SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Trizolin 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Trizolin film-coated tablet contains 400 mg of Norfloxacin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, scored, film-coated tablets with Remedica's logo on one side.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Broad-spectrum, bactericidal agent indicated for the treatment of:

- uncomplicated acute cystitis. In uncomplicated acute cystitis, Trizolin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- bacterial prostatitis.
- epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*.
- urethritis including cases due to susceptible *Neisseria gonorrhoeae*.
- complicated urinary tract infections (except complicated pyelonephritis).
- complicated acute cystitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Trizolin should be taken with a glass of water at least one hour before or two hours after a meal or milk ingestion. Multivitamins, products containing iron or zinc, antacids containing magnesium and aluminium, sucralfate or products containing didanosine should not be taken within 2 hours of administration of norfloxacin.

Susceptibility of the causative organism to Trizolin should be tested. However, therapy may be initiated before obtaining the results of these tests.

Diagnosis	Dosage	Therapy duration
Uncomplicated lower urinary tract infections (e.g. cystitis)*	400 mg twice daily	3 days
Urinary tract infections	400 mg twice daily	7-10 days
Chronic relapsing urinary tract infection**	400 mg twice daily	Up to 12 weeks

* Trials in over 600 patients have demonstrated the efficacy and tolerability of norfloxacin in the three – day treatment of uncomplicated urinary tract infections.
** If adequate suppression is obtained within the first four weeks of therapy, the dose of norfloxacin may be reduced to 400 mg daily.

Patients with renal impairment:
Trizolin is suitable for the treatment of patients with renal impairment. In studies involving patients whose creatinine clearance was less than 30 ml/min/1.73m^2, but who did not require haemodialysis, the plasma half-life of norfloxacin was approximately eight hours. Clinical studies showed there was no difference in the mean half-life of norfloxacin in patients with a creatinine clearance of less than 10 ml/min/1.73m^2, compared to patients with creatinine clearance of 10-30 ml/min/1.73m^2. Hence, for these patients, the recommended dose is one 400 mg tablet once daily. At this dosage, concentrations in appropriate body tissues or fluids exceed the MICs for most pathogens sensitive to norfloxacin.

Use in the elderly:
Pharmacokinetic studies have shown no appreciable changes when compared to younger patients, apart from a slight prolongation of half-life. In the absence of renal impairment, no adjustment of dosage is necessary. Limited clinical studies have shown norfloxacin to be well tolerated.

4.3 Contraindications

Hypersensitivity to any component of this product or any chemically related quinolone antibacterials.
Trizolin is contra-indicated in prepubertal children and growing adolescents.

4.4 Special warnings and precautions for use

The use of norfloxacin should be avoided in patients who have experienced serious adversereactions in the past when using quinolone or fluoroquinolone containing products (seesection 4.8). Treatment of these patients with norfloxacin should only be initiated in the absenceof alternative treatment options and after careful benefit/risk assessment (see also section4.3).

As with other drugs in this class, Trizolin should not be used in patients with a history of convulsions or known factors that predispose to seizures unless there is an overwhelming clinical need. Convulsions have been reported rarely with norfloxacin.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake offluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and afterconsideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease,or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence ofother risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Tuner syndrome, Behcet's disease, hypertension, rheumatoid arthritis or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult aphysician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Norfloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture
Tendinitis andtendon rupture (especially but not limited to Achilles tendon),sometimes bilateral may occur as early as within 48 hours of starting treatment with quinolone antibioticsandfluoroquinolones and have been reported to occur even up to several months afterdiscontinuation of treatment. The risk of tendinitis and tendon rupture is increased in olderpatients, patients with renal impairment, patients with solid organ transplants, and thosetreated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with norfloxacin should be discontinued and alternative treatment should be considered. The

affected limb(s)should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used ifsigns of tendinopathy occur.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia,dysesthesia, or weakness have been reported in patients receiving quinolones andfluoroquinolones. Patients under treatment with norfloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Photosensitivity reactions have been observed in patients who are exposed to excessive sunlight while receiving some members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if photosensitivity occurs.

Quinolones, including norfloxacin, may exacerbate the signs of myasthenia gravis and lead to life threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including Trizolin, in patients with myasthenia gravis (see section 4.8 'Undesirable effects').

Rarely, haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see 4.8 'Undesirable effects').

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

Use in children
As with other quinolones, Trizolin has been shown to cause arthropathy in immature animals. The safety of Trizolin in children has not been adequately explored and therefore the use of Trizolin in prepubertal children or growing adolescents is contra-indicated.

Cardiac disorders
Caution should be taken when using fluroquinolones, including norfloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heartfailure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including norfloxacin,in these populations(see section 4.2 Elderly, section 4,5, section 4,8, section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of probenecid does not affect serum concentrations of norfloxacin, but urinary excretion of the drug diminishes.

As with other organic acid antibacterials, antagonism has been demonstrated in vitro between norfloxacin and nitrofurantoin.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline-related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

Elevated serum levels of cyclosporin have been reported with concomitant use of norfloxacin. Cyclosporin serum levels should be monitored and appropriate cyclosporin dosage adjustments made when these drugs are used concomitantly.

Quinolones, including norfloxacin, may enhance the effects of the anticoagulant warfarin, or its derivatives, by displacing significant amounts from serum albumin-binding sites. When concomitant administration of these products cannot be avoided, measurements of prothrombin time or other suitable coagulation tests should be carried out.

Multivitamins, products containing iron or zinc, antacids or sucralfate should not be administered concomitantly with, or within two hours of, the administration of norfloxacin because they may interfere with absorption, resulting in lower serum and urine levels of norfloxacin.

Products containing didanosine should not be administered concomitantly with, or within 2 hours of the administration of norfloxacin, because the products may interfere with absorption resulting in lower serum and urine levels of norfloxacin.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its plasma half-life.

Animal data have shown that quinolones in combination with fenbufen can lead to convulsions. Therefore, concomitant administration of quinolones and fenbufen should be avoided.

Drugs known to prolong QT interval
Norfloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no evidence from animal studies that norfloxacin has any teratogenic or mutagenic effects. Embryotoxicity secondary to maternotoxicity was observed after large doses in rabbits. Embryonic losses were observed in cynomolgus monkeys without any teratogenic effects. The relevance of these findings for humans is uncertain.

The safe use of Trizolin in pregnant women has not been established; however, as with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals and therefore its use during pregnancy is not recommended.

Lactation
It is not known whether norfloxacin is excreted in human milk; administration to breast-feeding mothers is thus not recommended.

4.7 Effects on ability to drive and use machines

There are side-effects associated with this product that may affect some patients' ability to drive or operate machinery (see 4.8 'Undesirable effects').

4.8 Undesirable effects

The overall incidence of drug-related side effects reported during clinical trials was approximately 3%.

The most common side effects have been gastro-intestinal, neuropsychiatric and skin reactions, and include nausea, headache, dizziness, rash, heartburn, abdominal pain/cramps, and diarrhoea.

Less commonly, other side effects such as anorexia, sleep disturbances, depression, anxiety/nervousness, irritability, euphoria, disorientation, hallucination, tinnitus, and epiphora have been reported.

Abnormal laboratory side effects observed during clinical trials included:
leucopenia, elevation of ALAT (SGPT), ASAT (SGOT), eosinophilia, neutropenia, thrombocytopenia.

With more widespread use the following additional side effects have been reported:

Hypersensitivity reactions
Hypersensitivity reactions including anaphylaxis, angioedema, dyspnoea, vasculitis, urticaria, arthritis, myalgia, arthralgia and interstitial nephritis.

Skinand subcutaneous tissue disorders
Photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus.

Gastro-intestinal disorders
Pseudomembranous colitis, pancreatitis (rare), hepatitis, jaundice including cholestatic jaundice and elevated liver-function tests.

Musculoskeletal and connective tissue disorders[*]
Tendinitis, tendon rupture, exacerbation of myasthenia gravis.

Nervous system/psychiatric disorders[*]

Polyneuropathy including Guillaine-Barré syndrome, confusion, paraesthesia, psychic disturbances including psychotic reactions, convulsions, tremors, myoclonus.

Haematological disorders
Haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency.

Genito-urinary disorders
Vaginal candidiasis.

Renal function disorders
Renal failure.

Special senses disorders
Dysgeusia, visual disturbances.

*Cardiac disorders***
Not known: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9).

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversibleserious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).
** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal productisimportant. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

In the event of overdose, symptomatic treatment should be implemented.
ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Quinolone antibacterials, ATC code: J01MA06

Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level, three specific events were attributed to norfloxacin in Escherichia coli cells:
(1) Inhibition of the ATP‐dependent DNA supercoiling reaction catalysed by DNA gyrase
(2) Inhibition of the relaxation of supercoiled DNA
(3) Promotion of double‐stranded DNA breakage.

Spontaneous mutation resistance to norfloxacin has occurred rarely, and resistance of the organism during therapy has developed in less than 1% of patients treated.

Bacteriology
Norfloxacin has a broad spectrum of antibacterial activity against Gram-positive and Gram-negative aerobic pathogens. The fluorine atom at the 6 position provides increased potency against Gram-negative organisms and the piperazine moiety at the 7 position is responsible for the anti-pseudomonal activity.

Norfloxacin is active in vitro against the following bacteria:

Bacteria found in urinary tract infections:
Enterobacteriaceae
Citrobacter spp.
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter spp.
Enterobacter agglomerans
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Hafniaalvei.
Klebsiella spp.
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Proteus spp. (indole positive)
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Providencia rettgeri
Providencia stuartii
Serratia spp.
Serratia marcescens
Pseudomonadaceae
Pseudomonas aeruginosa
Pseudomonas cepacia
Pseudomonas fluorescens
Pseudomonas stutzeri

Other:

Flavobacterium spp.
Gram – positive cocci
Enterococci faecalis
Group G streptococci
Staphylococcus spp.
Staphylococcus Coag. Negative
Staphylococcus aureus (including penicillinase-producing and most Methicillin-resistant strains)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus agalactiae
Viridans group streptococci

In addition, norfloxacin is active against Bacillus cereus, Neiserria gonorrhoea, Ureaplasma urealyticum, Haemophilus influenzae and Haemophilus ducreyi.

Norfloxacin is not active against anaerobes, including Actinomyces spp., Fusobacterium spp., Bacteroides spp., and Clostridium spp., other than C. perfringens.

There is no cross-resistance between norfloxacin and structurally unrelated antibacterial agents such as penicillins, cephalosporins, tetracyclines, macrolides, aminocyclitols and sulphonamides, 2,4 diaminopyrimidines, or combinations thereof (e.g. co-trimoxazole).

5.2 Pharmacokinetic properties

Norfloxacin is rapidly absorbed following oral administration. In healthy volunteers, at least 30-40% of an oral dose of norfloxacin is absorbed. This results in a serum concentration of 1.5 mcg/ml being attained approximately 1 hour after administration of a 400 mg dose. Mean serum half-life is 3 to 4 hours, and is independent of dose.

The following are mean concentrations of norfloxacin in various fluids and tissues measured 1 to 4 hours post-dose after the two 400 mg doses, unless otherwise indicated:

Renal parenchyma	7.3 mcg/g
Prostate	2.5 mcg/g
Seminal fluid	2.7 mcg/ml
Testicle	1.6 mcg/g
Uterus/cervix	3.0 mcg/g
Vagina	4.3 mcg/g
Fallopian tube	1.9 mcg/g
Bile	6.9 mcg/ml (after 2 x 200mg doses)

Norfloxacin is eliminated through metabolism, biliary excretion and renal excretion. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773 and 82 mcg of norfloxacin/g of faeces 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 or more mcg/ml in healthy volunteers and remain above 30 mcg/ml for at least 12 hours. In the first 24 hours, 33 – 48% of the drug is recovered in the urine.

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.
Protein binding is less than 15%.

5.3 Preclinical safety data

Norfloxacin, when administered to 3- to 5-month-old dogs at doses four or more times the usual human dose, produced blister formation and eventual erosion of the articular cartilage of the weight-bearing joints. Similar changes have been produced by other structurally related drugs. Dogs six months or older were not susceptible to these changes.

Teratology studies in mice and rats and fertility studies in mice at oral doses of 30 to 50 times the usual dose for humans did not reveal teratogenic or fetal toxic effects. Embryotoxicity was observed in rabbits at doses of 100 mg/kg/day. This was secondary to maternal toxicity and it is a non-specific antimicrobial effect in the rabbit due to an unusual sensitivity to antibiotic-induced changes in the gut microflora.

Although the drug was not teratogenic in cynomolgus monkeys at several times the therapeutic human dosage, an increased percentage of embryonic losses was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Microcrystalline Cellulose
Croscarmellose Sodium
Colloidal Silicon Dioxide
Magnesium Stearate
Sodium Lauryl Sulfate
Talc

Coating
Hypromellose
Macrogol 400
Titanium Dioxide
Talc

6.2 Incompatibilities

No specific incompatibilities have been noted.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Trizolin tablets should be stored below 25°C,protected from light and moisture.

6.5 Nature and contents of container

PVC-PVDC/Aluminium blisters. Pack sizes of 14, 100 and 1000 tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd,
Aharnon Street, Limassol industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

04736/06834/REN/2018

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of latest renewal: 07-11-2019

10. DATE OF REVISION OF THE TEXT

18/07/2023