PROFESSIONAL INFORMATION FOR

UTIN-400 (FILM-COATED TABLETS)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

UTIN-400 (Film-coated tablets)

COMPOSITION:

Each film-coated tablet contains 400 mg norfloxacin.

Inactive ingredients are castor oil, colloidal silicon dioxide, colourant (sunset yellow lake), croscarmellose sodium, hydroxypropyl-methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, talc and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Norfloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial medicine structurally related to nalidixic acid. Fluoroquinolones are bactericidal; acting

intracellularly by inhibiting DNA gyrase. DNA gyrase is an essential bacterial enzyme that is a critical catalyst in the duplication, transcription and repair of bacterial DNA.

Fluoroquinolones, including norfloxacin, are active against a wide range of aerobic Gram-positive and Gram-negative organisms (broad spectrum).

Mechanism(s) of resistance:

The major mechanism of resistance to quinolones, including norfloxacin, is through mutations in the genes that encode for DNA gyrase and topoisomerase II and IV, the targets of quinolone action. Additional mechanisms of resistance lead to reduced concentration of fluoroquinolones at the site of action and include mutations in the cell membrane proteins, which alter membrane permeability and the development of efflux pumps.

Transferable, plasmid-coded resistance was demonstrated in Escherichia coli and Klebsiella species. There is a partial or complete cross-resistance between norfloxacin and structurally unrelated antibacterial medicines, such as penicillins, cephalosporins, tetracyclines, macrolides, aminoglycosides and sulphonamides, 2,4-diaminopyrimidines, or combinations thereof (e.g. co-trimoxazole).

Species for which acquired resistance may be a problem:

Gram-positive aerobes:

Enterococcus faecalis

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus agalactiae

Gram-negative aerobes:

Campylobacter jejuni

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia stuartii

Pseudomonas aeruginosa

Salmonella enterica (enteritis salmonella)

Serratia marcescens

Inherently resistant organisms:

Gram-positive aerobes:

Enterococcus faecium

Staphylococcus aureus (methicillin-resistant)

Streptococcus agalactiae

Gram-negative aerobes:

Stenotrophomonas maltophilia

Anaerobic micro-organisms:

Clostridium difficile

Other micro-organisms:

Chlamydia trachomatis

Mycoplasma hominis

Ureaplasma urealyticum

Pharmacokinetic properties:

Absorption:

Norfloxacin is well absorbed following oral administration. At least 30 – 40 % of an oral dose of norfloxacin is absorbed. This results in a serum concentration of 1,5 µg/mℓ being attained approximately 1 hour after administration of a 400 mg dose. The presence of food and/or dairy products may decrease absorption. Mean serum half-life is 3 to 4 hours and is independent of dose. Steady-state concentrations of norfloxacin

will be attained within two days of dosing. The half-life is doubled in patients with severe renal impairment.

Distribution:

Fluoroquinolones are widely distributed to most body fluids and tissues; high concentrations are attained in the kidneys, gall bladder, liver, lungs, gynaecological tissue, prostatic tissue, phagocytic cells, urine, sputum and bile. Fluoroquinolones are primarily excreted via the renal tract.

Mean concentrations in body fluids and tissues which have been measured 1 – 4 hours after 2 doses of 400 mg norfloxacin were within a range of 1,6 – 7,3 µg/ml.

Protein binding is less than 15 %.

Metabolism and elimination:

Norfloxacin is eliminated through metabolism, biliary excretion and renal excretion. In patients between 65-75 years of age with normal renal function, norfloxacin is eliminated more slowly because of their slightly decreased renal function. Medicine absorption appears unaffected. However, the effective half-life of norfloxacin in elderly patients is 4 hours.

There is no information on accumulation of norfloxacin with repeated administration in elderly patients. However, no dosage adjustment is required based on age alone. In

elderly patients with reduced renal function, the dosage should be adjusted as for other patients with renal impairment (see **"DOSAGE AND DIRECTIONS FOR USE"** *Renal impairment*).

After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773, and 82 µg of norfloxacin of feces were obtained at 12, 24, and 48 hours, respectively. Renal excretion occurs by both glomerular filtration and net tubular secretion, as evidenced by the high rate of renal clearance (approximately 275 mℓ/min). After a single 400 mg dose, urinary concentrations reach a value of 200 µg/mℓ or more in healthy volunteers and remain above 30 µg/mℓ for at least 12 hours. In the first 24 hours, 33 – 48 % of the medicine is recovered in the urine. Fecal recovery accounts for another 30 % of the administered dose. In elderly patients approximately 22 % of the administered dose was recovered in urine and renal clearance averaged 154 mL/min.

Norfloxacin exists in the urine as norfloxacin and six active metabolites of lesser antimicrobial potency. The parent compound accounts for over 70 % of total excretion. The bactericidal potency of norfloxacin is not affected by the pH of urine.

Concentrations of 2,5 mg/1 in human serum leads to binding to plasma proteins of nearly 13,8 %.

INDICATIONS:

UTIN-400 is indicated for:

- The treatment of complicated and uncomplicated, upper and lower urinary tract infections including cystitis, pyelitis, cystopyelitis and pyelonephritis caused by bacteria susceptible to **UTIN-400**.
- The treatment of infections caused by *Pseudomonas aeruginosa*; an aminoglycoside must be administered concomitantly.

CONTRAINDICATIONS:

UTIN-400 is contraindicated in:

- Patients who are hypersensitive to norfloxacin or any of the inactive ingredients of **UTIN-400**, or any chemically related quinolone antibacterials.
- Patients with a creatinine clearance of less than 30 mℓ per minute.
- Patients with a history of tendinitis and/or tendon rupture related to fluoroquinolone administration (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE EFFECTS"**).
- Children and adolescents up to the age of 18, because fluoroquinolones caused lameness in immature dogs due to permanent lesions of the cartilage of weight bearing joints. **UTIN-400** and other related quinolones have been reported to cause arthropathy in immature animals of various species.
- Pregnancy and lactation as the safe use of **UTIN-400** in pregnant women and women breastfeeding their infants has not been established (see **"HUMAN REPRODUCTION"**).

- Patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.

Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity reactions:

UTIN-400 can cause serious, potentially fatal hypersensitivity reactions (anaphylactic and anaphylactoid reactions), occasionally following the initial dose (see **"SIDE EFFECTS"**). Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Patients should be advised to discontinue treatment immediately if experiencing such reactions and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Use in patients with epilepsy and other CNS disorders:

As fluoroquinolones may cause central nervous system (CNS) stimulation or toxicity, **UTIN-400** should not be used in patients with CNS disorders including cerebral arteriosclerosis, epilepsy, a history of convulsions, or known factors that predispose to seizures. Convulsions have been reported with norfloxacin, as in **UTIN-400** (see **"SIDE EFFECTS"**). **UTIN-400** may lead to exacerbation and aggravation of the symptoms in patients with known or suspected psychiatric disorders, hallucinations and/or confusion.

In case of convulsive seizures, treatment with **UTIN-400** should be discontinued.

Tendinitis and/or tendon rupture:

Tendinitis and/or tendon rupture, particularly affecting the Achilles tendon, may occur with **UTIN-400** (see **"CONTRAINDICATIONS"** and **"SIDE EFFECTS"**). Such reactions have been observed, particularly in older patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue **UTIN-400** and rest the affected limbs. These reactions may occur even after treatment has been stopped.

Peripheral neuropathy:

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paraesthesias, hypoaesthesias, dysaesthesias and weakness have been reported in patients receiving quinolones, including **UTIN-400** (see **"SIDE EFFECTS"**. **UTIN-400** should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

Cardiac disorders:

Quinolones have been associated with prolongation of the QTc interval on the electrocardiogram and cases of dysrhythmia (including torsade de pointes) have been observed (see **"SIDE EFFECTS"**). Caution should be exercised when using **UTIN-400**

in patients with hypokalaemia, hypomagnesaemia, significant bradycardia or undergoing concurrent treatment with class Ia or class III antidysrhythmics. Caution should be exercised when using **UTIN-400** in patients with cardiac disease such as heart failure, myocardial infarction and bradycardia.

UTIN-400 should therefore be used with caution in patients taking cisapride, erythromycin, antipsychotics, tricyclic antidepressants or who have any personal or family history of QTc prolongation.

Elderly patients and women may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when using fluroquinolones, including **UTIN-400,** in these populations (see **"DOSAGE AND DIRECTIONS FOR USE"**, **"INTERACTIONS"** and **"KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT"**).

There is some evidence, although inconclusive, of a possible association between oral fluoroquinolone use, such as **UTIN-400**, and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones, including **UTIN-400**, should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see **"CONTRAINDICATIONS"**).

G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency:

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **"INTERACTIONS"** and **"SIDE EFFECTS"**).

Crystalluria:

In case of prolonged treatment, the occurrence of crystalluria should be monitored. The maximum recommended dosage of 400 mg twice daily should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Use in renal impairment:

In patients with severe renal impairment, the risk/benefit ratio of using **UTIN-400** should be carefully weighed for the individual (see **"DOSAGE AND DIRECTIONS FOR USE"**). The urinary concentration of **UTIN-400** may be reduced in patients with severely impaired renal function as **UTIN-400** is predominantly excreted via the kidney. Care is necessary in patients with impaired hepatic or renal function, or glucose-6-phosphate dehydrogenase deficiency. Haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial medicines, including **UTIN-400** (see **"SIDE EFFECTS"**).

Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **"CONTRAINDICATIONS"**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Photosensitivity:

Exposure to strong sunlight or sun lamps should be avoided. Photosensitivity reactions have been observed in patients who were exposed to excessive sunlight while receiving **UTIN-400**. **UTIN-400** therapy should be discontinued if photosensitivity occurs.

Use in patients with myasthenia gravis:

Exacerbation of myasthenia gravis has been reported with **UTIN-400** and may lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including **UTIN-400**, in patients with myasthenia gravis (see **"SIDE EFFECTS"**).

Pseudomembranous colitis:

Pseudomembranous colitis has been reported with **UTIN-400** and may range in severity from mild to life-threatening (see **"SIDE EFFECTS"**). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of **UTIN-400**. A toxin produced by *Clostridium difficile* is a primary cause of pseudomembranous colitis.

If *Clostridium difficile*-associated diarrhoea (CDAD) is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Syphilis Treatment:

UTIN-400 has not been shown to be effective in the treatment of syphilis. Antimicrobial medicines used in high doses for short periods of time to treat gonorrhoea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhoea should have a serologic test for syphilis at the time of diagnosis. Patients treated with **UTIN-400** should have a follow-up serologic test for syphilis after three months.

Cholestatic hepatitis:

Cholestatic hepatitis is commonly reported with **UTIN-400** (see **"SIDE EFFECTS"**). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Vision disorder:

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Use in children:

UTIN-400 has been shown to cause arthropathy in immature animals. The safety of **UTIN-400** in children has not been established and therefore the use of **UTIN-400** in prepubertal children or growing adolescents is contraindicated (see **"CONTRAINDICATIONS"** and **"DOSAGE AND DIRECTIONS FOR USE"**).

Effects on the ability to drive or operate machinery:

The ability to drive or operate machinery may be impaired by **UTIN-400**, especially when alcohol is also taken. **UTIN-400** may cause dizziness and light-headedness and, therefore, patients should know how they react to **UTIN-400** before they drive or operate machinery, or engage in activities requiring mental alertness and coordination.

INTERACTIONS:

Nitrofurantoin:

Antagonism has been demonstrated between **UTIN-400** and nitrofurantoin and they should not be prescribed together.

Urinary alkalisers:

Urinary alkalisers, such as citrates and sodium bicarbonate, may reduce solubility of **UTIN-400** in the urine. Patients should be observed for signs of crystalluria and nephrotoxicity.

Antacids and multivitamins:

Antacids, multivitamins, products containing ferrous sulphate or zinc and sucralphate may reduce the absorption of **UTIN-400** by chelation, resulting in lower serum and urine concentrations. **UTIN-400** should be taken at least 2 hours before or at least 4 hours after such products. The restriction does not apply to H_2-receptor antagonists.

Ciclosporin:

Concurrent use with ciclosporin has been reported to elevate serum creatinine concentrations. Elevated serum levels of ciclosporin have been reported with concomitant use of **UTIN-400**. Ciclosporin serum levels should be monitored and appropriate ciclosporin dosage adjustments made when these medicines are used concomitantly.

Didanosine:

Didanosine should not be administered concurrently with or within 2 hours of the administration of **UTIN-400**, because it may interfere with absorption, resulting in lower serum and urine levels of **UTIN-400**.

Probenecid:

Concurrent use with probenecid decreases the renal tubular secretion of **UTIN-400**, resulting in decreased urinary excretion of **UTIN-400**, prolonged elimination half-life, and increased risk of toxicity.

Warfarin:

Concurrent use with warfarin has been reported to increase the anticoagulant effect of warfarin (by displacing significant amounts from serum albumin binding sites), increasing the chance of bleeding. When concomitant administration of warfarin and **UTIN-400** cannot be avoided, the prothrombin time, (INR) should be carefully monitored in all patients.

Medicines metabolised by CYP1A2:

Quinolones, including **UTIN-400**, have been shown *in vitro* to inhibit CYP1A2. Concomitant use with medicines metabolised by CYP1A2 (e.g. caffeine, clozapine, ropinirole, tacrine, tizanidine, theophylline) may result in increased levels of these medicines, with the potential risk of increased toxicity. Patients taking any concomitant medicines metabolised by CYP1A2 should be carefully monitored.

Theophylline:

Elevated plasma levels of theophylline have been reported with concomitant theophylline and quinolone use. Isolated cases of theophylline-related side-effects have also been reported in patients on concomitant therapy with **UTIN-400** and theophylline. Monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Caffeine:

The metabolism of caffeine has been shown to be inhibited by quinolones and also by **UTIN-400**. This can result in delayed elimination and prolonged plasma half-life of

caffeine. During treatment with **UTIN-400**, the ingestion of caffeine-containing medicines (certain analgesics) should therefore be avoided where possible.

Nutritional solutions and dairy products:

Oral nutritional solutions and dairy products (milk or milk products such as yoghurt) reduce the absorption of **UTIN-400**. **UTIN-400** should therefore be taken at least 1 hour before or 2 hours after such products.

Fenbufen:

Concomitant administration of quinolones and fenbufen can cause seizures. Co-administration of quinolones and fenbufen should therefore be avoided.

Medicines known to prolong the QT intervals:

UTIN-400, like other fluoroquinolones, should be used with caution in patients receiving medicines known to prolong the QT intervals (Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Clozapine/ropinirole:

The dose of clozapine or ropinirole may need to be adjusted in patients already taking these medicines if **UTIN-400** is introduced or withdrawn.

Glibenclamide:

The concomitant administration of quinolones, including **UTIN-400**, with glibenclamide (a sulphonylurea medicine) may result in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these medicines are co-administered (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE EFFECTS"**).

Non-steroidal anti-inflammatory drugs (NSAIDs):

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including **UTIN-400**, may increase the risk of CNS stimulation and convulsive seizures. Therefore, **UTIN-400** should be used with caution in patients receiving NSAIDs concomitantly.

ACE inhibitors/renin-angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see **"CONTRAINDICATIONS"**).

HUMAN REPRODUCTION:

Pregnancy:

The safe use of **UTIN-400** in pregnant women has not been established; quinolones such as **UTIN-400** have been shown to cause arthropathy in immature animals and therefore its use during pregnancy is contraindicated (see **"CONTRAINDICATIONS"**).

Lactation:

It is known that quinolones pass into mother's milk. In case of treatment of breast-feeding mothers with **UTIN-400**, breast feeding must be stopped.

DOSAGE AND DIRECTIONS FOR USE:

Susceptibility of the causative organism to **UTIN-400** should be tested.

Adults:

Uncomplicated lower urinary tract infections (e.g. cystitis):

One tablet (400 mg) every twelve hours for three days.

Complicated urinary tract infections:

One tablet (400 mg) every twelve hours for 7 to 10 days.

Children:

Use is not recommended in infants and children, since **UTIN-400** causes arthropathy in immature animals (see **"CONTRAINDICATIONS"**).

Geriatrics:

No geriatric-specific problems have been demonstrated. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment in dosage.

Renal impairment:

Doses may need to be reduced in renal impairment; 400 mg once daily has been suggested when creatinine clearance is 30 mℓ per minute (see **"CONTRAINDICATIONS"**).

The presence of food in the stomach may slightly decrease or delay the absorption of norfloxacin. Therefore, **UTIN-400** should preferably be taken with a full glass (240 mℓ) of water on an empty stomach (either 1 hour before or 2 hours after meals or ingestion of milk).

Multivitamins, products containing iron or zinc, antacids containing magnesium and aluminium, sucralphate, or products containing didanosine should not be taken within 2 hours of administration of **UTIN-400** (see **"INTERACTIONS"**).

SIDE EFFECTS:

Infections and infestations:

Frequency unknown: Vaginal candidiasis.

Blood and lymphatic system disorders:

Less frequent: Leucopenia, thrombocytopenia, eosinophilia, reduced haematocrit, prolongation of prothrombin time, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Frequency unknown:	Neutropenia, agranulocytosis.

Immune system disorders:

Less frequent:	Hypersensitivity reactions, including skin rash, photosensitivity, itching or redness, Stevens-Johnson syndrome, (see **"Skin and subcutaneous tissue disorders"**), shortness of breath (dyspnoea), swelling of face or neck (angioedema), vasculitis.
Frequency unknown:	Anaphylaxis, urticaria, arthritis, myalgia, arthralgia and interstitial nephritis (as part of a hypersensitivity reaction).

Metabolism and nutrition disorders:

Less frequent:	Hypoglycaemia, particularly in diabetic patients (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).

Psychiatric disorders:

Frequent:	Insomnia, nervousness.
Less frequent:	Psychosis, depression, agitation, hallucinations, sleep disturbances, anxiety, irritability, euphoria, change in mood, euphoria, disorientation, confusion, psychic disturbance.

Nervous system disorders:

Less Frequent:	Central nervous system toxicity (dizziness, headache, drowsiness). Central nervous stimulation (convulsions, confusion, tremors), disorientation, insomnia, sleep disturbances, polyneuropathy, including Guillain-Barré syndrome and seizures, and possible exacerbation of myasthenia gravis (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
Frequency unknown:	Peripheral neuropathy.

Eye disorders:

Less frequent:	Visual disturbances, epiphora.

Ear and labyrinth disorders:

Less frequent:	Tinnitus.
Frequency unknown:	Hearing loss.

Cardiac disorders:

Frequency unknown:	Prolonged QTc interval and ventricular dysrhythmia (including torsade de pointes), (see **"WARNINGS AND SPECIAL PRECAUTIONS"**), tachycardia.

Vascular disorders:

Less frequent:	Leukocytoclastic vasculitis (see **"Immune system disorders"**), petechiate and haemorrhagic bullae/papules.

Gastrointestinal disorders:

Less Frequent:	Gastrointestinal effects (abdominal or stomach pain or cramps, nausea, anorexia, vomiting, diarrhoea and heartburn), loss of appetite, pancreatitis, pseudomembranous colitis.

Hepatobiliary disorders:

Frequent:	Cholestatic hepatitis, hepatitis.
Less frequent:	Elevation of ALT (SGOT), AST (SGPT) and alkaline phosphate.
Frequency unknown:	Jaundice including cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Less Frequent:	Skin reactions, including rash, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, erythema multiforme (see **"Immune system disorders"**), pruritus, urticaria, angiooedema.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Rhabdomyolysis.
Less frequent:	Tendinitis, muscle and/or joint pains, joint inflammation, tendon rupture (Achilles tendon), exacerbation of myasthenia gravis (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Renal and urinary disorders:

Less frequent:	Interstitial nephritis (bloody or cloudy urine, fever, rash, swelling of feet or lower legs), crystalluria.
Frequency unknown:	Renal failure.

General disorders and administration site conditions:

Less frequency:	Tiredness.

Investigations:

Frequency unknown:	Abnormal laboratory values observed include elevation of ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, blood urea and creatinine, elevated creatine kinase (CK).

Photosensitivity has been observed in patients who, during ongoing therapy with quinolone-like medications, have been extensively exposed to sunlight or sunbeds (phototoxic reactions, photosensitisation with vesiculation, redness, swelling and discoloration); (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Post-marketing:

Hypersensitive reactions:

Frequency unknown: Anaphylactoid reactions, angioedema, dyspnea, vasculitis, urticaria, arthritis, arthralgia and myalgia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Central nervous system disorders:

Frequency unknown: Seizures, myoclonus and tremors (see **"WARNINGS AND SPECIAL PRECAUTIONS"**), visual disturbances.

Metabolism and nutrition disorders:

Frequency unknown: Hyperglycaemia, hypoglycaemic coma (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**.

Skin and subcutaneous tissue disorders:

Frequency unknown: Toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, exfoliative dermatitis, photosensitivity/phototoxicity (see **"WARNINGS AND SPECIAL PRECAUTIONS"**), leukocytoclastic vasculitis, rash with eosinophilia and systemic symptoms.

Gastrointestinal disorders:

Frequency unknown: Pseudomembranous colitis, hepatitis, jaundice including cholestatic jaundice and elevated liver function tests, pancreatitis, stomatitis.

Liver disorders:

Frequency unknown: Hepatic failure, including fatal cases.

Cardiac disorders:

Frequency unknown: Prolonged QTc interval and ventricular arrhythmia including torsades de pointes. Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones, such as **UTIN-400**. Due to insufficient post-marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor,

or a contributory factor or played no role in the reported cases where mitral and/or aortic regurgitation cases was diagnosed.

Renal and urinary disorders:

Frequency unknown: Interstitial nephritis, renal failure.

Nervous system disorders:

Frequency unknown: Peripheral neuropathy, Guillain-Barré syndrome, ataxia, paraesthesia, hypoesthesia, psychic disturbances including psychotic reactions and confusion.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Tendinitis, tendon rupture; exacerbation of myasthenia gravis (see **"WARNINGS AND SPECIAL PRECAUTIONS"**); elevated creatine kinase (CK), muscle spasms.

Blood and lymphatic system disorders:

Frequency unknown: Neutropenia; leukopenia; agranulocytosis; hemolytic anemia, sometimes associated with glucose-6-phosphate dehydroqenase deficiency;

thrombocytopenia.

Ear and labyrinth disorders:

Frequency unknown: Hearing loss, tinnitus, diplopia, dysgeusia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Adequate hydration must be maintained. Treatment is symptomatic and supportive. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

IDENTIFICATION:

White coloured, oval shaped, uncoated tablets with biconvex faces.

PRESENTATION:

UTIN-400 tablets are available in blister packs of 6, 10, 20, and 100 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place. Protect from light.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

31/20.1.1/0517

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

RSA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 October 1997

Revised: 10 June 2020