monitored in patients with current chronic liver disease or severe renal dysfunction.

Severe and sometimes fatal hepatitis associated with isoniazid, as in DUOPIC 150/75, therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Therefore, patients should be monitored for the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, DUOPIC 150/75 should be discontinued promptly, since continued use of the isoniazid, as in DUOPIC 150/75, in these cases has been reported to cause a more severe form of liver damage.

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (See section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develops, the patient should be advised to immediately consult their medical practitioner. DUOPIC 150/75 should be permanently discontinued if an alternative etiology for the signs and symptoms cannot be established.

Care should be exercised in the treatment of elderly or malnourished patients who may also require vitamin B6 supplementation with the isoniazid, as in DUOPIC 150/75, therapy.

Use of isoniazid, as in DUOPIC 150/75, should be carefully monitored in patients with slow acetylator status, epilepsy, history of psychosis, history of peripheral neuropathy, diabetes, alcohol dependence, HIV infection or porphyria.

4.5 Interaction with other medicines and other forms of interaction

Food Interaction

Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), therefore can reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, and hypotension. Patients should be advised against ingesting foods rich in tyramine and/or histamine during treatment with isoniazid, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).

Interactions with other medicines

Interactions with saquinavir/ritonavir

When DUOPIC 150/75 is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of DUOPIC 150/75 with

saquinavir/ritonavir is contraindicated (see section 4.3).

Cytochrome P-450 enzyme interaction

Rifampicin is known to induce, and isoniazid is known to inhibit certain cytochrome P-450 enzymes. In general, the impact of the competing effects of rifampicin and isoniazid on the metabolism of medicines that undergo biotransformation through the affected pathways is unknown. Therefore, caution should be used when prescribing DUOPIC 150/75 with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of medicines metabolised by these enzymes may require adjustment when starting or stopping DUOPIC 150/75.

Interactions with Rifampicin

Pharmacodynamic interactions

The potential for hepatotoxicity is increased with an anaesthetic.

When rifampicin, as in DUOPIC 150/75, is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both DUOPIC 150/75 should be monitored closely for hepatotoxicity.

The concomitant use of rifampicin with other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (specially with high doses).

Effect of rifampicin on other medicines

Induction of Drug Metabolising Enzymes and Transporters

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters. Enzymes and transporters reported to be affected by DUOPIC 150/75 include cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Most medicines are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by DUOPIC 150/75 simultaneously. Therefore, DUOPIC 150/75 may accelerate the metabolism and reduce the activity of certain co-administered medicines and has the potential to perpetuate clinically important interactions against many medicines and across many medicine classes. To maintain optimum therapeutic blood levels, dosages of medicines may require adjustment when starting or stopping concomitantly administered DUOPIC 150/75.

Examples of medicine or medicine classes affected by DUOPIC 150/75:

- Anti-dysrhythmics such as disopyramide, lorcainide, mexiletine, quinidine, propafenone, tocainide, digitoxin as well as digoxin may have enhanced metabolism resulting in significantly lower serum antidysrhythmic concentrations; serum antidysrhythmic concentrations should be monitored and dosage adjustment may be necessary.
- Antiepileptics (e.g. phenytoin): The elimination of phenytoin is increased and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after DUOPIC 150/75 therapy.
- Anticoagulants: Rifampicin may enhance the metabolism of anticoagulants (e.g. warfarin), resulting in a considerable decrease in the activity and efficacy of the anticoagulants; prothrombin time determinations may be required as frequently as once a day; dosage adjustments of anticoagulants may be required before and after DUOPIC 150/75 therapy.
- Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole, caspofungin): Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs. After two weeks of repeated administration of rifampicin, though levels of caspofungin were 30 % lower than in adult subjects who received caspofungin alone.
- Antivirals: Rifampicin accelerates the metabolism of zidovudine, protease inhibitors (e.g. ritonavir and saquinavir, indinavir, amprenavir, nelfinavir, atazanavir and lopinavir) NNRTIs (e.g. delavirdine, efavirenz and nevirapine) through induction of hepatic P450 cytochrome oxidases, resulting in sub-therapeutic levels of the these ARVs; in addition, these protease inhibitors and NNRTIs retard the metabolism of rifampicin, resulting in increased serum levels of rifampicin and the likelihood of increased toxicity. Rifampicin also decreases the serum concentration of the CCR-5 receptor antagonist maraviroc.
- Systemic hormonal contraceptives including estrogens and progestogens: Rifampicin treatment reduces the systemic exposure of oral contraceptives. Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during DUOPIC 150/75 therapy
- Corticosteroids, glucocorticoid and mineralocorticoids: Rifampicin may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; rifampicin has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison's disease.
- Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone): Diabetes may become more difficult to control.
- Enalapril: Decrease enalapril active metabolite exposure. Dosage adjustments should be made

if indicated by the patient's clinical condition.

- Hepatitis-C antiviral medicines (e.g. daclatasvir, simeprevir, sofosbuvir, telaprevir): Concurrent use of treatment of hepatitis-C antiviral medicines and rifampicin should be avoided.
- Analgesics (e.g. methadone, narcotic analgesics): Plasma concentrations of oxycodone and morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.
- Lurasidone: Rifampicin 600mg was shown to decrease lurasidone AUC by 81 %. Therefore, markedly reduced exposure of lurasidone can be expected when lurasidone is given concomitantly with a CYP3A4 inducer such as rifampicin (see section 4.3).
- Clopidogrel: Increases active metabolite exposure. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.
- Dapsone: Rifampicin has also been shown to increase the clearance of dapsone and the production of the hydroxylamine metabolite of dapsone which could increase the risk of methaemoglobinaemia, haemolytic anaemia, agranulocytosis, and haemolysis.
- Mifepristone: Rifampicin was shown to decrease mifepristone AUC by 6.3-fold and its metabolites 22-hydroxymifepristone and N-demethyl mifepristone by 20-fold and 5.9-fold, respectively. Therefore, reduced efficacy can be expected when mifepristone is given concomitantly with a potent CYP inducer such as rifampicin.
- Alcohol: concurrent daily consumption of alcohol may increase the risk of rifampicin-induced hepatotoxicity and increased metabolism of rifampicin; dosage adjustments of rifampicin and therefore DUOPIC 150/75 may be necessary, and patients should be monitored closely for signs of hepatotoxicity (see sections 4.3 and 4.4).
- Hormone antagonist (anti-estrogens e.g. tamoxifen, toremifene, gestinone)
- Antipsychotics (e.g. haloperidol, aripiprazole)
- Barbiturates
- Beta-blockers (e.g. bisoprolol, propranolol)
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem)
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine)
- Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin)
- Clofibrate
- Immunosuppressive medicines (e.g. ciclosporin, sirolimus, tacrolimus)
- Irinotecan

- Thyroid hormone (e.g. levothyroxine)
- Losartan
- Praziquantel
- Quinine
- Riluzole
- Selective 5-HT3 receptor antagonists (e.g. ondansetron)
- Statins metabolised by CYP 3A4 (e.g. simvastatin)
- Theophylline
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)
- Cytotoxics (e.g. imatinib)
- Diuretics (e.g. eplerenone)

Rifampicin may reduce the effect of antiemetics (e.g. aprepitant), drugs used in erectile dysfunction (e.g. tadalafil), oral hypoglycaemic agents (e.g. nateglinide, repaglinide) and NSAIDS (e.g. etoricoxib).

If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

Effect of other medicines on rifampicin

- Antacids: Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of DUOPIC 150/75 should be given at least 1 hour before the ingestion of antacids.
- Paracetamol: Concomitant use of paracetamol with rifampicin may increase the risk of hepatotoxicity.

Other medicine interactions with rifampicin

When the two medicines were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Interactions with Isoniazid

The following medicines may interact with isoniazid:

- Antiepileptics: Isoniazid inhibits the hepatic metabolism of such medicines as carbamazepine, ethosuximide, primidone and phenytoin causing increased concentrations and potentially leading to increased toxicity.
- Stavudine: There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine.

- Zalcitabine: Concomitant use of zalcitabine with isoniazid has been shown to approximately double the renal clearance if isoniazid in HIV infected patients.
- Prednisolone: Administration of prednisolone 20 mg to 13 slow acetylators and 13 fast acetylators for receiving isoniazid 10mg/kg reduced plasma concentrations of isoniazid by 25 % and 40 %, respectively. The clinical significance of this effect has not been established.
- Alcohol: The effect of acute alcohol intake (serum levels 1g/L maintained for 12 hours) on the metabolism of isoniazid (300 mg/d for 2 days) was studied in 10 healthy volunteers in a controlled cross over design. The metabolism of isoniazid and its metabolite, acetyl isoniazid, was not modified by this acute alcohol intake. The metabolism of isoniazid may be increased in chronic alcoholics; however, this effect has not been quantified. Appropriate adjustments of these medicines should be made.
- Acetaminophen and paracetamol: Concomitant use of isoniazid and paracetamol may increase the risk of hepatoxicity.
- Alfentanil: Isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil.
- Anticoagulants such as warfarin display decreased hepatic metabolism thus resulting in increased concentrations or toxicity.
- Benzodiazepines such as diazepam, triazolam, chlordiazepoxide, flurazepam and prazepam may have decreased metabolism and thus increased plasma concentrations of benzodiazepines.
- Clofazimine: Isoniazid has been associated with increased concentrations and enhanced effects or toxicity of clofazimine.
- Disulfiram: concurrent use in alcoholics may result in increased incidence of CNS effects such as dizziness, incoordination, irritability or insomnia; reduced dosage or discontinuation of disulfiram may be necessary.
- Pyridoxine: Isoniazid may cause peripheral neuritis by acting as a pyridoxine antagonist or increasing renal excretion of pyridoxine; requirements for pyridoxine may be increased in patients receiving isoniazid.
- Central nervous system (CNS) medicines: Isoniazid may reduce the therapeutic effects of levodopa.
- Antipsychotics (e.g. Chlorpromazine): Concomitant use with isoniazid may impair the metabolism of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Other Interactions

- Para-aminosalicylic acid: May increase the plasma concentration and elimination half-life of isoniazid by competing for acetylating enzymes.

- General anaesthetics: May increase the hepatotoxicity of isoniazid. Enflurane may increase formation of the potentially nephrotoxic inorganic fluoride metabolite.
- Antacids: The absorption of isoniazid is reduced by antacids.
- Clycloserine: The risk of CNS toxicity is increased when isoniazid is given with cycloserine.
- Ketoconazole and Itraconazole: Isoniazid may reduce plasma concentration of ketoconazole. Concurrent use should be well monitored, and dosage increases made if necessary.
  Concomitant administration of isoniazid with itraconazole may result in significant decreases in itraconazole serum concentrations and therapeutic failure. Co-administration is not recommended.
- Theophylline: Isoniazid may increase plasma concentration of theophylline.
- Procainamide: Concomitant use of procainamide and isoniazid may increase the isoniazid plasma concentrations.

Interference with laboratory and diagnostic tests

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus, alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin has been reported. Rifampicin 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 rifampicin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of DUOPIC 150/75 has not been established in pregnant or lactating women.

Rifampicin

Rifampicin has been shown to be teratogenic in rodents when given in large doses. There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis medicines, on the human foetus is not known.

When administered during the last few weeks of pregnancy, rifampicin can cause post-natal haemorrhages in the mother and infant, for which treatment with Vitamin K1 may be indicated**.**

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocardial effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have

been found in reproduction studies in mammalian species (mice, rats, rabbits).

Breastfeeding

Rifampicin and isoniazid are excreted in breast milk and infants should not be breast fed by a patient receiving DUOPIC 150/75.

In breast-fed infants whose mothers are taking isoniazid, there is a theoretical risk of convulsions and neuropathy (associated with vitamin B6 deficiency), therefore they should be monitored for early signs of these effects and consideration should be given to treating both mother and infant prophylactically with pyridoxine.

Fertility

No human data available.

4.7 Effects on ability to drive and use machines

Isoniazid, as in DUOPIC 150/75, has been associated with vertigo, visual disorders and psychotic reactions (see section 4.8). Patients should be informed of these, and advised that if affected, they should not drive, operate machinery or take part in any activities where these symptoms may put either themselves or others at risk.

4.8 Undesirable effects

Rifampicin

Reactions to rifampicin occurring with either daily or intermittent dosage regimens include:

System Organ Class (MedDRA)	**Frequency**	**Adverse reaction**
Infections and infestations	*Frequency unknown*	Pseudomembranous colitis, influenza
Blood and lymphatic system disorders	*Frequent*	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if medicine is discontinued as soon as purpura occurs
	Less frequent	Leukopenia
	Frequency unknown	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, disseminated intravascular coagulation,

		eosinophilia agranulocytosis, haemolytic anaemia, Vitamin K dependent coagulation disorders
Immune system disorders	*Frequency unknown*	Anaphylactic reaction
Endocrine disorders	*Frequency unknown*	Adrenal insufficiency in patients with compromised adrenal function have been observed
Metabolism and nutrition disorders	*Frequency unknown*	Decreased appetite
Psychiatric disorders	*Frequency unknown*	Psychotic disorder
Nervous system disorders	*Frequent*	Headache, dizziness
	Less frequent	Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	*Frequency unknown*	Tear discolouration
Vascular disorders	*Frequency unknown*	Shock, flushing, vasculitis, bleeding
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Dyspnoea, wheezing, discoloured sputum, interstitial lung disease (including pneumonitis)
Gastrointestinal disorders	*Frequent*	Nausea, vomiting
	Less frequent	Diarrhoea
	Frequency unknown	Gastrointestinal disorder, abdominal discomfort, tooth discolouration (which may be permanent)
Hepato-biliary disorders	*Frequency unknown*	Drug-induced liver injury (including fatal cases especially when used in combination with other anti-tuberculosis medicines), hepatitis, hyperbilirubinaemia (see section 4.4)
Skin and subcutaneous tissue disorders	*Frequency unknown*	Erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) (see section 4.4), skin reaction,

		pruritus, rash pruritic, urticaria, allergic dermatitis, pemphigoid, sweat discolouration
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Muscle weakness, myopathy, bone pain
Renal and urinary disorders	*Frequency unknown*	Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis, chromaturia
Pregnancy, puerperium and perinatal conditions	*Frequency unknown*	Post-partum haemorrhage, foetal-maternal haemorrhage
Reproductive system and breast disorders	*Frequency unknown*	Menstrual disorder
Congenital, familial and genetic disorders	*Frequency unknown*	Porphyria
General disorders and administration site conditions	*Frequent*	Pyrexia, chills
	Less frequent	Oedema
	Frequency unknown	Paradoxical drug reaction
Investigations	*Frequent*	Increased blood bilirubin, aspartate aminotransferase, alanine aminotransferase
	Frequency unknown	Decreased blood pressure, increased blood creatinine and hepatic enzyme

Isoniazid

System Organ Class (MedDRA)	**Frequency**	**Adverse reaction**

Blood and lymphatic system disorders	*Frequency unknown*	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, eosinophilia, agranulocytosis, thrombocytopenia, anaemia (including aplastic, haemolytic and sideroblastic anaemia), lymphadenopathy
Immune system disorders	*Frequency unknown*	Anaphylactic reactions
Endocrine disorders	*Frequency unknown*	Gynaecomastia
Metabolism and nutrition disorders	*Frequency unknown*	Hyperglycaemia, pellagra
Nervous system disorders	*Less frequent*	Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis
	Frequency unknown	Vertigo, polyneuritis, presenting as paraesthesia, muscle weakness, loss of tendon reflexes, etc, is unlikely to occur with the recommended daily dose of DUOPIC 150/75. The incidence is higher in "slow acetylators". The possibility that the frequency of seizures may be increased in patients with epilepsy should be borne in mind. Cerebellar syndrome (including cerebellar ataxia, ataxia, dysdiadochokinesis, balance disorders, nystagmus, dysmetria) mainly in patients with chronic kidney disease.
Vascular disorders	*Frequency unknown*	Vasculitis

Gastrointestinal disorders	*Frequency unknown*	Constipation, dry mouth, nausea, vomiting, epigastric distress, pancreatitis
Hepato-biliary disorders	*Less frequent*	Severe and sometimes fatal hepatitis may occur with isoniazid therapy
Skin and subcutaneous tissue disorders	*Frequency unknown*	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4), rash, acne, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, alopecia
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Systemic lupus erythematous-like syndrome
General disorders and administration site conditions	*Frequency unknown*	Fever
Investigations	*Frequency unknown*	Anti-nuclear bodies

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Reporting can also be done directly to Adcock Ingram Limited at Adcock.aereports@adcock.com.

4.9 Overdose

Signs and Symptoms

Rifampicin

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange

colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular dysrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, non-fatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and non-fatal reports. Non-fatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Isoniazid

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, and visual hallucinations (including bright colours and strange designs) are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycaemia are typical laboratory findings.

Management

In cases of overdosage with DUOPIC 150/75, antiemetic medicine may be required to control severe nausea and vomiting.

Intensive supportive measures should be instituted, including airway patency, and individual symptoms treated as they arise.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.3 Tuberculostatics

Pharmacotherapeutic group: Antimycobacterials, Combinations of drugs for treatment of

tuberculosis. ATC code: J04AM02

Rifampicin and isoniazid are active bactericidial antituberculosis medicines which are particularly active against the rapidly growing extracellular organisms and also have bactericidal activity intracellularly. Rifampicin has activity against slow and intermittently growing *M. tuberculosis*.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Cross-resistance to rifampicin has only been shown with other rifamycins.

Isoniazid acts against actively growing tubercle bacilli.

5.2 Pharmacokinetic properties

Rifampicin

Rifampicin is readily absorbed from the stomach and the duodenum. Peak serum concentrations of the order of 10 µg/ml occur about 2-4 hours after a dose of 10mg/kg body weight on an empty stomach.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5,1 hours after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600 mg/day, the half-life does not differ in patients with renal failure and consequently, no dosage adjustment is required.

After absorption, rifampicin is rapidly eliminated in the bile and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30 % of a dose is excreted in the urine, with about half of this being unchanged drug. Absorption of rifampicin is reduced when the drug is ingested with food.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80 % protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

Isoniazid

After oral administration isoniazid produces peak blood levels within 1 to 2 hours which decline to 50 % or less within 6 hours. Ingestion of isoniazid with food may reduce its absorption. It diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). From 50 to 70 % of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolised primarily by acetylation and dehydrasination. The rate of acetylation is genetically determined.

Pharmacokinetic studies in normal volunteers have been shown that the two ingredients in DUOPIC 150/75 have comparable bioavailability whether they are given together as individual dose forms or as DUOPIC 150/75.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the professional information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

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

Coating materials:

Hypromellose
Iron oxide red
Polyethylene glycol 4000
Simethicone emulsion
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

PVC/PVDC blister pack:

Store at or below 25 °C.

Store in the original container to protect from light and moisture.

Aluminium foil blister pack:

Store at or below 30 °C**.**

6.5 Nature and contents of container

DUOPIC 150/75 tablets are packed in Alu/Alu blister packs or PVC/PVDC blister packs. The blisters strips are packed in an outer cardboard carton with a package leaflet.

Pack sizes: 56, 84, 90 or 672 tablets.

Not all pack sizes and pack types may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
South Africa
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

55/20.2.3/0304

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 May 2022

10. DATE OF REVISION OF THE TEXT

20 October 2025

PI 282230 09/2025

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