HAUTE AUTORITÉ DE SANTÉ

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

**TRANSPARENCY COMMITTEE**

OPINION

17 October 2012

***The draft opinion approved by the Transparency Committee on 18 July 2012 was examined at a hearing on 17 October 2012***

**DIFICLIR 200 mg, film-coated tablet**
**B/20 tablets (CIP code: 222 376-7)**
**B/100 tablets (CIP code: 582 403-6)**

**Applicant: ASTELLAS PHARMA SAS**

fidaxomicin

ATC: A07AA12 (Intestinal anti-infectives: antibiotic)

List I

Date of Marketing Authorisation (Centralised procedure): 5 December 2011

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

fidaxomicin

## 1.2. Background

Fidaxomicin is a novel antibiotic belonging to the category of macrocyclic antibacterial agents. It is a narrow-spectrum antibiotic, with bactericidal activity against *Clostridium difficile*. Fidaxomicin does not have any intrinsic activity against Gram negative bacteria.

## 1.3. Indication

“DIFICLIR is indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as C. difficile-associated diarrhoea (CDAD).
Consideration should be given to official guidelines on the appropriate use of antibacterial agents.”

## 1.4. Dosage

“Adults and the elderly (≥65 years)
The recommended dose is 200 mg (one tablet) administered twice daily (once every 12 hours) for 10 days.

Paediatric population
The safety and efficacy of fidaxomicin in children aged below 18 years has not yet been established. No data are available.

Renal impairment
No dose adjustment is considered necessary. Due to the limited clinical data in this population, DIFICLIR should be used with caution in patients with severe renal impairment.

Hepatic impairment
No dose adjustment is considered necessary. Due to the limited clinical data in this population, DIFICLIR should be used with caution in patients with moderate to severe hepatic impairment.

Method of administration
DIFICLIR is intended for oral administration. DIFICLIR can be taken with or without food.”

## 1.5. Contraindications

“Hypersensitivity to the active substance or to any of the excipients (see section 6.1. of the SPC).”

### 1.6. Special warnings and precautions for use

“Due to limited clinical data, fidaxomicin should be used with caution in patients with severe renal impairment or moderate to severe hepatic impairment.

Due to limited clinical data, fidaxomicin should be used with caution in patients with pseudomembranous colitis, fulminant or life-threatening CDI.

There are no data in patients with concomitant inflammatory bowel disease. Fidaxomicin should be used with caution in these patients due to the risk of enhanced absorption and the potential risk of systemic adverse reactions.

The concomitant administration of potent P-glycoprotein inhibitors (P.gp) such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone, is not recommended.

Description of the patient population in clinical trials
In the two clinical trials of patients with CDI, 47.9% (479/999) of patients (per protocol population) were ≥65 years of age and 27.5% (275/999) of patients were treated with concomitant antibiotics during the study period. Twenty-four percent of patients met at least one of the following three criteria at baseline for disease scoring severity: body temperature >38.5℃, leukocyte count >15,000, or creatinine val ue ≥1.5 mg/dl. Patients with fulminant colitis and patients with multiple episodes of CDI (defined as more than one prior episode within the previous 3 months) were excluded from these studies”.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2011)

| | |
|---|---|
| A | Alimentary tract and metabolism |
| A07 | Antidiarrheals, intestinal antiinflammatory /antiinfective agents |
| A07A | Intestinal antiinfectives |
| A07AA | Antibiotics |
| A07AA12 | fidaxomicin |

### 2.2. Medicines in the same therapeutic category

None.

### 2.3. Medicines with a similar therapeutic aim

Comparable medicinal products are metronidazole (FLAGYL and its generics) and vancomycin (generics only).
In both cases, these antibiotics are active against *Clostridium difficile*, come from different categories and display different mechanisms of action. These products are not specifically indicated for "*C. difficile* infection”.
In France, there is no vancomycin formulation that is appropriate for the oral treatment of CDI.

# 3 ANALYSIS OF AVAILABLE DATA

## 3.1. Background and therapeutic need

In the case of a *C. difficile* infection (CDI), especially when it is mild to moderate, simply discontinuing the antibiotic incriminated may enable recovery. More often, and particularly in the event of severe infections, this is not sufficient and targeted antibiotic therapy must be initiated.
The two antibiotics most frequently employed in this disease setting are metronidazole and vancomycin, both of which are taken orally. These two products are effective in most cases of CDI, but nearly one-third of patients who initially recover experience a relapse. The probable causes suggested are changes to the intestinal flora caused by vancomycin and metronidazole themselves, and the persistent presence of *C. difficile* spores in the digestive tract.
Because metronidazole is administered by mouth and is almost completely absorbed, its systemic exposure is associated with adverse events. Vancomycin is one of the antibiotics used to treat serious diseases caused by multi-resistant bacteria such as methicillin-resistant *S. aureus* (MRSA). The emergence of MRSA and vancomycin-resistant enterococci (VRE) is a problem that is increasingly frequently encountered. In order to try and slow down the emergence of vancomycin-resistant strains, it is recommended to restrict its use to cases where it is absolutely necessary.
In this context, an alternative to metronidazole and vancomycin that displays at least the same efficacy and safety profiles is required.

## 3.2. Efficacy

The dossier includes two phase III studies with similar methodologies:

- study 003,[1] carried out in the USA and Canada, between May 2006 and August 2008
- study 004,[2] carried out in the USA, Canada and Europe (52% of centres), between April 2007 and December 2009.

[1] Louie TJ et al. Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection. N Engl J Med 2011; 364: 422-31.

[2] Cornely OA et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. www.thelancet.com/infection Published online February 8, 2012 DOI:10.1016/S1473-3099 (11)70374-7.

### 3.2.1. Study methods

**Table 1: Methods for the two phase III studies**

| | **Study 003** | **Study 004** |
|---|---|---|
| Aim and method | Controlled, randomised, double-blind studies, comparing the efficacy and safety of fidaxomicin (200 mg X 2/day) versus oral vancomycin (125 mg X 4/day). | |
| Duration of study | 10 days of treatment, followed by 30 days of monitoring | |
| Main patient selection criteria | Inclusion: patients aged at least 16 years, with *C. difficile* infection (CDI), defined by:<br>- diarrhoea (more than 3 loose stools or 200 ml of loose stools) during the 24 hours prior to randomisation<br>- and the presence of A or B C*. Difficile* toxin in the stools in the 48 hours prior to randomisation (or 96 hours in cases of previous treatment for CDI for trial 004).<br>Inclusion of patients with a failed treatment, who were resistant to a three-day treatment with metronidazole was possible.<br>Non inclusion: patients with life-threatening CDI or fulminant colitis, toxic megacolon or pseudomembranous colitis, patients with more than one episode of CDI over the last 3 months and those with a history of ulcerative colitis or Crohn's disease. | |
| Primary efficacy endpoint | **Clinical recovery* at Day 10**. Non-inferiority of fidaxomicin compared with vancomycin was established if the lower limit of the 95% confidence interval of the differences between the recovery rates was above -10% (*per protocol* analysis). | |
| Secondary endpoints | - relapse**<br>- persistent recovery*** at Day 40 | |
| Exploratory endpoints | Clinical recovery, occurrence of relapses and persistent recovery in the sub-group of patients defined according to relapse risk factors: age, presence of previous episode, severity of CDI on inclusion according to clinical investigator and based on ESCMID criteria[3] and concomitant antibiotic treatment. | |
| Method of analysis of results | In order to demonstrate non-inferiority for the main efficacy endpoint, a superiority analysis was planned for the **relapse and persistent recovery at Day 40** secondary endpoints (hierarchical model). | |

*Clinical recovery:
- Patients with at most 3 loose stools over 2 consecutive days and feeling well until treatment discontinuation.
Or
- Patients displaying a marked reduction in the number of loose stools at the end of treatment but with mild residual abdominal discomfort considered as being on the way to recovery by the investigator, in the absence of any worsening in the signs and symptoms of CDI during the 2 to 3 days following treatment discontinuation.
And
- Patients who, according to the investigator, did not require treatment for CDI, 2 days after discontinuation of the study treatment.
**Relapse: recurrence in a recovered patient, during the 4-week follow-up period, of diarrhoea with the presence of A or B toxin, and requiring further treatment with an anti-infective agent for CDI.
***Persistent recovery: no relapse during the 4-week follow-up period without treatment in patients experiencing a clinical recovery at the end of the treatment period.

Three analyses defined *a posteriori* were carried out:
- a combined analysis of the two pivotal studies;
- an analysis of relapses as a function of the date of onset (<14 days; ≥ 14 days), performed in response to the request from the EMA);
- a sub-group analysis according to severity, defined using ESCMID criteria, agreed after the start of the studies).

***Definition of the study populations***

Modified intention to treat population (mITT) for recovery: patients with CDI confirmed by a positive test for at least one toxin and who received at least one dose of the study drug.

mITT population for relapse: patients in the mITT population for recovery considered as having clinically recovered at the end of treatment.

[3] European Society of Clinical Microbiology and Infectious Diseases

Per Protocol Population (PP) for recovery: patients in the mITT population for recovery, with no major deviations from the protocol (treatment for at least 3 days before being defined as a failure, treatment for at least 8 days for clinical recovery, and completion of an end-of-study evaluation).
PP population for relapse: patients in the PP population for recovery, who had clinically recovered by the end of treatment, had been followed for at least 25 days or had relapsed before that time, and not receiving any concomitant treatment that could hamper this evaluation.

Results

- Study populations

The demographic and medical characteristics were comparable between the two treatment arms in the two studies. The mean age of patients was over 60 years, with more than half being female and the majority being hospitalised at the time of onset of their CDI . The mean number of stools during the 24 hours prior to treatment initiation was close to eight (Table 2).

**Table 2: Characteristics of patients included (mITT population for recovery) expressed as a mean ± standard deviation or numerically (percentage)**

| | **Study 003** | | **Study 004** | |
|---|---|---|---|---|
| | **Fidaxomicin N = 287 n - (%)** | ***Oral* vancomycin N = 309 n - (%)** | **Fidaxomicin N = 252 n - (%)** | ***Oral* vancomycin N = 257 n - (%)** |
| Age (years) | 60 ± 17 | 63 ± 17 | 64 ± 18 | 63 ± 18 |
| > 65-74 years | 47 (16) | 66 (21) | 55 (22) | 44 (17) |
| ≥ 75 years | 75 (26) | 86 (28) | 87 (35) | 87 (34) |
| Male | 123 (43) | 140 (45) | 104 (41) | 95 (37) |
| Hospitalised patients[1] | 167 (58) | 187 (61) | 174 (69) | 173 (67) |
| At least 1 episode previously | 48 (17) | 54 (18) | 40 (16) | 36 (14) |
| No. bowel movements/24 h before starting treatment | 8.1 ± 4.2 | 8.3 ± 5.4 | 7.5 ± 4.4 | 7.5 ± 4.3 |
| Initial severity of CDI[2] | | | | |
| Mild | 64 (22) | 80 (26) | 77 (31) | 95 (37) |
| Moderate | 111 (39) | 106 (34) | 82 (33) | 73 (28) |
| Severe | 112 (39) | 123 (40) | 90 (36) | 88 (34) |
| Missing data | - | - | 3 (1) | 1 (<1) |
| Severity according to ESCMID[3] | 72 (25) | 83 (27) | 63 (25) | 61 (24) |
| Previous antibiotic treatment for CDI | 128 (45) | 139 (45) | 225 (89) | 220 (86) |
| Failure with metronidazole | 13 (5) | 17 (6) | 12 (5) | 8 (3) |
| Concomitant antibiotic treatment | 127 (44) | 140 (45) | 149 (59) | 165 (64) |

[1] at the time of CDI occurring;
[2] Severity defined in the modified CDI severity Index as follows: mild: 4-5 loose stools/day or leukocytes ≤ 12,000/mm$^3$; moderate: 6-9 loose stools/day or leukocytes > 12,000 and ≤ 15,000/mm$^3$; severe: ≥ 10 loose stools per day or leukocytes ≥ 15,000/mm$^3$;
[3] Severity defined by an increase in creatininaemia ≥ 50% compared with initial value or leukocytes > 15,000/mm$^3$ or temperature > 38.5°C.

- *Primary efficacy endpoint: recovery at the end of treatment*

In both studies, fidaxomicin (200 mg X 2/day, over 10 days) was non-inferior to vancomycin (125 mg X 4/day, over 10 days), with percentage recovery > 90% in the PP analysis. These results are confirmed in the modified intention to treat population (mITT) and in the combined analysis of the two studies (Table 3).

**Table 3: Primary endpoint - clinical recovery at end of treatment**

| | | Fidaxomicin | Oral vancomycin | Difference |
|---|---|---|---|---|
| **PP Population** | | | | |
| Study 003 | N | 265 | 283 | |
| | n (%) | 244 (92.1) | 254 (89.8) | 2.3 |
| | 95% CI | 88.1; 94.8 | 85.6; 92.8 | -2.6; 7.1 |
| Study 004 | N | 216 | 235 | |
| | n (%) | 198 (91.7) | 213 (90.6) | 1.0 |
| | 95% CI | 87.1; 94.7 | 86.1; 93.8 | -4.3; 6.3 |
| Pooled analysis | N | 481 | 518 | |
| | n (%) | 442 (91.9) | 467 (90.2) | 1.7 |
| | 95% CI | 89.1; 94.0 | 87.3; 92.4 | -1.8; 5.3 |
| **mITT Population** | | | | |
| Study 003 | N | 287 | 309 | |
| | n (%) | 253 (88.2) | 265 (85.8) | 2.4 |
| | 95% CI | 83.8; 91.4 | 81.4; 89.2 | -3.1; 7.8 |
| Study 004 | N | 252 | 257 | |
| | n (%) | 221 (87.7) | 223 (86.8) | 0.9 |
| | 95% CI | 83.0; 91.2 | 82.0; 90.4 | -4.9; 6.7 |
| Pooled analysis | N | 539 | 566 | |
| | n (%) | 474 (87.9) | 488 (86.2) | 1.7 |
| | 95% CI | 84.9; 90.4 | 83.1; 88.8 | -2.3; 5.7 |

- *Secondary endpoints: relapse and persistent recovery*

In both studies, fidaxomicin (200 mg X 2/day, for 10 days) was superior to vancomycin (125 mg X 4/day, for 10 days) regarding the occurrence of relapses during the four weeks following treatment, with relapse rates of 13% to 15% in the fidaxomicin arms versus 25-27% in the vancomycin arms under the mITT analysis (Table 4).

The time to onset of the first relapse was longer among patients treated with fidaxomicin (18 and 20 days) than in treated with vancomycin (8 days in both studies).
The rates of persistent recovery were also higher in the fidaxomicin arms than in the vancomycin arms in both studies: 75% versus 64% under the mITT analysis (Table 5).

**Table 4**: **Relapse rate – mITT and PP populations**

| | | Fidaxomicin | Oral vancomycin | Difference | p |
|---|---|---|---|---|---|
| **Relapse (mITT)** | | | | | |
| Study 003 | N | 253 | 265 | | |
| | n **(%)** | 39 (**15.4**) | 67 (**25.3**) | **-9.9** | **0.005** |
| | 95% CI | 11.5; 20.4 | 20.4; 30.9 | **-16.6; -2.9** | |
| Study 004 | N | 221 | 223 | | |
| | n **(%)** | 28 (**12.7**) | 60 (**26.9**) | **-14.2** | **<0.001** |
| | 95% CI | 8.9; 17.8 | 21.5; 33.1 | **-21.4; -6.8** | |
| Combined analysis | N | 474 | 488 | | |
| | n **(%)** | 67 (**14.1**) | 127 (**26.0**) | **-11.9** | **<0.001** |
| | 95% CI | 11.3; 17.6 | 22.3; 30.1 | **-16.8; -6.8** | |
| **Relapse (PP)** | | | | | |
| Study 003 | N | 211 | 221 | | |
| | n **(%)** | 28 (**13.3**) | 53 (**24.0**) | **-10.7** | **0.004** |
| | 95% CI | 9.3; 18.6 | 18.8; 30.1 | **-17.9; -3.3** | |
| Study 004 | N | 180 | 182 | | |
| | n **(%)** | 23 (**12.8**) | 46 (**25.3**) | **-12.5** | **0.002** |
| | 95% CI | 8.6; 18.5 | 19.5; 32.1 | **-20.3; -4.4** | |
| Combined analysis | N | 391 | 403 | | |
| | n **(%)** | 51 (**13.04**) | 99 (**24.57**) | **-11.52** | **<0.001** |
| | 95% CI | 9.99; 16.85 | 20.53; 29.10 | **-16.83; -6.09** | |

**Table 5: Persistent recovery – mITT and PP populations**

| | | Fidaxomicin | Oral vancomycin | Difference | p |
|---|---|---|---|---|---|
| **Persistent recovery (mITT)** | | | | | |
| Study 003 | N | 287 | 309 | | |
| | n **(%)** | 214 (**74.6**) | 198 (**64.1**) | **10.5** | **0.006** |
| | 95% CI | 69.2; 79.3 | 58.6; 69.2 | **3.1; 17.7** | |
| Study 004 | N | 252 | 257 | | |
| | n **(%)** | 193 (**76.6**) | 163 (**63.4**) | **13.2** | **0.001** |
| | 95% CI | 71.0; 81.4 | 57.4; 69.1 | **5.2; 20.9** | |
| Combined analysis | N | 539 | 566 | | |
| | n **(%)** | 407 (**75.5**) | 361 (**63.8**) | **11.7** | **<0.001** |
| | 95% CI | 71.7; 78.9 | 59.7; 67.6 | **6.3; 17.0** | |
| **Persistent recovery (PP)** | | | | | |
| Study 003 | N | 265 | 283 | | |
| | n **(%)** | 206 (**77.7**) | 190 (**67.1**) | **10.6** | **0.006** |
| | 95% CI | 72.3; 82.3 | 61.5; 72.3 | **3.1; 17.9** | |
| Study 004 | N | 216 | 235 | | |
| | n **(%)** | 172 (**79.6**) | 154 (**65.5**) | **14.1** | **<0.001** |
| | 95% CI | 73.7; 84.5 | 59.1; 71.3 | **5.9; 22.1** | |
| Combined analysis | N | 481 | 518 | | |
| | n **(%)** | 378 (**78.59**) | 344 (**64.1**) | **12.18** | **<0.001** |
| | 95% CI | 74.61; 82.09 | 62.15; 70.42 | **6.66; 17.59** | |

- *Exploratory and post-hoc analyses*

The results of sub-group analyses (according to age, the existence of a prior episode of CDI, the severity of CDI at inclusion and the presence of concomitant systemic antibiotic therapy) and the analysis of relapse as a function of its date of onset (<14 days; ≥14 days) (in response to the request from the EMA) were consistent with those of the analyses for the primary and secondary endpoints.

The onset of a relapse during the first 14 days following the end of treatment was less frequent among patients treated with fidaxomicin than among those treated with vancomycin (7.4% versus 19.3%); however, during the following two weeks, the frequency of onset was similar (6.6% vs. 8.1%). This result indicates that fidaxomicin reduced the risk of relapse (early relapse, during the 2 weeks following the end of treatment) although the risk of a delayed relapse (possible re-infections) was similar in the two treatment arms. Nevertheless, these studies had not been designed to demonstrate the prevention of re-infection by a different bacterial strain.

## 3.3. Tolerance

### 3.3.1. Tolerance during the clinical studies

Tolerance was evaluated through a combined analysis of the two phase III studies.
The majority of patients included in the two studies experienced at least one adverse event, with a similar incidence across both groups. The incidence of adverse events considered as being possibly linked to the study drug was 11%. Fewer than 10% of patients discontinued their treatment because of an adverse event (Table 6).

**Table 6: Overall assessment of safety – combined analysis – safety population**

| Number of patients | **fidaxomicin N = 564 n - (%)** | **Oral vancomycin N = 583 n - (%)** |
|---|---|---|
| At lease 1 AE | 373 (66.1) | 372 (63.8) |
| At least 1 severe AE | 107 (19.0) | 98 (16.8) |
| At least 1 AE linked or possibly linked | 60 (10.6) | 65 (11.1) |
| At least 1 SAE | 145 (25.7) | 135 (23.2) |
| At least 1 AE leading to discontinuation of treatment | 45 (8.0) | 49 (8.4) |

AE: adverse event; SAE: serious adverse event

The most frequently reported adverse events (in at least 5% of patients in the fidaxomicin arms) during the two studies were: nausea (9.9% in both arms), hypokaliaemia (7.1% versus 6%), headaches (6.2% versus 4.3%), vomiting (6% versus 5.8%) and abdominal pain (5.7% versus 3.1%). Adverse events considered as being possibly linked to the study drug are presented in Table 7.
The most frequently reported serious adverse events (in more than 1% of patients in the fidaxomicin arm) during both studies were: colitis due to *C. difficile* (8 versus 9), pneumonia (8 versus 10), sepsis (7 versus 5) and hyponatraemia (6 versus 3).
During these two studies, 36 deaths occurred in the fidaxomicin arm and 38 in the vancomycin arm. The most common causes of death were septicaemia (3 patients versus 4 patients), respiratory failure (4 patients versus 2 patients), and pneumonia (3 patients versus 2 patients). No deaths were considered by the investigator as being linked to the study drug.

**Table 7: Adverse events linked to treatment (for at least 1% of patients in the fidaxomicin group) –combined analysis – safety population**

| Number of patients | **Fidaxomicin N = 564** | **Oral vancomycin N = 583** |
|---|---|---|
| At least 1 AE linked to treatment, n (%) | 60 (10.6) | 65 (11.1) |
| Nausea | 15 (2.7) | 20 (3.4) |
| Vomiting | 7 (1.2) | 8 (1.4) |
| Constipation | 7 (1.2) | 3 (0.5) |
| Dizziness | 5 (0.9) | 1 (0.2) |

### 3.3.2. Risk management plan

The Risk Management Plan stipulates the performance of two studies:

- a non-comparative, multi-centre, prospective European study[4] (approximately 60 centres), with the aim of evaluating the tolerance and efficacy of treatment with fidaxomicin for 20 days in patients experiencing a relapse of CDI during the 3 months following initial effective treatment with fidaxomicin for 10 days.
  It is planned to include 100 patients. The evaluation of efficacy will be based on clinical recovery at the end of treatment, maintenance of this response 30 days after discontinuation of the study drug, and the occurrence of relapses during this 30-day follow-up period. Tolerance will be evaluated based on reported adverse events, vital signs, laboratory test data and ECG findings.

- a multi-centre, retrospective European study,[5] the primary aim being to evaluate the use of fidaxomicin in real-life (primary endpoint), especially in patients with irritable bowel syndrome.
  Safety data and data concerning the indication, dose and duration of treatment constitute secondary endpoints.
  It is planned to include 500 patients. The data collected (demographic, nature and severity of the illness, associated diseases, dosage, duration of treatment with fidaxomicin and tolerance) will be recorded between their admission to hospital and 30 days after the last administration of fidaxomicin.

[4] A Multi-National, Multi-Center, Open-Label Study to Examine the Safety and Efficacy of Extended Treatment with Fidaxomicin in Subjects with Recurrence of Clostridium difficile Infection Previously Treated with Fidaxomicin.

[5] *A drug utilisation study of the use of oral fidaxomicin in the clinical setting*

## 3.4. Conclusion

Fidaxomicin was evaluated in the treatment of *Clostridium difficile* infection (CDI) by means of two controlled, randomised double-blind studies (study 003 and study 004), comparing the efficacy and tolerance of fidaxomicin (200 mg x 2/day) versus vancomycin (125 mg x 4/day) over 10 days in patients with diarrhoea due to *Clostridium difficile*. The vancomycin formulation used during these studies was a pharmaceutical form intended for oral administration, available in the United States. The primary efficacy endpoint was clinical recovery at 10 days of treatment. The treatment period was followed by a 4-week follow-up period for all patients, enabling determination of the frequency of relapses[6] and persistent recovery[7] (secondary endpoints). These endpoints were significant because of the context of the rising incidence, severity and life-threatening potential of *C. difficile* infections and the emergence of a particularly virulent strain (strain 027).

The mean age of the patients included was over 60 years (approximately 50% of patients ≥ 65 years) and the majority were hospitalised at the onset of their CDI. The infection was considered by the investigator to be moderate to severe in more than 70% of cases, and approximately 25% of patients experienced severe CDI according to ESCMID criteria[3] (increase in serum creatinine ≥ 50% or leukocytes > 15,000/mm$^3$ or temperature > 38.5°C).

In both studies, treatment with fidaxomicin was non-inferior to treatment with vancomycin over 10 days, with recovery rates of 92.1% versus 89.8% in study 003 and 91.7% versus 90.6% in study 004, under the PP analysis.
With regard to the secondary endpoints, the results of the ITT analysis indicated the superiority of fidaxomicin over vancomycin regarding the relapse rate (15.4% vs. 25.3% in study 003 and 12.7% versus 26.9% in study 004) and persistent recovery (74.6% versus 64.1% and 76.6% versus 63.4%) during the 4 weeks following treatment.

Overall, the treatment was well tolerated with a safety profile similar to that of oral vancomycin. During the two studies, 11% of patients experienced an adverse event considered to be linked to the study drug, and fewer than 10% of patients discontinued the treatment due to an adverse event. The principal adverse events linked to the study drug were: nausea, vomiting, constipation and dizziness.

It should be noted that these studies did not include the most severe clinical forms, in particular patients with life-threatening CDI or cases of fulminant colitis, toxic megacolon or pseudomembranous colitis, patients with recurring infections (more than one episode of CDI during the past 3 months), a history of ulcerative colitis or Crohn's disease, which thus limits the transferability of results to these patient populations. Furthermore, there was a lack of data regarding the benefits of the repeated use of fidaxomicin (see SPC - special warnings and precautions for use), in the event of a relapse.

[6] Relapse: recurrence in a recovered patient, during the 4 week follow-up period, of diarrhoea with the presence of A or B or A and B toxin, and requiring further treatment with an anti-infective agent for CDI.

[7] Persistent recovery: absence of relapse during the 4-week follow-up period with no treatment in patients experiencing a clinical recovery at the end of the treatment period.

# 4 TRANSPARENCY COMMITTEE CONCLUSIONS

## 4.1. Actual benefit

*Clostridium difficile* is responsible for 15 to 25% of cases of diarrhoea following antibiotic therapy, and more than 95% of cases of pseudomembranous colitis, and is the main cause of hospital-acquired diarrhoea in adults. Infections due to *C. difficile* diagnosed in hospital are hospital-acquired in more than 70% of cases, most often occurring in the form of epidemics in at-risk departments (ICU, infectious diseases, haematology and geriatric medicine).[8] In recent years, the incidence, severity and the life-threatening nature of *C. difficile* infections has increased and this development is linked to the emergence of a particularly virulent strain. The risk of death due to *C. difficile* infection ranges from 0.6 to 1.5%, but reaches 35 to 50% in cases of the complications of pseudomembranous colitis.[9]

DIFICLIR is intended as a curative therapy.

The efficacy/adverse effects ratio is high. However, it is poorly established in more severe clinical forms (notably in patients with life-threatening CDI or fulminant colitis, toxic megacolon or pseudomembranous colitis).

This medicinal product is a first-line therapy that should be strictly reserved for use in *C. difficile* infections.

Few therapeutic alternatives are available.

> Public health benefit:
> The public health burden represented by patients likely to benefit from DIFICLIR (diarrhoea due to *Clostridium difficile*) is small.
> The availability of new compounds to address the spread of pathogenic bacteria that have acquired resistance mechanisms to antibiotics, notably within the context of hospital-acquired infections, is a public health need.
> For the population of patients with a less serious form, corresponding to those in the studies, a small impact is expected on the reduction of morbidity (fewer relapses and better persistence in rate of recovery) compared with other treatments used in everyday practice.
> The route of administration (by mouth) enables better access to treatment. However, it may also encourage incorrect use by facilitating its administration in any patient presenting with post–antibiotic diarrhoea, without systematic investigation of the *Clostridium difficile* toxin.
> The transferability of the results is limited, due to exclusion from the studies of more severely ill patients.
> Under satisfactory conditions of use, this proprietary medicinal product may have an impact in terms of reducing the ecological risk linked to the spread of resistant bacteria.
> DIFICLIR is therefore likely to provide a partial response to a public health need.
> Consequently, there is expected to be a small public health benefit for DIFICLIR in this indication.

The actual benefit of DIFICLIR is substantial in the context of documented *C. difficile* infections (presence of the toxin being demonstrated in stools). For infections where *C. difficile* has not been identified, the actual benefit is insufficient.

[8] French High Council for Public Health (Haut Conseil de la Santé Publique). Opinion relating to the control of the spread of *Clostridium difficile* infections in French healthcare establishments. 20 June 2008.

[9] INVS - RAISIN. CClin EST, CClin Ouest, CClin Paris-Nord, CClin Sud-Est, CClin Sud-Ouest. Path to take: diagnosis, investigation, monitoring, and methods of prevention and control of *Clostridium difficile* infections. Occupational document 2006.

### 4.2. Improvement in actual benefit (IAB)

In view of the data available, the Committee considers that DIFICLIR enables a moderate improvement in actual benefit (ASMR III) in the management of documented *C. difficile* infections.

### 4.3. Therapeutic use

A diagnosis of CDI should always be considered in the event of diarrhoea following antibiotic therapy, and also in cases of bowel obstruction accompanied by fever, abdominal pain and hyperleukocytosis, especially in elderly patients with a history of antibiotic therapy. Determination of the presence of *C. difficile* by identifying the A and/or B toxin should be systematic in all cases of diarrhoea occurring after the third day of hospitalisation.

In its opinion issued in 2008[8] , the French High Council for Public Health (HCSP) specified that, in addition to measures to prevent *C. difficile* infection (CDI), the therapeutic strategies to be applied were as follows:

- For an initial episode, in cases of mild to moderate CDI, oral metronidazole should be used first-line at a dose of 500 mg x 3/day for 7 to 14 days. If the health of the patient deteriorates or they do not respond to treatment, the use of oral vancomycin is required, 250 mg to 500 mg x 4/day over 14 days.
- For cases of severe CDI or if metronidazole is contraindicated, vancomycin at the doses stated above should be used from the start.
- In cases of bowel obstruction or megacolon, oral vancomycin at the same doses, administered via a nasogastric tube, should be combined with IV metronidazole (500 mg x 3/day).
- For the first relapse, if there was a satisfactory response to metronidazole during the first episode, the same compound should be used, at the same doses. If this is not the case then oral vancomycin should be used. Regardless of the treatment selected, it should be taken for 10 to 14 days.
- In the case of any further relapses, the HCSP recommends seeking an additional opinion.

In all cases, in 25% of cases, withdrawal of the antibiotic responsible enables a recovery within two to three days.

In 2009, ESCMID published similar recommendations:[10]

- Withdrawal of the antibiotic responsible, when possible, in cases of mild to moderate CDI that have clearly been caused by use of this antibiotic, together with close monitoring of the clinical outcome. If the patient's clinical state deteriorates, treatment should be initiated immediately.
- There is no evidence to suggest any benefit in switching to an antibiotic with a “lower risk of CDI” or one with a narrower spectrum, if the initial antibiotic cannot be discontinued. It does however seem rational to try and use antibiotics with a spectrum that is as narrow as possible.
- For severe CDI, antibiotic therapy should be implemented and possibly even initiated before the diagnosis is confirmed, where there is satisfactory clinical evidence.

[10] Bauer MP et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect 2009; 15: 1067-1079.

- The compounds used vary according to the severity of CDI.
    - in the case of an initial episode, for mildly to moderately severe forms of CDI, metronidazole (500 mg x 3/day, for 10 days) is recommended as first-line treatment,
    - in cases of severe symptoms from the outset, or in patients not responding to metronidazole or who have an intolerance to this antibiotic, vancomycin (125 mg x 4/day, over 10 days) is recommended.

The intravenous route should only be used if the use of oral medication is not possible. For mild to moderate forms, the use of metronidazole is preferred (500 mg x 3/days for 10 days). For severe forms, metronidazole should be used at the same dose in combination with vancomycin administered via a nasogastric tube (500 mg 4 x/day) and/or vancomycin enemas (500 mg in 100 ml saline solution every 4 to 12 hours).

**Table 8: Summary of recommendations (HCSP 2008 and ESCMID 2009)**

| | First CDI episode | | First relapse | Subsequent relapses |
|---|---|---|---|---|
| Severity | Mild to moderate | Severe (or no response/contraindication to metronidazole) | | |
| HCSP 2008 | metronidazole 500 mg x 3/day orally, 7 to 14 days | oral vancomycin, 250 mg to 500 mg x 4/day, 14 days<br><br>In cases of bowel obstruction or megacolon:<br>oral vancomycin, 250 mg to 500 mg x 4/day, via nasogastric tube + IV metronidazole 500 mg x 3/day | metronidazole if effective during first episode<br>If not, vancomycin.<br>Treatment for 10 to 14 days. | Additional opinion |
| ESCMID 2009 | Oral route possible:<br>metronidazole 500 mg x 3/day, 10 days<br>Oral route not possible:<br>metronidazole IV 500 mg x 3/day, 10 days | Oral route possible: oral vancomycin 125 mg x 4/day, 10 days<br>Oral route not possible:<br>IV metronidazole 500 mg x 3/day + vancomycin by nasogastric tube 500 mg 4 x/day and/or vancomycin enema 500 mg in 100 ml saline solution every 4 to 12 hours | Idem first episode, depending on severity | Oral route possible: Idem First severe episode<br>Decreasing or intermittent doses advised.<br>Oral route not possible:<br>Idem first severe episode |

Place of fidaxomicin

The two antibiotics most widely used to treat infections due to *Clostridium difficile* are metronidazole and vancomycin, administered orally. These two medicinal products are effective in the majority of CDI cases, however nearly one-third of patients who initially recover experience a relapse.

Fidaxomicin constitutes an alternative first-line therapy for *Clostridium difficile* infections, because of its comparable safety and efficacy profile with vancomycin in curing the infection, but with a lower risk of relapse and greater convenience of use than vancomycin. However, in more severe clinical forms, the absence of efficacy and safety data should limit its use (see SPC - Special warnings and precautions for use).

## 4.4. Target population

The target population for DIFICLIR is represented by adult patients suffering from *Clostridium difficile* infection (CDI) being treated during hospitalisation.
In France, the incidence of CDI in hospitals is estimated at between 0.5 and 3 per 10,000 patient-days.[11] On this basis, the number of cases of CDI occurring each year in French healthcare establishments may be between 6900 and 41,000, including all types of hospital stay.
For information, analysis of the 2010 PMSI MCO (medicine/surgery/obstetrics) database on *Clostridium difficile* infections enabled identification of the number of hospitalisations in France in 2010: 8563 stays involving CDI, corresponding to 7467 patients. This estimate did not take account of medium- and long-stay activities in hospitals.

In summary, the target population for DIFICLIR is estimated at between 6900 and 41,000 patients per year.

## 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.

The Committee highlights that there is a risk of misuse, with the potential use of fidaxomicin in cases of diarrhoea linked to antibiotics without *Clostridium difficile* infection being present. A case of diarrhoea associated with the use of antibiotics may not be due to *Clostridium difficile* but, for example, as the result of poor colonic fermentation through depletion of the dominant gut flora. In these cases, as it usually only lasts a short period of time, the doctor may not be able to distinguish between the efficacy of fidaxomicin in this indication and the absence of treatment.
Also, treatment should only be proposed in cases of CDI with the presence of A and/or B toxin in the stools.

[11] INVS - RAISIN. CClin EST, CClin Ouest, CClin Paris-Nord, CClin Sud-Est, CClin Sud-Ouest. Path to take: diagnosis, investigation, monitoring, and methods of prevention and control of Clostridium difficile infections. Occupational document 2006.