ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quofenix 300 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains delafloxacin meglumine equivalent to 300 mg delafloxacin.
After reconstitution each ml contains 25 mg of delafloxacin.

Excipient(s) with known effect

Each vial contains 2 480 mg of sulfobutylbetadex sodium.
Each vial contains 175 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
Light yellow to tan cake, which may exhibit cracking and shrinkage and slight variation in texture and colour.

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 dose is 300 mg delafloxacin every 12 hours administered over 60 minutes by intravenous infusion. Switch to delafloxacin 450 mg tablet orally every 12 hours is possible at the discretion of the physician. The total duration of treatment is 5 to 14 days for ABSSSI and 5 to 10 days for CAP.

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 moderate renal impairment (CrCl of ≥30 mL/min). Dosing in patients with severe renal impairment (CrCl of <30 mL/min) should be decreased to 200 mg intravenously every 12 hours; alternatively patients should receive 450 mg delafloxacin orally every 12 hours (see sections 4.4 and 5.2).
Quofenix is not recommended in patients with End Stage Renal Disease (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

Intravenous use.
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

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 must 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

Dose adjustment is needed in patients with severe renal impairment (see section 4.2).
The safety and efficacy of the dose adjustment guidance 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.
Accumulation of the intravenous vehicle sulfobutylbetadex sodium occurs in patients with moderate to severe renal impairment; therefore, serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to switch to delafloxacin 450 mg tablet every 12 hours.
Quofenix is not recommended in patients with End Stage Renal Disease (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 sulfobutylbetadex sodium. In patients with moderate to severe renal impairment, accumulation of cyclodextrins may occur.

This medicinal product contains 175 mg sodium per vial, equivalent to 8.8% 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

There are no available data concerning specific effects of other medicinal products on delafloxacin. Known fluoroquinolones-associated possible interactions shall be considered.

Effect of delafloxacin on other medicinal products

Chelation active substance: antacids, sucralfate, metal cations, multivitamins
There are no data concerning an interaction of intravenous delafloxacin with multivitamins, didanosine, or metal cations. However, delafloxacin should not be co-administered with any solution containing multivalent cations, e.g. magnesium, through the same intravenous line (see sections 4.2 and 6.2).

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. Non-clinical 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	*Clostridioides 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

System Organ Class	Common	Uncommon	Rare
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*	Infusion site reaction	Pyrexia Local swelling Fatigue	Oedema peripheral Chills Medical device complication
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 the national reporting system listed in Appendix V.

4.9 Overdose

The highest daily intravenous dose administered in clinical studies was 1 200 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 the 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 intravenous use of 300 mg delafloxacin every 12 hours, *steady state* concentrations are achieved after approximately 3-5 days with about 10% accumulation after multiple administrations. The half-life of IV delafloxacin is approximately 10 hours. Delafloxacin pharmacokinetic is comparable in patients with ABSSSI or CAP and healthy volunteers.

Absorption

Peak plasma delafloxacin concentrations are achieved at the end of the 1 hour intravenous infusion. The 300-mg IV formulation and 450 mg tablet are bioequivalent with regard to total exposure (AUC).

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 glucuronosyltransferases 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

After single intravenous dose of ^{14}C-labeled delafloxacin, 65% of the radioactivity is excreted in the urine and 28% is excreted in the faeces. Delafloxacin is excreted both unchanged and as glucuronide metabolites in urine. The radioactivity recovered from faeces is unchanged delafloxacin.

Obese patients ($\geq$ 30 kg/m^2 BMI)

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

Hepatic impairment

No clinically meaningful changes in delafloxacin C_{max} and AUC_{∞} were observed, following administration of a single 300 mg intravenous dose of delafloxacin into patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B and C) compared to matched healthy control subjects.

Renal impairment

Following single intravenous (300 mg) administration to patients with mild, moderate, or severe renal impairment or ESRD on haemodialysis with and without haemodialysis after dosing, mean total exposure (AUC_t) were 1.3, 1.7, 2.1, 3.5 and 4.1-fold higher than values for matched control subjects.

Peak concentrations for the mild and moderate renal impairment patients were similar to that of healthy subjects, whereas peak concentrations were 2.1-fold, 5.9-fold and 6.4-fold higher for patients with severe renal impairment and ESRD on haemodialysis with and without haemodialysis after dosing, respectively.
In patients with moderate, or severe renal impairment or ESRD on haemodialysis, accumulation of the intravenous vehicle sulfobutylbetadex sodium occurs. The mean systemic exposure (AUC) increased 2.2-fold, 5.3-fold, 8.5-fold and 29.8-fold for patients with moderate impairment, severe impairment and ESRD with and without haemodialysis after dosing, respectively compared to the normal control group. The mean peak exposure (C_{max}) increased about 2-fold, 5-fold and 7-fold for patients with severe impairment and ESRD with and without haemodialysis after dosing, respectively compared to the normal control group.
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

Meglumine
Sulfobutylbetadex sodium
Disodium edetate
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid, concentrated (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

5 years.
Chemical and physical in-use stability has been demonstrated for 24 hours at 20 to 25ºC or at 2 to 8°C. From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.
Do not freeze.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml clear type I glass vials outfitted with 20 mm type I rubber stoppers and 20 mm flip-off caps.
Pack-size: 10 vials.

6.6 Special precautions for disposal

Quofenix must be reconstituted under aseptic conditions, using 10.5 mL of dextrose 50 mg/ml (5%) solution for injection (D5W) or sodium chloride 9 mg/ml (0.9%) solution for injection for each 300 mg vial.

- The vial should be vigorously shaken until contents are completely dissolved. The reconstituted vial contains 300 mg per 12 mL of delafloxacin as a clear yellow to amber coloured solution.
- The reconstituted solution must be then diluted in 250mL IV bag (either 0.9% Sodium Chloride Injection or D5W) prior to administration.
- Prepare the required dose for intravenous infusion by withdrawing the volume of 12 ml for Quofenix 300 mg or 8 ml for Quofenix 200 mg from the reconstituted vial.
- The required dose of Quofenix reconstituted solution should be aseptically transferred from the vial to a 250 mL intravenous bag. (Any unused portion of the reconstituted solution should be discarded).
- After reconstitution and dilution, Quofenix is to be administered via intravenous infusion, using a total infusion time of 60 minutes.

Quofenix must not be co-infused with other medicinal products. If a common intravenous line is being used to administer other medicinal products in addition to Quofenix the line should be flushed before and after each Quofenix infusion with sodium chloride 9 mg/ml (0.9%) solution for injection or D5W.
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/1/19/1393/001

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

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

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		Dyspnoea	Cough Dry throat

mediastinal disorders			
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 the national reporting system listed in Appendix V.

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

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Tablets

AlfaSigma
1 Via Enrico Fermi
65020 Alanno (PE)
Italy

or

Special Product's Line S.p.A.
1 Via Fratta Rotonda Vado Largo
03012 Anagni (FR)
Italy

Powder for concentrate for solution for infusion

Patheon Italia S.p.A.
2° Trav. SX Via Morolense 5
03013 Ferentino (FR)
Italy

or

AlfaSigma
1 Via Enrico Fermi
65020 Alanno (PE)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIALS)

1. NAME OF THE MEDICINAL PRODUCT

Quofenix 300 mg powder for concentrate for solution for infusion
delafloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg of delafloxacin (as meglumine).
After reconstitution, each ml contains 25 mg of delafloxacin.

3. LIST OF EXCIPIENTS

Meglumine, sulfobutylbetadex sodium, disodium edetate, sodium hydroxide, hydrochloric acid, concentrated.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
10 single-dose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1393/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quofenix 300mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNIT

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quofenix 300 mg powder for concentrate
delafloxacin
Intravenous use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Quofenix 450 mg tablets
delafloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 450 mg of delafloxacin (as meglumine)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
20 tablets
30 tablets
50 tablets
60 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1393/002 10 tablets
EU/1/19/1393/003 20 tablets
EU/1/19/1393/004 30 tablets
EU/1/19/1393/005 50 tablets
EU/1/19/1393/006 60 tablets
EU/1/19/1393/007 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quofenix 450 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM/ALUMINIUM BLISTER (TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Quofenix 450mg tablets
delafloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

A. Menarini – Industrie Farmaceutiche Riunite – s.r.l.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Quofenix 300 mg powder for concentrate for solution for infusion
delafloxacin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Quofenix is and what it is used for

Quofenix is an antibiotic that contains the active substance delafloxacin. It belongs to a group of medicines called fluoroquinolones.

It is used to treat adults with serious short-term infections caused by certain bacteria when usual antibiotics cannot be used or have not worked:
- infections of the skin and tissue under the skin
- infection of the lungs called ‘pneumonia’.

It works by blocking bacteria enzymes needed to copy and to repair their DNA. By blocking these enzymes, Quofenix kills bacteria that cause the infection.

2. What you need to know before you are given Quofenix

You must not be given Quofenix:
- If you are allergic to delafloxacin or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to any other fluoroquinolone or quinolone antibacterial medicine.
- If you have ever had a problem with your tendons such as tendonitis that was related to treatment with a ‘quinolone antibiotic’. A tendon is the cord that joins your muscle to your skeleton.
- If you are pregnant, might become pregnant, or think you might be pregnant.
- If you are breast-feeding.
- If you are a child or growing adolescent below 18 years of age.

Warnings and precautions

Before you are given this medicine
You should not be given fluoroquinolone/quinolone antibacterial medicines, including Quofenix, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

When you are given this medicine

- Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping Quofenix therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking Quofenix, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.
- You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking Quofenix and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

Talk to your doctor or pharmacist or nurse before you are given Quofenix if:

- You have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).
- You have experienced a previous episode of aortic dissection (a tear in the aorta wall).
- You have been diagnosed with leaking heart valves (heart valve regurgitation).
- You have a family history of aortic aneurysm or aortic dissection or congenital heart valve disease, or other risk factors or predisposing conditions (e. g. connective tissue disorders such as Marfan syndrome, or Ehlers-Danlos syndrome, Turner syndrome, Sjögren's syndrome [an inflammatory autoimmune disease], or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis, rheumatoid arthritis [a disease of the joints] or endocarditis [an infection of the heart]).
- You have had tendon problems during previous treatment with a fluoroquinolone or quinolone antibiotic.
- You have or may have problems with the central nervous system (e.g. severe cerebral arteriosclerosis, epilepsy) or have other risk factors that may put you at more risk of having seizures (fits). In those cases your doctor will consider if this treatment is the best option for you.
- You have a myasthenia gravis (a type of muscle weakness), because symptoms can become worse.
- You are suffering from diarrhoea, or have previously suffered from diarrhoea while taking antibiotics or up to 2 months afterwards. Contact your doctor straight away if you have diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.
- You have kidney problems.
- You had sometimes long treatment with antibiotics; it can mean that you get another infection caused by other bacteria (superinfection) which cannot be treated by the antibiotic. Talk to your doctor if you have any concerns or questions about this and using Quofenix.
- You may have a severe skin reaction such as blistering or lesion.
- You or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase.
- You have diabetes. Fluoroquinolone antibiotics, including Quofenix, may cause levels of glucose in the blood to rise too high or fall too low. If you have diabetes, you should monitor your blood glucose levels carefully.

If you feel sudden, severe pain in your abdomen, chest or back, which can be symptoms of aortic aneurysm and dissection, go immediately to an emergency room. Your risk may be increased if you are being treated with systemic corticosteroids.

If you start experiencing a rapid onset of shortness of breath, especially when you lie down flat in your bed, or you notice swelling of your ankles, feet or abdomen, or a new onset of heart palpitations (sensation of rapid or irregular heartbeat), you should inform a doctor immediately.

Prolonged, disabling and potentially irreversible serious side effects
Fluoroquinolone/quinolone antibacterial medicines have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue, and severe sleep disorders.
If you experience any of these side effects after receiving Quofenix, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class.

Children and adolescents
This medicine must not be used in children and adolescents, as it has not been studied enough in these groups.

Other medicines and Quofenix
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Quofenix should not be given together with any solution containing substances such as calcium and magnesium, through the same intravenous line.

Pregnancy and breast-feeding
Quofenix must not be used if you are pregnant or breast-feeding. Quofenix must not be used in women of childbearing potential not using contraception.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor before you are given this medicine.
If you might become pregnant you have to use effective contraception during treatment with Quofenix.

Driving and using machines
Quofenix can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how Quofenix affects you.

Quofenix contains cyclodextrin
This medicine contains 2 480 mg of sulfobutylbetadex sodiumin each vial.

Quofenix contains sodium
This medicine contains 175 mg of sodium (main component of cooking salt) in each vial. This is equivalent to 8.8% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Quofenix

Quofenix will be given to you by a nurse or doctor via an infusion (drip) into a vein.

You will be given one infusion of Quofenix, containing 300 mg of the medicine, twice a day between 5 and 14 days for skin infections and between 5 and 10 days for pneumonia, at the discretion of your doctor. Each infusion will last about an hour. Your doctor will decide how many days treatment is needed.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

If you have any further questions on the use of this medicine, ask your doctor.

If you are given more Quofenix than you should

Tell your doctor or nurse immediately if you are concerned that you may have been given too much Quofenix.

If you miss a dose of Quofenix
Tell your doctor or nurse immediately if you are concerned that you may have missed a dose.
If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Please, inform your doctor or nurse immediately if you get any of these symptoms, as the medicine should be stopped and you may need urgent medical attention:

- Difficulty in swallowing or difficulty in breathing and cough; swelling of your lips, face, throat or tongue; dry throat or throat tightening and severe rash. These may be signs and symptoms of a hypersensitivity (allergic) reaction and may be life-threatening. These severe reactions are uncommon side effects that may affect up to 1 in 100 people.
- Drop in blood pressure; blurred vision; dizziness. This severe reaction is an uncommon side effect that may affect up to 1 in 100 people.
- Abdominal (belly) pain with possible severe diarrhoea; fever and nausea. These may be signs of an infection of the bowel, which shouldn't be treated with diarrhoea medicines that stop your bowels from moving. Infection of the bowel (*Clostridioides difficile* infection) is an uncommon side effect that may affect up to 1 in 100 people.

Other side effects may include:

Common side effects (may affect up to 1 in 10 people):
- Fungal infection
- Headache
- Vomiting
- Swelling, redness or pain around the needle where the medicine is given into a vein (infusion site reaction)
- Increase in the amount of enzymes produced by your liver called transaminases - shown in blood tests
- Itching

Uncommon side effects (may affect up to 1 in 100 people):
- Reduction in the number of white cells in the blood (leukopenia)
- Low haemoglobin level (anaemia)
- Allergic reaction
- High blood glucose levels
- Decreased appetite
- Insomnia
- Muscle weakness in the extremities
- Sensations like numbness, tingling, pins and needles
- Reduced tactile sensation
- Change in taste
- Feeling your heart beat (palpitation)
- High blood pressure
- Flushing (e.g. redness of the face or neck)
- Inflammation of the lining of the stomach, inflammation of the internal tissues of the mouth, abdominal pain, stomach discomfort/pain or indigestion, dry mouth, flatulence

- Abnormal sweat
- Allergic skin reaction
- Itchiness, red rash
- Joint pain
- Pain and swelling of the tendons
- Muscle and musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness
- Increased level of creatine phosphokinase in blood (an indicator of muscle damage)
- Reduced kidney function
- Feeling tired
- Blood test alteration related to liver function (blood alkaline phosphatase increased)
- Raised body temperature (pyrexia)
- Lower limb swelling

Rare side effects (may affect up to 1 in 1000 people):

- Urinary tract infection
- Inflammation of the nasal mucosa tract
- Low white blood cell count (reduction of an amount of blood cells)
- Decrease of special blood cells necessary for blood clotting
- Changes in tests which measure how well your blood clots
- Seasonal allergy
- Low blood glucose levels
- High level of uric acid
- High level of blood potassium
- Low level blood potassium
- Hearing things that do not exist (auditory hallucination)
- Anxiety
- Abnormal dreams
- Confusion
- Somnolence
- Feeling lightheaded or faint, usually because of a drop in blood pressure
- Dry eye
- Dizziness or loss of balance (vertigo)
- Ringing or buzzing in the ears (tinnitus)
- Alteration of the sense of balance
- Irregular or rapid heart beats, decrease of heart beat
- Swollen, red, irritated veins (phlebitis)
- Blood clot, known as a thrombus in the deep vein
- Heartburn/acid regurgitation
- Loss of tactile sensation at the mouth
- Reduced tactile sensation at the mouth
- Burning sensation in the mouth
- Discoloured faeces
- Blood test alteration related to liver function (blood albumin decreased and gamma-glutamyltransferase increased)
- Cold sweat
- Night sweat
- Abnormal hair loss
- Muscle spasm
- Muscle inflammation/pain
- Inflammation of joints, pain in hands or feet, back pain
- Blood in urine
- Cloudy urine because of the presence of solid component
- Chills

- Worsening of a wound
- Oedema peripheral
- Medical device occlusion

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), fatigue, memory and concentration impairment, mental health effects (which may include sleep disorders, anxiety, panic attacks, depression and suicidal ideation), as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Cases of an enlargement and weakening of the aortic wall or a tear in the aortic wall (aneurysms and dissections), which may rupture and may be fatal, and of leaking heart valves have been reported in patients receiving fluoroquinolones. See also section 2.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Quofenix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister after “EXP”. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions if kept unopened in the original container.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 20 to 25ºC or at 2 to 8°C. From a microbiological point of view, the product should be used immediately after reconstitution and dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

Do not freeze.

6. Contents of the pack and other information

What Quofenix contains
- The active substance is delafloxacin. Each vial of powder contains 300 mg of delafloxacin (as meglumine).
- The other excipients are meglumine, sulfobutylbetadex sodium,disodium edetate, sodium hydroxide (for pH-adjustment), hydrochloric acid, concentrated (for pH-adjustment).

What Quofenix looks like and contents of the pack
Quofenix powder for concentrate for solution for infusion is provided in 20 ml clear glass vial. The vial contains light yellow to tan cake powder.
It is available in packs containing 10 vials.

Marketing Authorisation Holder
A. Menarini – Industrie Farmaceutiche Riunite – s.r.l.

Via Sette Santi 3
50131 Florence
Italy

Manufacturer
Patheon Italia S.p.A.
2° Trav. SX Via Morolense 5
03013 Ferentino (FR)
Italy

or

AlfaSigma
1 Via Enrico Fermi
65020 Alanno (PE)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Menarini Benelux NV/SA
Tél/Tel: + 32 (0)2 721 4545

Lietuva
UAB "BERLIN-CHEMIE MENARINI BALTIC"
Tel: +370 52 691 947

България
Берлин-Хеми/А. Менарини България ЕООД
тел.: +359 2 454 0950

Luxembourg/Luxemburg
Menarini Benelux NV/SA
Tél/Tel: + 32 (0)2 721 4545

Česká republika
Berlin-Chemie/A.Menarini Ceska republika s.r.o.
Tel: +420 267 199 333

Magyarország
Berlin-Chemie/A. Menarini Kft.
Tel.: +36 17997320

Danmark
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Malta
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Deutschland
Berlin-Chemie AG
Tel: +49 (0) 30 67070

Nederland
Menarini Benelux NV/SA
Tel: +32 (0)2 721 4545

Eesti
OÜ Berlin-Chemie Menarini Eesti
Tel: +372 667 5001

Norge
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Ελλάδα
MENARINI HELLAS AE
Τηλ: +30 210 8316111-13

Österreich
A. Menarini Pharma GmbH.
Tel: +43 1 879 95 85-0

España
Laboratorios Menarini S.A.
Tel: +34-93 462 88 00

France
MENARINI France
Tél: +33 (0)1 45 60 77 20

Hrvatska
Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: + 385 1 4821 361

Ireland
A. Menarini Pharmaceuticals Ireland Ltd
Tel: +353 1 284 6744

Ísland
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Italia
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Κύπρος
MENARINI HELLAS AE
Τηλ: +30 210 8316111-13

Latvija
SIA Berlin-Chemie/Menarini Baltic
Tel: +371 67103210

Polska
Berlin-Chemie/Menarini Polska Sp. z o.o.
Tel.: +48 22 566 21 00

Portugal
A. Menarini Portugal – Farmacêutica, S.A.
Tel: +351 210 935 500

România
Berlin-Chemie A. Menarini S.R.L.
Tel: +40 21 232 34 32

Slovenija
Berlin-Chemie / A. Menarini Distribution Ljubljana d.o.o.
Tel: +386 01 300 2160

Slovenská republika
Berlin-Chemie / A. Menarini Distribution Slovakia s.r.o. Tel: +421 2 544 30 730

Suomi/Finland
Berlin-Chemie/A.Menarini Suomi OY
Puh/Tel: +358 403 000 760

Sverige
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

United Kingdom (Northern Ireland)
A. Menarini Farmaceutica Internazionale S.R.L.
Tel: +44 (0)1628 856400

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

For single use only.

Quofenix must be reconstituted under aseptic conditions, using 10.5 mL of dextrose 50 mg/ml (5%) solution for injection (D5W) or sodium chloride 9 mg/ml (0.9%) solution for injection for each 300 mg vial.

- The vial should be vigorously shaked until contents are completely dissolved. The reconstituted vial contains 300 mg per 12 mL of delafloxacin as a clear yellow to amber coloured solution.
- The reconstituted solution must be then diluted in 250mL IV bag (either 0.9% Sodium Chloride Injection or D5W) prior to administration.

- Prepare the required dose for intravenous infusion by withdrawing the volume of 12 ml for Quofenix 300 mg or 8 ml for Quofenix 200 mg from the reconstituted vial.
- The required dose of Quofenix reconstituted solution should be aseptically transferred from the vial to a 250 mL intravenous bag. (Any unused portion of the reconstituted solution should be discarded).
- After reconstitution and dilution, Quofenix is to be administered via intravenous infusion, using a total infusion time of 60 minutes.

Quofenix must not be co-infused with other medications. If a common intravenous line is being used to administer other medicinal products in addition to Quofenix the line should be flushed before and after each Quofenix infusion with sodium chloride 9 mg/ml (0.9%) solution for injection or D5W. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user
Quofenix 450 mg tablets
delafloxacin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Quofenix is and what it is used for

Quofenix is an antibiotic that contains the active substance delafloxacin. It belongs to a group of medicines called fluoroquinolones.

It is used to treat adults with serious short-term infections caused by certain bacteria when usual antibiotics cannot be used or have not worked:
- infections of the skin and tissue under the skin
- infection of the lungs called ‘pneumonia’.

It works by blocking bacteria enzymes needed to copy and to repair their DNA. By blocking these enzymes Quofenix kills bacteria that cause the infection.

2. What you need to know before you take Quofenix

Do not take Quofenix:
- If you are allergic to delafloxacin or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to any other fluoroquinolone or quinolone antibacterial medicine.
- If you have ever had a problem with your tendons such as tendonitis that was related to treatment with a ‘quinolone antibiotic’. A tendon is the cord that joins your muscle to your skeleton.
- If you are pregnant, might become pregnant, or think you might be pregnant.
- If you are breast-feeding.
- If you are a child or growing adolescent below 18 years of age.

Warnings and precautions

Before taking this medicine
You should not take fluoroquinolone/quinolone antibacterial medicines, including Quofenix, if you have experienced any serious adverse reaction in the past when taking a quinolone or fluoroquinolone. In this situation, you should inform your doctor as soon as possible.

When taking this medicine

- Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping Quofenix therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking Quofenix, contact your doctor and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

- You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking Quofenix and inform your doctor immediately in order to prevent the development of potentially irreversible condition.

Talk to your doctor or pharmacist or nurse before taking Quofenix if:
- You have been diagnosed with an enlargement or "bulge" of a large blood vessel (aortic aneurysm or large vessel peripheral aneurysm).
- You have experienced a previous episode of aortic dissection (a tear in the aorta wall).
- You have been diagnosed with leaking heart valves (heart valve regurgitation).
- You have a family history of aortic aneurysm or aortic dissection or congenital heart valve disease, or other risk factors or predisposing conditions (e. g. connective tissue disorders such as Marfan syndrome, or Ehlers-Danlos syndrome, Turner syndrome, Sjögren's syndrome [an inflammatory autoimmune disease], or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet's disease, high blood pressure, or known atherosclerosis, rheumatoid arthritis [a disease of the joints] or endocarditis [an infection of the heart]).
- You have had tendon problems during previous treatment with a fluoroquinolone or quinolone antibiotic.
- You have or may have problems with the central nervous system (e.g. severe cerebral arteriosclerosis, epilepsy) or have other risk factors that may put you at more risk of having seizures (fits). In those cases yor doctor will consider if this treatment is the best option for you.
- You have a myasthenia gravis (a type of muscle weakness), because symptoms can become worse.
- You are suffering from diarrhoea, or have previously suffered from diarrhoea while taking antibiotics or up to 2 months afterwards. Contact your doctor straight away if you have diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.
- You have kidney problems.
- You had sometimes long treatment with antibiotics; it can mean that you get another infection caused by other bacteria (superinfection) which cannot be treated by the antibiotic. Talk to your doctor if you have any concerns or questions about this and using Quofenix.
- You may have a severe skin reaction such as blistering or lesion.
- You or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase.
- You have diabetes. Fluoroquinolone antibiotics, including Quofenix, may cause levels of glucose in the blood to rise too high or fall too low. If you have diabetes, you should monitor your blood glucose levels carefully.

If you feel sudden, severe pain in your abdomen, chest or back, which can be symptoms of aortic aneurysm and dissection, go immediately to an emergency room. Your risk may be increased if you are being treated with systemic corticosteroids.

If you start experiencing a rapid onset of shortness of breath, especially when you lie down flat in your bed, or you notice swelling of your ankles, feet or abdomen, or a new onset of heart palpitations (sensation of rapid or irregular heartbeat), you should inform a doctor immediately.

Prolonged, disabling and potentially irreversible serious side effects
Fluoroquinolone/quinolone antibacterial medicines have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible. This includes tendon, muscle and joint pain of the upper and lower limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, numbness or burning (paraesthesia), sensory disorders including impairment of vision, taste and smell, and hearing, depression, memory impairment, severe fatigue and severe sleep disorders.
If you experience any of these side effects after taking Quofenix, contact your doctor immediately prior to continuing treatment. You and your doctor will decide on continuing the treatment considering also an antibiotic from another class.

Children and adolescents
This medicine must not be used in children and adolescents as it has not been studied enough in these groups.

Other medicines and Quofenix
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Quofenix tablets should be taken at least 2 hours before or 6 hours after:

- an antacid, multivitamin, or other product that has magnesium, aluminium, iron, or zinc
- sucralfate
- didanosine buffered tablets for oral suspension or the paediatric powder for oral solution

Pregnancy and breast-feeding
Quofenix must not be used if you are pregnant or breast-feeding. Quofenix must not be used in women of childbearing potential not using contraception.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor before you are taking this medicine.
If you might become pregnant you have to use effective contraception during treatment with Quofenix.

Driving and using machines
Quofenix can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how Quofenix affects you.

Quofenix contains sodium
This medicine contains 39 mg of sodium (main component of cooking salt) in each tablet. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Quofenix
Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
The recommended dose is 450 mg oral every 12 hours for a total duration of 5 to 14 days for skin infections and 5 to 10 days for pneumonia, at the discretion of your doctor. The tablets are swallowed whole with a sufficient amount of water, and can be taken with or without food.

If you take more Quofenix than you should
If you accidentally take more tablets than you should, tell a doctor or get other medical advice. Take the medicine pack with you.

If you forget to take Quofenix
If you miss a dose, you should take it as soon as possible anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, wait until the next scheduled dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Quofenix
If you stop taking Quofenix without the advice of your doctor, your symptoms may get worse. Talk to your doctor or pharmacist before you stop taking your medicine.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Please, inform your doctor or nurse immediately if you get any of these symptoms, as the medicine should be stopped and you may need urgent medical attention:

- Difficulty in swallowing or difficulty in breathing and cough; swelling of your lips, face, throat or tongue; dry throat or throat tightening and severe rash. These may be signs and symptoms of a hypersensitivity (allergic) reaction and may be life-threatening. These severe reactions are uncommon side effects that may affect up to 1 in 100 people.
- Drop in blood pressure; blurred vision; dizziness. This severe reaction is an uncommon side effect that may affect up to 1 in 100 people.
- Abdominal (belly) pain with possible severe diarrhoea; fever and nausea. These may be signs of an infection of the bowel, which should not be treated with diarrhoea medicines that stop your bowels from moving. Infection of the bowel (*Clostridioides difficile* infection) is an uncommon side effect that may affect up to 1 in 100 people.

Other side effects may include:

Common side effects (may affect up to 1 in 10 people):
- Fungal infection
- Headache
- Vomiting
- Increase in the amount of enzymes produced by your liver called transaminases -shown in blood tests
- Itching

Uncommon side effects (may affect up to 1 in 100 people):
- Reduction in the number of white cells in the blood (leukopenia)
- Low haemoglobin level (anaemia)
- Allergic reaction
- High blood glucose levels
- Decreased appetite
- Insomnia
- Muscle weakness in the extremities
- Sensations like numbness, tingling, pins and needles
- Reduced tactile sensation
- Change in taste
- Feeling your heart beat (palpitation)
- High blood pressure
- Flushing (e.g. redness of the face or neck)
- Inflammation of the lining of the stomach, inflammation of the internal tissues of the mouth, abdominal pain, stomach discomfort/pain or indigestion, dry mouth, flatulenced
- Abnormal sweat
- Allergic skin reaction
- Itchiness, red rash
- Joint pain

- Pain and swelling of the tendons
- Muscle and musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness
- Increased level of creatine phosphokinase in blood (an indicator of muscle damage)
- Reduced kidneys function
- Feeling tired
- Blood test alteration related to liver function (blood alkaline phosphatase increased)
- Raised body temperature (pyrexia)
- Lower limb swelling

Rare side effects (may affect up to 1 in 1000 people):

- Urinary tract infection
- Inflammation of the nasal mucosa tract
- Low white blood cell count (reduction of an amount of blood cells)
- Decrease of special blood cells necessary for blood clotting
- Changes in tests which measure how well your blood clots
- Seasonal allergy
- Low blood glucose levels
- High level of uric acid
- High level of blood potassium
- Low level blood potassium
- Hearing things that do not exist (auditory hallucination)
- Anxiety
- Abnormal dreams
- Confusion
- Somnolence
- Feeling lightheaded or faint, usually because of a drop in blood pressure
- Dry eye
- Dizziness or loss of balance (vertigo)
- Ringing or buzzing in the ears (tinnitus)
- Alteration of the sense of balance
- Irregular or rapid heart beats, decrease of heart beat
- Swollen, red, irritated veins (phlebitis)
- Blood clot, known as a thrombus in the deep vein
- Heartburn/acid regurgitation
- Loss of tactile sensation at the mouth
- Reduced tactile sensation at the mouth
- Burning sensation in the mouth
- Discoloured faeces
- Blood test alteration related to liver function (blood albumin decreased and gamma-glutamyltransferase increased)
- Cold sweat
- Night sweat
- Abnormal hair loss
- Muscle spasm
- Muscle inflammation/pain
- Inflammation of joints, pain in hands or feet, back pain
- Blood in urine
- Cloudy urine because of the presence of solid component
- Chills
- Worsening of a wound
- Oedema peripheral

Very rare cases of long lasting (up to months or years) or permanent adverse drug reactions, such as tendon inflammations, tendon rupture, joint pain, pain in the limbs, difficulty in walking, abnormal sensations such as pins and needles, tingling, tickling, burning, numbness or pain (neuropathy), fatigue, memory and concentration impairment, mental health effects (which may include sleep disorders, anxiety, panic attacks, depression and suicidal ideation), as well as impairment of hearing, vision, and taste and smell have been associated with administration of quinolone and fluoroquinolone antibiotics, in some cases irrespective of pre-existing risk factors.

Cases of an enlargement and weakening of the aortic wall or a tear in the aortic wall (aneurysms and dissections), which may rupture and may be fatal, and of leaking heart valves have been reported in patients receiving fluoroquinolones. See also section 2.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Quofenix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister after “EXP”. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Quofenix contains
- The active substance is delafloxacin. Each tablet contains 450 mg of delafloxacin (as meglumine).
- The other ingredients are cellulose microcrystalline, povidone, crospovidone, sodium hydrogen carbonate, sodium dihydrogen phosphate monohydrate, citric acid, magnesium stearate.

What Quofenix looks like and contents of the pack
Quofenix is a beige to mottled beige, oblong biconvex tablets.

It is available in blister pack of 5 tablets, into pack size of 10, 20, 30, 50, 60 or 100 tablets per carton. Not all pack sizes may be marketed.

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

Manufacturer

AlfaSigma
1 Via Enrico Fermi
65020 Alanno (PE)
Italy

or

Special Product's Line S.p.A.
1 Via Fratta Rotonda Vado Largo
03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Menarini Benelux NV/SA
Tél/Tel: + 32 (0)2 721 4545

Lietuva
UAB "BERLIN-CHEMIE MENARINI BALTIC"
Tel: +370 52 691 947

България
Берлин-Хеми/А. Менарини България ЕООД
тел.: +359 2 454 0950

Luxembourg/Luxemburg
Menarini Benelux NV/SA
Tél/Tel: + 32 (0)2 721 4545

Česká republika
Berlin-Chemie/A.Menarini Ceska republika s.r.o.
Tel: +420 267 199 333

Magyarország
Berlin-Chemie/A. Menarini Kft.
Tel.: +36 17997320

Danmark
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Malta
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Deutschland
Berlin-Chemie AG
Tel: +49 (0) 30 67070

Nederland
Menarini Benelux NV/SA
Tel: +32 (0)2 721 4545

Eesti
OÜ Berlin-Chemie Menarini Eesti
Tel: +372 667 5001

Norge
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Ελλάδα
MENARINI HELLAS AE
Τηλ: +30 210 8316111-13

Österreich
A. Menarini Pharma GmbH.
Tel: +43 1 879 95 85-0

España
Laboratorios Menarini S.A.
Tel: +34-93 462 88 00

Polska
Berlin-Chemie/Menarini Polska Sp. z o.o.
Tel.: +48 22 566 21 00

France
MENARINI France
Tél: +33 (0)1 45 60 77 20

Hrvatska
Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: + 385 1 4821 361

Ireland
A. Menarini Pharmaceuticals Ireland Ltd
Tel: +353 1 284 6744

Ísland
A. Menarini -Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Italia
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

Κύπρος
MENARINI HELLAS AE
Τηλ: +30 210 8316111-13

Latvija
SIA Berlin-Chemie/Menarini Baltic
Tel: +371 67103210

Portugal
A. Menarini Portugal – Farmacêutica, S.A.
Tel: +351 210 935 500

România
Berlin-Chemie A. Menarini S.R.L.
Tel: +40 21 232 34 32

Slovenija
Berlin-Chemie / A. Menarini Distribution Ljubljana d.o.o.
Tel: +386 01 300 2160

Slovenská republika
Berlin-Chemie / A. Menarini Distribution Slovakia s.r.o. Tel: +421 2 544 30 730

Suomi/Finland
Berlin-Chemie/A.Menarini Suomi OY
Puh/Tel: +358 403 000 760

Sverige
A. Menarini - Industrie Farmaceutiche Riunite - s.r.l.
Tel: +39-055 56801

United Kingdom (Northern Ireland)
A. Menarini Farmaceutica Internazionale S.R.L.
Tel: +44 (0)1628 856400

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.