HAUTE AUTORITÉ DE SANTÉ

# TRANSPARENCY COMMITTEE

## SUMMARY

## 16 DECEMBER 2020

*The legally binding text is the original French opinion version*

***delafloxacin***

**QUOFENIX 300 mg powder for concentrate for solution for infusion**
**QUOFENIX 450 mg tablets**

**First assessment**

### Key points

Favourable opinion for reimbursement in the treatment of severe, microbiologically documented, polymicrobial including methicillin-resistant *Staphylococcus aureus* (MRSA) acute bacterial skin and skin structure infections (ABSSSI), and only as second-line treatment, i.e., when it is considered inappropriate to use other antibacterial agents that are commonly recommended as first-line treatment of these infections, in particular for reasons related to resistance, safety, allergy or administration method.

Unfavourable opinion for reimbursement in the other clinical situations.

### What therapeutic improvement?

No clinical added value in the therapeutic strategy.

## Role in the care pathway?

The usual treatment of these infections generally requires antibiotics appropriate to the identified or probable bacteria. A number of options are possible, depending on the bacteria and their resistance rate.

**Role of the medicinal product in the care pathway**

Acute bacterial skin and skin structure infections (ABSSSI) are usually monomicrobial, except in the case of necrotizing bacterial cellulitis. The use of antibiotic therapy targeting both Gram-positive and Gram-negative bacteria is only justified in severe infections. Following microbiological documentation, for methicillin-susceptible *Staphylococcus aureus* (MSSA), the very low minimum inhibitory concentrations (MIC) of delafloxacin do not justify its use in these situations, and for methicillin-resistant *Staphylococcus aureus* (MRSA), other antibiotics with a narrower spectrum are available.

Delafloxacin may therefore be valuable as second-line treatment in the event of severe, microbiologically documented, polymicrobial including MRSA, delafloxacin-susceptible infections, when it is considered inappropriate to use other antibacterial agents that are commonly recommended as first-line treatment of these infections, in particular for reasons related to resistance, safety, allergy or administration method.

## Special recommendations

**Specific requests inherent to funding**

Considering:
- current uncertainties with respect to the safety profile of delafloxacin in view of the known adverse effects of other fluoroquinolone antibiotics,
- the risk of the emergence of resistance to delafloxacin, particularly in patients with prior fluoroquinolone exposure,
- the need to restrict its use to second-line treatment only in order to preserve it,

the Committee recommends that the therapeutic decision be taken after consulting an antibiotic expert.

## COMMITTEE'S CONCLUSIONS

### Clinical benefit

◗ Skin and skin structure infections are composed of a very varied range of clinical entities, for which the development conditions, treatment and prognosis are variable, from ulcers, infected wounds, abscesses, erysipelas and diabetic foot ulcers through to the most serious forms, including bacterial cellulitis and necrotizing fasciitis.

◗ QUOFENIX (delafloxacin) is a curative treatment for acute bacterial skin and skin structure infections (ABSSSI).

◗ The efficacy/adverse effects ratio of QUOFENIX (delafloxacin) has not been established in non-serious infections (erysipelas/non-necrotising cellulitis, infected wounds and major skin abscesses), primarily staphylococcal, including methicillin-resistant Staphylococcus, in the same way as other fluoroquinolone antibiotics.
In more serious forms requiring intensive care treatment and/or due to multi-drug resistant bacteria, which are relevant for this antibiotic in view of the approved indications, the efficacy/adverse effects ratio is yet to be specified. However, the bacteriological data and pharmacokinetic profile suggest that delafloxacin may be of value in these situations in the absence of an acquired resistance mechanism.

◗ There are therapeutic alternatives, including for multi-drug resistant bacteria.

◗ QUOFENIX (delafloxacin)is a second-line treatment only in the event of severe infections, following microbiological documentation, when it is considered inappropriate to use other antibacterial agents that are commonly recommended as first-line treatment of these infections, in particular for reasons related to resistance, safety, allergy or administration method.
It has no role in the treatment of non-serious infections.

◗ <u>Public health impact</u>
Considering:
- the seriousness of the infections concerned,
- the medical need to have access to new antibiotics in order to respond to the spread of resistance to the antibiotics currently recommended in the treatment of these infections,
- the available efficacy data and its limitations in terms of the transposability of results in severe infections and/or those due to multi-drug resistant bacteraemia,
- uncertainties with respect to the safety profile of delafloxacin in view of the known adverse effects of other fluoroquinolone antibiotics, the restrictions and precautions of use of which are applicable to delafloxacin,
- concerns about the long-term risk of resistance selection due to the very broad spectrum of activity, particularly in patients with prior fluoroquinolone exposure,
- a potential impact of QUOFENIX (delafloxacin) on the care and life pathway of patients due to simplification of the administration regimen (monotherapy active against Gram-positive and negative bacteria, particularly on MRSA) and the availability of an oral form for patients (although the non-inferiority of the IV to oral switch sequence was not demonstrated versus the comparator),

On the basis of currently available data, QUOFENIX (delafloxacin) is likely to have an impact on public health.

**Considering these elements, the Committee deems that the clinical benefit of QUOFENIX (delafloxacin) is:**

- **substantial only in the treatment of severe, microbiologically documented, polymicrobial including MRSA, delafloxacin-susceptible acute bacterial skin and skin structure infections (ABSSSI), and only as second-line treatment, i.e., when it is considered inappropriate to use other antibacterial agents that are commonly recommended as first-line treatment of these infections, in particular for reasons related to resistance, safety, allergy or administration method;**
- **insufficient to justify public funding cover in all other clinical situations.**

**The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages only in the treatment of severe, microbiologically documented, polymicrobial including methicillin-resistant *Staphylococcus aureus* (MRSA) acute bacterial skin and skin structure infections (ABSSSI), and only as second-line treatment, when it is considered inappropriate to use other antibacterial agents that are commonly recommended as first-line treatment of these infections, in particular for reasons related to resistance, safety, allergy or administration method.**

**The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other clinical situations of the MA.**

## Clinical Added Value

**Considering:**
- **its activity against Gram-negative and Gram-positive bacteria, in particular methicillin-resistant Staphylococcus,**
- **the simplification of the administration regimen (monotherapy active against Gram-positive and negative bacteria),**
- **the demonstrated non-inferiority of delafloxacin IV compared to vancomycin/aztreonam IV on the clinical recovery rate at the follow-up visit (EMA primary endpoint) in patients with mild to moderate skin or skin structure infection;**

**but considering:**
- **inadequate documentation of its clinical efficacy in severe skin infections and/or those due to multi-drug resistant bacteria,**
- **concerns about its safety profile in view of the known adverse effects (including tendinopathy and peripheral neuropathy) of fluoroquinolone antibiotics,**
- **the absence of demonstration of the non-inferiority of delafloxacin (IV then oral) versus vancomycin/aztreonam IV dual therapy, not formally supporting the clinical value of the oral form despite its value for patients,**

**the Committee considers that QUOFENIX (delafloxacin) provides no clinical added value (CAV V) in the treatment of severe, microbiologically documented, polymicrobial including MRSA acute bacterial skin and skin structure infections (ABSSSI) and as second-line treatment.**