

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

## **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 2480 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 acute bacterial skin and skin structure infections (ABSSSI) in adults 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.

#### Special population

##### *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  $\geq 30$  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 section 4.4 and 5.2).

Quofenix is not recommended in patients with End Stage Renal Disease (ESRD).

#### *Hepatic impairment*

No dosage 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

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

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 in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

#### 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 Quofenix, careful inquiry should be made about previous hypersensitivity reactions to other quinolone or fluoroquinolone antibacterial medicinal products. If an anaphylactic reaction to Quofenix 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 Quofenix 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/mm<sup>3</sup>) or severely immunocompromised patients were not included in the studies. There is limited experience in patients aged > 75 years.

#### 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-insusceptible 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 occurs.

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 section 4.2 and 6.2).

Based on *in vitro* data on metabolising enzymes and transporters delafloxacin possesses a low potential to alter the disposition of other medicinal products (see section 5.2).

#### **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. 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 involving 868 patients exposed to delafloxacin, intravenous or oral formulation, were diarrhoea and nausea (6.91% and 7.83%, 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 classified by preferred term and System Organ Class, and by frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>
<b>Infections and infestations</b>	Fungal infection	<i>Clostridioides difficile</i> infection (see section 4.4) Urinary tract infection Sinusitis
<b>Blood and lymphatic system disorders</b>		Thrombocytopenia Haematocrit decreased White blood cell count decreased Haemoglobin decreased Red blood cell count decreased
<b>Immune system disorders</b>		Hypersensitivity (see section 4.4) Seasonal allergy
<b>Metabolism and nutrition disorders</b>		Hypoglycaemia (see section 4.4) Hyperglycaemia (see section 4.4) Decreased appetite
<b>Psychiatric disorders*</b>		Hallucination, auditory Anxiety Insomnia Abnormal dreams
<b>Nervous system disorders*</b>	Headache	Peripheral neuropathy (including paraesthesia and hypoaesthesia) (see section 4.4) Dizziness Presyncope Dysgeusia
<b>Eye disorders*</b>		Vision blurred Dry eye
<b>Ear and labyrinth disorders*</b>		Vertigo Tinnitus
<b>Cardiac disorders</b>		Sinus tachycardia Palpitations Bradycardia
<b>Vascular disorders</b>		Hypertension Hypotension Flushing Phlebitis
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea Cough Dry throat

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>
<b>Gastrointestinal disorders</b>	Diarrhoea Vomiting Nausea	Gastritis erosive Stomatitis Abdominal pain Dyspepsia Gastroesophageal reflux disease Paraesthesia oral Hypoesthesia oral Glossodynia Dry mouth Flatulence Constipation Faeces discoloured
<b>Hepatobiliary disorders</b>	Hypertransaminaemia	Blood alkaline phosphatase increased Blood albumin decreased
<b>Skin and subcutaneous tissue disorders</b>	Pruritus	Dermatitis allergic Urticaria Rash Alopecia Hyperhidrosis Cold sweat Night sweat
<b>Musculoskeletal and connective tissue disorders*</b>		Arthritis reactive Arthralgia Myalgia Myositis Tendonitis (see section 4.4) Musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness Muscle spasm Blood creatine phosphokinase increased
<b>Renal and urinary disorders</b>		Renal impairment Haematuria Crystal urine present
<b>General disorders and administration site conditions*</b>	Injection/infusion site reaction	Pyrexia Oedema peripheral Local swelling Fatigue Chills Medical device complication
<b>Injury, poisoning and procedural complications</b>		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, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

#### 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 1200 mg; the patients who receive 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

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for delafloxacin are as follows:

Organism	MIC breakpoints (mg/L)	
	Susceptible (S ≤)	Resistant (R >)
<i>Staphylococcus aureus</i>	0.25	0.25
<i>Streptococcus pyogenes</i>	0.03	0.03
<i>Streptococcus dysgalactiae</i>	0.03	0.03
<i>Streptococcus agalactiae</i>	0.03	0.03
<i>Streptococcus anginosus</i> group	0.03	0.03
<i>Escherichia coli</i>	0.125	0.125

#### Pharmacokinetic/pharmacodynamic relationship

The fAUC<sub>24</sub>/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 following pathogens that were susceptible to delafloxacin *in vitro*.

Gram-positive micro-organisms:

- *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 micro-organisms:

- *Escherichia coli*
- *Enterobacter cloacae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

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 (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 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.

### 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 <sup>14</sup>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 ( $\geq 30 \text{ kg/m}^2$ BMI)

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

### Hepatic impairment

No clinically meaningful changes in delafloxacin  $C_{\text{max}}$  and  $\text{AUC}_{\infty}$  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 ( $\text{AUC}_t$ ) 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 ( $C_{\text{max}}$ ) 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. 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  $\geq 15$  times the estimated human plasma exposure based on AUC.

## **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**

4 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 20 to 25°C 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 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.

## **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

## **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>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 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 acute bacterial skin and skin structure infections (ABSSSI) in adults 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 at the discretion of the physician. Delafloxacin tablets can be taken with or without food.

#### Special population

##### *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 section 4.4 and 5.2). Quofenix is not recommended in patients with ESRD.

##### *Hepatic impairment*

No dosage 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

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

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 in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

### 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 Quofenix, careful inquiry should be made about previous hypersensitivity reactions to other quinolone or fluoroquinolone antibacterial medicinal products. If an anaphylactic reaction to Quofenix 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/mm<sup>3</sup>) or severely immunocompromised patients were not included in the studies. There is limited experience in patients aged > 75 years.

### 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-insusceptible 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 agents.

#### Effect of delafloxacin on other medicinal products

Based on *in vitro* data on metabolising enzymes and transporters delafloxacin possesses a low potential to alter the disposition of other medicinal products (see section 5.2).

### **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. 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 involving 868 patients exposed to delafloxacin intravenous or oral formulation, were diarrhoea and nausea ( 6.91% and 7. 83%, 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 classified by preferred term and System Organ Class, and by frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>
<b>Infections and infestations</b>	Fungal infection	<i>Clostridioides difficile</i> infection (see section 4.4) Urinary tract infection Sinusitis
<b>Blood and lymphatic system disorders</b>		Thrombocytopenia Haematocrit decreased White blood cell count decreased Haemoglobin decreased Red blood cell count decreased
<b>Immune system disorders</b>		Hypersensitivity (see section 4.4) Seasonal allergy
<b>Metabolism and nutrition disorders</b>		Hypoglycaemia (see section 4.4) Hyperglycaemia (see section 4.4) Decreased appetite
<b>Psychiatric disorders*</b>		Hallucination auditory Anxiety Insomnia Abnormal dreams
<b>Nervous system disorders*</b>	Headache	Peripheral neuropathy (including paraesthesia and hypoesthesia) (see section 4.4) Dizziness Presyncope Dysgeusia
<b>Eye disorders*</b>		Vision blurred Dry eye
<b>Ear and labyrinth disorders*</b>		Vertigo Tinnitus
<b>Cardiac disorders</b>		Sinus tachycardia Palpitations Bradycardia
<b>Vascular disorders</b>		Hypertension Hypotension Flushing Phlebitis
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea Cough Dry throat
<b>Gastrointestinal disorders</b>	Diarrhoea Vomiting Nausea	Gastritis erosive Stomatitis Abdominal pain Dyspepsia Gastrooesophageal reflux disease Paraesthesia oral Hypoesthesia oral Glossodynia Dry mouth Flatulence Constipation Faeces discoloured
<b>Hepatobiliary disorders</b>	Hypertransaminasaemia	Blood alkaline phosphatase increased Blood albumin decreased
<b>Skin and subcutaneous tissue disorders</b>	Pruritus	Dermatitis allergic Urticaria

		Rash Alopecia Hyperhidrosis Cold sweat Night sweat
<b>Musculoskeletal and connective tissue disorders*</b>		Arthritis reactive Arthralgia Myalgia Myositis Tendonitis (see section 4.4) Musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness Muscle spasm Blood creatine phosphokinase increased
<b>Renal and urinary disorders</b>		Renal impairment Haematuria Crystal urine present
<b>General disorders and administration site conditions*</b>		Pyrexia Oedema peripheral Local swelling Fatigue Chills
<b>Injury, poisoning and procedural complications</b>		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, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

#### 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 receive 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

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for delafloxacin are as follows:

Organism	MIC breakpoints (mg/L)	
	Susceptible (S ≤)	Resistant (R >)
<i>Staphylococcus aureus</i>	0.25	0.25
<i>Streptococcus pyogenes</i>	0.03	0.03
<i>Streptococcus dysgalactiae</i>	0.03	0.03
<i>Streptococcus agalactiae</i>	0.03	0.03
<i>Streptococcus anginosus</i> group	0.03	0.03
<i>Escherichia coli</i>	0.125	0.125

### Pharmacokinetic/pharmacodynamic relationship

The fAUC<sub>24</sub>/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 following pathogens that were susceptible to delafloxacin *in vitro*.

Gram-positive micro-organisms:

- *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 micro-organisms:

- *Escherichia coli*

- *Enterobacter cloacae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

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 (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 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<sub>∞</sub>) 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.

### 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 <sup>14</sup>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<sup>2</sup> BMI)

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

### 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. 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  $\geq 15$  times the estimated human plasma exposure based on AUC.

## **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**

3 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**

No special requirements.

Any unused 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

## **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

*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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## **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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **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
2. What you need to know before you are given Quofenix
3. How to use Quofenix
4. Possible side effects
5. How to store Quofenix
6. Contents of the pack and other information

#### **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 of the skin and tissues under the skin caused by certain bacteria when usual antibiotics cannot be used or have not worked.

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 a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e. g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet’s disease, high blood pressure, or known atherosclerosis).
- 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, go immediately to an emergency room.

#### **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.

There are no data concerning an interaction of intravenous delafloxacin with multivitamins, other supplements or didanosine. However, 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 2480 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 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):

- Urinary tract infection
- Inflammation of the nasal mucosa tract
- Haematocrit decreased (reduction of an indicator of amount of blood cells)
- Low white blood cell count (reduction of an amount of blood cells)
- Low haemoglobin level (anaemia)
- Low red blood cell count (reduction of amount of blood cells)
- Decrease of special blood cells necessary for blood clotting
- Allergic reaction
- Seasonal allergy
- Low blood glucose levels
- High blood glucose levels
- Decreased appetite
- Hearing things that do not exist (auditory hallucination)
- Anxiety
- Insomnia
- Abnormal dreams
- Muscle weakness in the extremities
- Feeling lightheaded or faint, usually because of a drop in blood pressure
- Sensations like numbness, tingling, pins and needles

- Reduced tactile sensation
- Change in taste
- Dry eye
- Dizziness or loss of balance (vertigo)
- Ringing or buzzing in the ears (tinnitus)
- Irregular or rapid heart beats, feeling your heart beat (palpitation), decrease of heart beat
- High blood pressure
- Flushing (e.g. redness of the face or neck)
- Swollen, red, irritated veins
- 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, discoloured faeces
- Heartburn/acid regurgitation
- Loss of tactile sensation at the mouth
- Reduced tactile sensation at the mouth
- Burning sensation in the mouth
- Abnormal sweat
- Cold sweat
- Night sweat
- Allergic skin reaction
- Itchiness, red rash
- Abnormal hair loss
- Joint pain
- Pain and swelling of the tendons
- Inflammation of joints, pain in hands or feet, back pain, muscle spasm
- Muscle inflammation/pain
- Muscle and musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness
- Reduced kidney function
- Blood in urine
- Cloudy urine because of the presence of solid component
- Feeling tired
- Chills
- Blood test alteration related to kidney or liver function (blood alkaline phosphatase increased, blood albumin decreased)
- Worsening of a wound
- Lower limb swelling
- 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), depression, fatigue, sleep disorders, memory impairment, 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.

### **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 25°C 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**

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**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>.

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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 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 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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**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
2. What you need to know before you take Quofenix
3. How to take Quofenix
4. Possible side effects
5. How to store Quofenix
6. Contents of the pack and other information

**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 of the skin and tissues under the skin caused by certain bacteria when usual antibiotics cannot be used or have not worked.

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 a family history of aortic aneurysm or aortic dissection or other risk factors or predisposing conditions (e. g. connective tissue disorders such as Marfan syndrome, or vascular Ehlers-Danlos syndrome, or vascular disorders such as Takayasu arteritis, giant cell arteritis, Behcet’s disease, high blood pressure, or known atherosclerosis).
- 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, go immediately to an emergency room.

### **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 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):

- Urinary tract infection
- Inflammation of the nasal mucosa tract
- Haematocrit decreased (reduction of an indicator of amount of blood cells)
- Low white blood cell count (reduction of amount of blood cells)
- Low haemoglobin level (anaemia)
- Low red blood cell count (reduction of amount of blood cells)
- Decrease of special blood cells necessary for blood clotting
- Allergic reaction
- Seasonal allergy
- Low blood glucose levels
- High blood glucose levels
- Decreased appetite
- Hearing things that do not exist (auditory hallucination)
- Anxiety
- Insomnia
- Abnormal dreams
- Muscle weakness in the extremities
- Feeling lightheaded or faint, usually because of a drop in blood pressure
- Sensations like numbness, tingling, pins and needles)
- Reduced tactile sensation
- Change in taste
- Dry eye
- Dizziness or loss of balance (vertigo)
- Ringing or buzzing in the ears (tinnitus)

- Irregular or rapid heart beats, feeling your heart beat (palpitation), decrease of heart beat
- High blood pressure
- Flushing (e.g. redness of the face or neck)
- Swollen, red, irritated veins
- 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, discoloured faeces
- Heartburn/acid regurgitation
- Loss of tactile sensation at the mouth
- Reduced tactile sensation at the mouth
- Burning sensation in the mouth
- Abnormal sweat
- Cold sweat
- Night sweat
- Allergic skin reaction
- Itchiness, red rash
- Abnormal hair loss
- Joint pain
- Pain and swelling of the tendons
- Inflammation of joints, pain in hands or feet, back pain, muscle spasm
- Muscle inflammation/pain
- Muscle and musculoskeletal pain (e.g. pain in extremity, back pain, neck pain), muscle weakness
- Reduced kidneys function
- Blood in urine
- Cloudy urine because of the presence of solid component
- Feeling tired
- Chills
- Blood test alteration related to kidney or liver function (blood alkaline phosphatase increased, blood albumin decreased)
- Worsening of a wound
- Lower limb swelling

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), depression, fatigue, sleep disorders, memory impairment, 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.

### **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

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### Manufacturer

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Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.