SUMMARY

norfloxacin

NORFLOXACINE ZENTIVA 400 mg,

film-coated tablets

New indication(s)

Adopted by the Transparency Committee on 10 May 2023

The legally binding text is the original French opinion version

Key points

Favourable opinion for reimbursement only “in the primary and secondary prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C)”.

Role in the care pathway?

NORFLOXACINE ZENTIVA (norfloxacin) is a reference therapeutic option based on the opinions of learned societies (SPILF - French-speaking Society for Infectious Diseases, AFEF – French Association for Liver Studies), for the primary and secondary prophylactic treatment of spontaneous bacterial peritonitis in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C).

In this indication, the treatment regimen recommended by national and European learned societies is a daily oral dose of 400 mg of norfloxacin as long-term treatment6,7,12.

The prescription of NORFLOXACINE ZENTIVA (norfloxacin) must take into account the risk of emergence of resistant bacteria, particularly in the event of quinolone prophylaxis with a long duration of treatment and in patients with significant acquired or passive immunosuppression (e.g. corticosteroid therapy). In addition, in hospitalised patients, the risk of carrying methicillin-resistant Staphylococcus aureus (MRSA) is increased by prior antibiotic prophylaxis with norfloxacin14.

The Summary of Product Characteristics (SmPC) and the Risk Management Plan (RMP) must be followed.

The use of this medicinal product in pregnant or breast-feeding women must comply with the SmPC (http://lecrat.fr/).

Within the scope included in the MA but not retained for reimbursement:

NORFLOXACINE ZENTIVA (norfloxacin) has no role in the other MA situations.

Special recommendations

➔ **Special recommendations in view of the quality and safety of care requirements related to the medicinal product**

In view of the product's specificities in terms of safety (risk of tendinopathy, QT interval prolongation, aortic aneurysm or dissection), the risk of emergence of resistant bacteria, particularly in the event of quinolone prophylaxis with a long duration of treatment and in patients with significant acquired or passive immunosuppression (e.g. corticosteroid therapy), and in order to guarantee the restricted use of NORFLOXACINE ZENTIVA (norfloxacin), it is proposed that initial prescription be reserved for specialists in the management of spontaneous bacterial peritonitis, i.e. hepato-gastroenterology specialists, infectious diseases specialists, internal medicine specialists and intensive care specialists.

Transparency Committee's conclusions

Clinical Benefit

Gastrointestinal infections

- ➔ Bacterial infections represent a major cause of mortality in cirrhosis patients. Spontaneous bacterial peritonitis (SBP) is a specific complication of cirrhosis that is both common (10 to 30% of bacterial infections in hospitalised patients) and serious (following a first episode of SBP, mortality in hospital ranges from 10 to 50%).
- ➔ This is a preventive treatment for spontaneous bacterial peritonitis (SBP).
- ➔ The efficacy/adverse effects ratio of this antibiotic is:
  - low in the primary and secondary prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C),
  - inadequately established in the other clinical situations covered by the MA wording.
- ➔ There are alternatives to this medicinal product (generic norfloxacin medicines, CIFLOX (ciprofloxacin) and its generics, and BACTRIM (sulfamethoxazole/trimethoprim) and its generics).
- ➔ This is a first-line treatment in view of the therapies available.

➔ **Public health benefit**

Considering:

- the seriousness of the disease and its prevalence (10 to 30% of bacterial infections in hospitalised patients),

- the partially met medical need in the prevention of spontaneous bacterial peritonitis and its recurrence in cirrhosis patients,
- the fact that NORFLOXACINE ZENTIVA (norfloxacin) could provide a response to the identified medical need in terms of the prevention of SBP and its recurrence in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C),
- the absence of any demonstrated additional impact on morbidity and mortality compared to the other antibiotics currently recommended (ciprofloxacin, sulfamethoxazole/trimethoprim),
- an expected impact on the organisation of care (absence of dosage adjustment in patients with renal impairment or folinic acid supplementation), as relayed by learned societies: AFEF and SPILF,

NORFLOXACINE ZENTIVA (norfloxacin) is unlikely to have an additional impact on public health. A negative impact on public health cannot be excluded due to a risk of emergence of resistance in the event of quinolone prophylaxis with a long duration of treatment and in patients with significant acquired or passive immunosuppression (e.g. corticosteroid therapy). In addition, in hospitalised patients, the risk of carrying methicillin-resistant MRSA is increased by prior antibiotic prophylaxis with norfloxacine. Hence, strict prescribing control is necessary to ensure the restricted use of this medicinal product, in order to reduce the risk of emergence of resistance in the event of wider use, particularly in urinary tract infections.

Considering all these elements, the Committee deems that the clinical benefit of NORFLOXACINE ZENTIVA (norfloxacin) 400 mg film-coated tablets is:

- **low only in the primary and secondary prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C),**
- **insufficient to justify public funding in the other MA situations.**

The Committee issues a favourable opinion for inclusion of NORFLOXACINE ZENTIVA (norfloxacin) 400 mg film-coated tablets in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only in the primary and secondary prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C), and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion of NORFLOXACINE ZENTIVA (norfloxacin) 400 mg film-coated tablets in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other MA situations.

➔ **Recommended reimbursement rate for inclusion in the retail list of reimbursed proprietary medicinal products approved for use: 15%**

Clinical Added Value

Primary and secondary prophylaxis of spontaneous bacterial peritonitis in cirrhosis patients

Considering:

- **the partially met medical need in the preventive treatment of spontaneous bacterial peritonitis and its recurrence in cirrhosis patients;**
- **the bibliographic data available, with a low level of evidence, showing an efficacy of norfloxacin in the prevention of SBP and its recurrence in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C);**
- **its well-established use in national and international medical practice;**

But:

- **the absence of any demonstrated superiority of norfloxacin compared to the other antibiotics currently recommended (ciprofloxacin, sulfamethoxazole/trimethoprim);**
- **a safety profile well known to include adverse reactions such as neurological and psychological disorders and rare but serious musculoskeletal system disorders that are persistent, disabling and potentially irreversible;**
- **the risk of emergence of resistant bacteria, particularly in the event of long-term treatment in immunocompromised patients;**

the Transparency Committee deems that NORFLOXACINE ZENTIVA (norfloxacin) 400 mg film-coated tablets provide no clinical added value (CAV V) in the prevention of spontaneous bacterial peritonitis and its recurrence in patients with cirrhosis complicated by severe low-protein ascites (< 15 g/L) and associated with impaired liver function (Child-Pugh class C).