HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
07 OCTOBER 2020
The legally binding text is the original French opinion version

fidaxomicin
DIFICLIR 200 mg film-coated tablets
DIFICLIR 40 mg/mL granules for oral suspension

New indication
Availability of a new form

Key points

Favourable opinion for reimbursement in the treatment of *Clostridioides difficile* infections (CDI) in paediatric patients (for more details, see MA).

What therapeutic improvement?

Therapeutic improvement in management.

Role in the care pathway?

The two most commonly used antibiotics in the treatment of *C. difficile* infections (CDI) are metronidazole and vancomycin, by the oral route. These two products are effective in most CDI cases but almost a third of initially recovered patients relapse.

Role of the medicinal product in the care pathway

Fidaxomicin is a first-line therapy in the treatment of *C. difficile* infections due to its comparable efficacy and safety profile to that of vancomycin in terms of recovery from the infection, but with a lower risk of relapse and a greater convenience of use than vancomycin.

Special recommendations

The Committee reiterates that there is a risk of misuse, with potential use of fidaxomicin in cases of antibiotic-associated diarrhoea without established *C. difficile* infection (CDI). However, not all cases of antibiotic-associated diarrhoea are linked to *C. difficile* and may be due to poor colonic fermentation as a result of a reduction in the dominant flora, for example. Since this is generally a short-term situation, it will be difficult for clinicians to differentiate between the efficacy of fidaxomicin in this indication and that of no treatment.

Hence treatment should only be considered in the event of CDI with the presence of toxin A and/or B in the stools. It should be noted that the presence of toxins in the stools before the age of 3 years only has a diagnostic value in the event of intestinal blockage.

Clinical benefit

◗ *Clostridium difficile* is responsible for 15 to 25% of cases of post-antibiotic diarrhoea and more than 95% of cases of pseudomembranous colitis. It is the leading cause of nosocomial diarrhoea in adults. In the past few years, the incidence, severity and mortality rates of *C. difficile* infections (CDI) have been increasing and this trend is related to the emergence of a particularly virulent strain. The mortality rates for *C. difficile* infection range from 0.6 to 1.5%, but reach 35 to 50% in the event of pseudomembranous colitis.
CDI is characterised by an increased risk of relapse (true recurrence or reinfection) within two months, that can be as high as 20 to 30%, despite well-managed antibiotic treatment. Factors associated with a high risk of recurrence include the continuation of antibiotic therapy other than for CDI, severe comorbidity and renal impairment, more than one previous episode of CDI, the concomitant use of a PPI, and the severity of the initial disease.
◗ DIFICLIR (fidaxomicin) is part of a curative treatment regimen.
◗ Its efficacy/adverse effects ratio is high.
◗ There are recommended therapeutic alternatives (metronidazole, vancomycin).
◗ It is a first-line treatment.

Public health impact

Considering:

- the seriousness of CDI, particularly in the event of complications,
- the increased incidence, severity and mortality related to the emergence of a particularly virulent strain of *C. difficile*,
- the high frequency of new episodes of CDI despite well-managed antibiotic treatment,
- the medical need to have access to new effective treatment and preventive approaches and tools, particularly in patients with severe infections and/or at high risk of recurrence,
- the partial response to the identified medical need due to a comparable efficacy profile to that of vancomycin in less severe forms in terms of clinical response at the end of treatment, with an advantage in favour of fidaxomicin for recovery rate, duration of resolution of diarrhoea and overall clinical recovery at the end of the follow-up period (30 days after the end of treatment),
- the expected impact on morbidity (lower frequency of recurrences and better persistence of recovery rate) compared to the treatments used in current practice (metronidazole, vancomycin),
- a potential impact on the care and life pathway by reducing the occurrence of new CDI episodes and the ecological risk related to the dissemination of resistant microorganisms,

DIFICLIR (fidaxomicin) is likely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of DIFICLIR (fidaxomicin) is substantial in the MA indications.

The Committee issues a favourable opinion for inclusion of DIFICLIR (fidaxomicin) in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indications and dosages.

Clinical Added Value

◗ **CAV in paediatric patients (for all forms)**

Considering:

- **available data in the paediatric population suggesting an efficacy profile for fidaxomicin comparable to that of vancomycin in terms of clinical response at the end of treatment (77.6% *versus* 70.5%, a difference adjusted by 7.5% ($CI_{95\%}$: [-7.4; 23.9]);**
- **a suggested advantage in terms of reduction in the rate of recurrence of *C. difficile*-associated diarrhoea compared to vancomycin (11.8% *versus* 29.0%);**
- **a size effect of the same magnitude as that described in adults with a comparable safety profile;**
- **a simplification of use compared to vancomycin with the availability of an appropriate paediatric formulation;**
- **the absence of robust data in the most severe forms (ileus, toxic megacolon, septic shock) and/or with multiple recurrent infections (more than one previous episode of *C. difficile* infection);**

the Committee considers that, in the same way as in adults, DIFICLIR (fidaxomicin) provides a moderate clinical added value (CAV III) in the treatment of *Clostridioides difficile* infections in paediatric patients.

◗ CAV in adults (for the oral suspension form)

This medicinal product is a range supplement that does not provide any clinical added value (CAV V) compared to the 200 mg film-coated tablet form already approved. This form may be used in adult patients with difficulties swallowing tablets.