ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quofenix 450 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains delafloxacin meglumine equivalent to 450 mg delafloxacin.

Excipient(s) with known effect
Each tablet contains 39 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Beige to mottled beige, oblong biconvex tablets of approximately 10 mm width x 21 mm length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quofenix is indicated for the treatment of the following infections in adults:

- acute bacterial skin and skin structure infections (ABSSSI)
- community-acquired pneumonia (CAP)

when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

The recommended regimen of delafloxacin is 450 mg oral every 12 hours for a total duration of 5 to 14 days for ABSSSI and 5 to 10 days for CAP at the discretion of the physician. Delafloxacin tablets can be taken with or without food.

Special populations

Elderly
No dose adjustment is required. As per fluoroquinolone class patients aged over 60 years are at increased risk for developing severe tendon disorders including tendon rupture (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild to severe renal impairment (see sections 4.4 and 5.2). Quofenix is not recommended in patients with ESRD.

Hepatic impairment

No dose adjustment is necessary (see section 5.2).

Paediatric population
Quofenix is contraindicated in children and adolescents (see section 4.3).

Method of administration

Oral use.
Tablets should be swallowed and can be taken with or without food.
The patient should drink a sufficient amount of fluids while taking Quofenix.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to any fluoroquinolone or quinolone antibacterial medicinal product.
Previous history of tendon disorders related to fluoroquinolone administration.
Pregnancy, women of childbearing potential not using contraception and breast-feeding (see section 4.6).
Children or growing adolescents below 18 years of age (see section 4.2).

4.4 Special warnings and precautions for use

The use of delafloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with delafloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

Contraception

If women of a sexually mature age are treated, effective contraception must be used during treatment (see section 4.6).

Aortic dissection and aneurysm, 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 of fluoroquinolones.
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 after consideration 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 of other 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, Turner 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 a physician 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.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated 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 delafloxacin 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 if signs of tendinopathy occur (see section 4.8).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with delafloxacin 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).

Central Nervous System Effects

Fluoroquinolones have been associated with an increased risk of central nervous system (CNS) reactions, including: convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis. Fluoroquinolones may also cause CNS reactions of nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and suicidal thoughts or acts. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving delafloxacin, delafloxacin should be discontinued immediately and appropriate measures should be instituted. Delafloxacin should be used when the benefits of treatment exceed the risks in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse reactions, including deaths and requirement for ventilator support, have been associated with fluoroquinolone use in persons with myasthenia gravis. The use of delafloxacin is not recommended in patients with known history of myasthenia gravis.

Clostridioides difficile-associated disease

Clostridioides difficile-associated disease has been reported in users of nearly all systemic antibacterial medicinal products, with severity ranging from mild diarrhoea to fatal colitis. *Clostridioides difficile*-associated disease must be considered in all patients who present with diarrhoea. If *Clostridioides difficile*-associated disease is suspected or confirmed treatment with delafloxacin should be discontinued and appropriate supportive measures together with the specific antibacterial treatment of *C. difficile* should be considered.
Medicinal products inhibiting the peristalsis are contraindicated if *Clostridioides difficile*-associated disease is suspected.

Hypersensitivity reactions

Patients with known hypersensitivity to delafloxacin or other fluoroquinolones should not take Quofenix (see section 4.3). Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving fluoroquinolone antibacterial medicinal products. Before

initiating therapy with delafloxacin, careful inquiry should be made about previous hypersensitivity reactions to other quinolone or fluoroquinolone antibacterial medicinal products. If an anaphylactic reaction to delafloxacin occurs, the medicinal product should be discontinued immediately and appropriate therapy should be instituted.

Patients with renal impairment

The safety and efficacy of the dose recommendation in patients with severe renal impairment has not been clinically evaluated and is based on pharmacokinetic modelling data. Delafloxacin should only be used in such patients when it is considered that the expected clinical benefit outweighs the potential risk. Clinical response to treatment and renal function should be closely monitored in these patients. Administration of oral delafloxacin in patients with severe renal impairment and low body weight may lead to increased systemic exposures. Quofenix is not recommended in patients with ESRD.

Limitations of the clinical data

In the two major trials in ABSSSI the types of infections treated were confined to cellulitis/erysipelas, abscesses and wound infections only. Other types of skin infections have not been studied. Patients with toxic shock, neutropenia (neutrophil counts <500 cells/mm3) or severely immunocompromised patients were not included in the studies. There is limited experience in patients aged > 75 years. However, the CAP population was older than the one studied in ABSSSI (48.3 % of subjects were ≥ 65 years and 23.9% ≥ 75 years). In the CAP study 90.7% of patients had CURB-65 score of ≤2. However 69.3% of patients were categorised to PORT class III and 30.7% of patients had a PORT score >III.

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. Delafloxacin 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.

Superinfection

Fluoroquinolone non-susceptible microorganisms may result in superinfection with the use of delafloxacin. If superinfection occurs during therapy, appropriate measures should be taken.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.
There are no data available on severe cases of hypoglycaemia resulting in coma or death after delafloxacin use.

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with other fluoroquinolones. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with other quinolones. Therefore, delafloxacin should be used with caution in these patients.

Excipients

This medicinal product contains 39 mg sodium per tablet, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on delafloxacin

Chelation active substance: antacids, sucralfate, metal cations, multivitamins
Fluoroquinolones form chelates with alkaline earth and transition metal cations. Oral administration of delafloxacin with antacids containing aluminium or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as didanosine buffered tablets for oral suspension or the paediatric powder for oral solution, may substantially interfere with the absorption of delafloxacin, resulting in systemic concentrations considerably lower than desired. Therefore, delafloxacin should be taken at least 2 hours before or 6 hours after these medicinal products.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment with delafloxacin.

Pregnancy

There are no or limited amount of data from the use of delafloxacin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In the absence of human data and findings in non-clinical studies at human therapeutic exposures, delafloxacin is contraindicated during pregnancy and in women of childbearing potential not using contraception (see sections 4.3 and 4.4).

Breast-feeding

It is unknown whether delafloxacin/metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of delafloxacin/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Breast-feeding is contraindicated during treatment with delafloxacin.

Fertility

The effects of delafloxacin on fertility in humans have not been studied. Nonclinical studies conducted with delafloxacin in rats do not indicate harmful effects with respect to fertility or reproductive performance (see section 5.3).

4.7 Effects on ability to drive and use machines

Quofenix has moderate influence on the ability to drive and use machines. Some adverse drug reactions (e.g. dizziness, headache, visual disorders) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where the patient operates an automobile or machinery or engages in other activities requiring mental alertness and coordination.

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions reported in ABSSSI (Phase 2 and 3 studies) and CAP (Phase 3 study) exposed to delafloxacin, intravenous or oral formulation, were diarrhoea, nausea and hypertransaminasaemia (5.86%, 5.47% and 2.85% respectively) which were mild to moderate in intensity.

Tabulated list of adverse reactions

The following adverse reactions have been identified in four comparative ABSSSI Phase 2 and 3 studies and in one CAP Phase 3 study classified by preferred term and System Organ Class, and by frequency. Frequencies are defined as: very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Class	**Common**	**Uncommon**	**Rare**
Infections and infestations	Fungal infection	C*lostridioides difficile* infection (see section 4.4)	Urinary tract infection Sinusitis
Blood and lymphatic system disorders		Anaemia Leukopenia	Thrombocytopenia Neutropenia International normalised ratio increased
Immune system disorders		Hypersensitivity (see section 4.4)	Seasonal allergy
Metabolism and nutrition disorders		Hyperglycaemia (see section 4.4) Decreased appetite	Hypoglycaemia (see section 4.4) Hyperuricaemia Hypokalaemia Blood potassium increased
Psychiatric disorders*		Insomnia	Hallucination, auditory Anxiety Abnormal dreams Confusional state
Nervous system disorders*	Headache	Peripheral neuropathy (including paraesthesia and hypoaesthesia) (see section 4.4) Dizziness Dysgeusia	Presyncope Somnolence
Eye disorders*		Vision blurred	Dry eye
Ear and labyrinth disorders*			Vertigo Tinnitus Vestibular disorder
Cardiac disorders**		Palpitations	Sinus tachycardia Bradycardia
Vascular disorders**		Hypertension Hypotension Flushing	Deep vein thrombosis Phlebitis

Respiratory, thoracic and mediastinal disorders		Dyspnoea	Cough Dry throat
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Stomatitis Abdominal pain Dyspepsia Dry mouth Flatulence Constipation	Gastritis erosive Gastrooesophageal reflux disease Paraesthesia oral Hypoaesthesia oral Glossodynia Faeces discoloured
Hepatobiliary disorders	Hypertransaminasaemia	Blood alkaline phosphatase increased	Blood albumin decreased Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Pruritus	Dermatitis allergic Urticaria Rash Hyperhidrosis	Alopecia Cold sweat Night sweat
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia Tendonitis (see section 4.4) Musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness Blood creatine phosphokinase increased	Arthritis reactive Myositis Muscle spasm
Renal and urinary disorders		Renal impairment	Haematuria Crystal urine present
General disorders and administration site conditions*		Pyrexia Local swelling Fatigue	Oedema peripheral Chills
Injury, poisoning and procedural complications			Wound complication

Description of selected adverse drug reactions

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious 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 and neuralgia, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, 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 product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

The highest daily oral dose administered in clinical studies was 1600 mg; the patients who received this dose did not have any adverse drug reactions or notable clinical laboratory test findings during the study. Treatment of overdose with delafloxacin should consist of observation and general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, fluoroquinolones, ATC code: J01MA23

Mechanism of action

Delafloxacin inhibits bacterial topoisomerase IV and DNA gyrase (topoisomerase II), enzymes required for bacterial DNA replication, transcription, repair, and recombination.

Resistance

Resistance to fluoroquinolones, including delafloxacin, can occur due to mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase referred to as Quinolone-Resistance Determining Regions (QRDRs), or through other resistance mechanisms such as efflux mechanisms.

Cross-resistance between delafloxacin and other fluoroquinolones may be observed, although some isolates resistant to other fluoroquinolone may retain susceptibility to delafloxacin.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for delafloxacin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Pharmacokinetic/pharmacodynamic relationship

The $fAUC_{24}$/MIC ratio, as for other quinolone antibiotics, resulted in the pharmacokinetic/ pharmacodynamic parameter most closely associated with efficacy of delafloxacin.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to delafloxacin *in vitro*.

Acute bacterial skin and skin structure infections

Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-resistant [MRSA])
- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Staphylococcus lugdunensis*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius,* and *Streptococcus constellatus*)
- *Streptococcus dysgalactiae*
- *Streptococcus mitis group* (including *Streptococcus cristatus, Streptococcus gordonii*, *Streptococcus oralis, Streptococcus mitis,* and *Streptococcus sanguinis*)
- *Streptococcus pyogenes*
- *Enterococcus faecalis*

Gram-negative microorganisms:
- *Escherichia coli*
- *Enterobacter cloacae*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*

Community-acquired pneumonia

Gram-positive microorganisms:
- *Streptococcus pneumoniae*
- *Staphylococcus aureus (MSSA)*

Gram-negative microorganisms:
- *Haemophilus influenzae*
- *Escherichia coli*

Atypical:
- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

The European Medicines Agency has waived the obligation to submit the results of studies with Quofenix in all subsets of the paediatric population in the treatment of local infections of skin and subcutaneous tissues and community-acquired pneumonia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following oral administration of 450 mg of delafloxacin every 12 hours, *steady state* concentrations are achieved after approximately 5 days with about 36% accumulation after multiple administrations. The half-life of oral delafloxacin is approximately 14 hours. Delafloxacin pharmacokinetic is comparable in patients with ABSSSI or CAP and healthy volunteers.

Absorption

Peak plasma delafloxacin concentrations are achieved within about 1 hour after oral administration under fasting conditions. The 450-mg tablet and 300-mg IV formulations are bioequivalent with regard to total exposure (AUC). Delafloxacin may be administered with or without food as total systemic exposure (AUC_{∞}) is unchanged between fasted and fed (high-fat, high-calorie) conditions.

Distribution

The steady state volume of distribution of delafloxacin is about 40 L which approximates total body water. The plasma protein binding of delafloxacin, is approximately 84%; it primarily binds to albumin. Plasma protein binding of delafloxacin is not significantly affected by the degree of renal impairment.
Following IV administration of 7 doses of 300 mg of delafloxacin to 30 healthy volunteers, the mean delafloxacin AUC_{0-12} (3.6 hr*µg/mL) in alveolar macrophages was 83% of the free-plasma AUC_{0-12}, and the mean delafloxacin AUC_{0-12} (2.8 hr*µg/mL) in epithelial lining fluid was 65% of the free-plasma AUC_{0-12}.

Biotransformation

Glucuronidation of delafloxacin is the primary metabolic pathway with oxidative metabolism representing <1% of an administered dose. The glucuronidation of delafloxacin is mediated mainly by UGT1A1, UGT1A3 and UGT2B15. Unchanged parent drug is the predominant component in plasma. There are no significant circulating metabolites (mean=9.6%) in humans.
In vitro data indicate that delafloxacin at clinically relevant concentrations does not inhibit cytochrome P450 CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 nor UDP glucuronosyl transferases isoforms UGT1A1 and UGT2B7. Delafloxacin does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C8, CYP2C19 or CYP3A4/5.
Likewise at clinically relevant concentrations delafloxacin does not inhibit the transporters MDR1, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K and BSEP.
Delafloxacin is a probable substrate of BCRP.

Elimination

Following a single oral dose of ^{14}C-labeled delafloxacin, 50% of the radioactivity is excreted in the urine as unchanged delafloxacin and glucuronide metabolites and 48% is excreted unchanged in the faeces.

Obese patients (≥30 kg/m^2 BMI)

Pharmacokinetic parameters are not altered in obese patients (BMI ≥ 30 kg/m^2).

Hepatic impairment

No clinically meaningful changes in delafloxacin pharmacokinetics when administered delafloxacin in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B and C) compared to matched healthy control subjects. Therefore, no dosage adjustment is necessary.

Renal impairment

Following a single oral (400 mg) administration to patients with mild, moderate or severe renal impairment, mean total exposure (AUC_t) was about 1.5-fold higher for subjects with moderate and severe renal impairment compared with healthy subjects, whereas total systemic exposures were comparable to subjects with mild renal impairment. Peak exposure (C_{max}) was not statistically significantly different between renal impaired and healthy subjects.
For dosing instructions in subjects with renal impairment refer to section 4.2.

Elderly

The pharmacokinetics of delafloxacin is not significantly altered with age; therefore, dose adjustment is not necessary based on age.

Paediatric population

No clinical trials have been conducted with delafloxacin in paediatric patients.

Gender

Clinically significant gender-related differences in delafloxacin pharmacokinetics have not been observed in healthy subjects or in patients with ABSSSI or CAP. No dose adjustment is recommended based on gender.

5.3 Preclinical safety data

In repeat dose toxicity studies in rats and dogs, gastrointestinal effects were the main findings: these included dilated cecum (oral only), abnormal stool, and decreased food intake and / or body weight in rats, and emesis, salivation and abnormal stool / diarrhoea in dogs. In addition increases in serum ALT and ALP, and reduced total protein and globulin values were recorded at the end of the treatment period in the pivotal 4-week IV dog study at the high dose (75 mg/kg) in individual dogs. Importantly, gastrointestinal effects and slightly elevated liver enzymes in dogs were not associated with histopathological changes of gastrointestinal and annexed tissues (pancreas, liver). No adverse effects were seen in rats at exposures about 2-fold higher than humans, or in dogs at exposures approximately equal to humans.
In embryo-fetal development studies carried out in rats and rabbits, delafloxacin was devoid of teratogenic effects but induced foetal growth retardation and ossification delays at levels of dose producing maternal toxicity. In rats foetal effects occurred at a level of exposure exceeding about 2-fold that observed in humans based on the AUC, but in rabbits, a species known to be extremely sensitive to maternal toxicity of antibacterial drugs, the effects on foetuses were recorded at levels of exposure well below that observed in humans. As delafloxacin is excreted in milk, severe toxicity was observed in newborn rats during lactation when mothers were treated during pregnancy and lactation with delafloxacin at a dose producing a systemic exposure about 5-fold higher than observed in humans. However, no such effects and no other developmental abnormalities occurred in the progeny of mothers exposed up to a level about 2-fold higher than observed in humans. No effects were detected on rat male and female fertility at a level of exposure about 5-fold higher than that observed in humans.

Long-term carcinogenicity studies have not been conducted with delafloxacin.

No genotoxicity hazard was identified *in vitro* and it was negative *in vivo* at the highest possible dose ≥ 15 times the estimated human plasma exposure based on AUC.

Environmental risk assessment studies have shown that delafloxacin may pose a risk to aquatic compartment(s).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Povidone
Crospovidone
Sodium hydrogen carbonate
Sodium dihydrogen phosphate monohydrate
Citric acid
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Laminated aluminium/aluminium foil blisters.

Pack sizes of 10, 20, 30, 50, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

A. Menarini – Industrie Farmaceutiche Riunite – s.r.l.
Via Sette Santi 3, 50131 Florence, Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1393/002-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2019
Date of latest renewal: 22 August 2024

10. DATE OF REVISION OF THE TEXT

25th February 2025

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu