FINAL CDEC RECOMMENDATION

FIDAXOMICIN
(Dificid – Optimer Pharmaceuticals Canada Inc.)
Indication: *Clostridium difficile* Infection in Adults

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that fidaxomicin not be listed at the submitted price.

Reasons for the Recommendation:

1. Based on the results of two randomized controlled trials (RCTs), fidaxomicin was shown to have similar efficacy for achieving clinical cure in patients with *Clostridium difficile* infection when compared with vancomycin. However, at the recommended doses, fidaxomicin (200 mg twice daily for 10 days; $2,200) is more expensive compared with vancomycin (125 mg to 500 mg four times per day for seven to 10 days; $158 to $900).
2. Although fidaxomicin demonstrated superiority to vancomycin in clinical recurrence and sustained cure over a four-week period, limitations in the estimates of recurrence beyond the first recurrence make the cost-effectiveness of fidaxomicin uncertain. When more conservative estimates of the effects of fidaxomicin beyond the first recurrence were considered, the incremental cost of fidaxomicin compared with vancomycin exceeded $90,000 per quality-adjusted life-year (QALY).

Of Note:
Based on a review of the clinical evidence, the Committee felt that a reduced price would increase the likelihood of a recommendation to “list” or “list with clinical criteria and/or conditions.”

Background:
Fidaxomicin has a Health Canada indication for treatment of *Clostridium difficile* (*C. difficile*) infection in adults (≥ 18 years of age). Fidaxomicin is a narrow spectrum macrocyclic bactericidal antibiotic. It is available as a 200 mg film-coated tablet and the Health Canada recommended dose is 200 mg (1 tablet) orally, twice daily for 10 days, with or without food.

A priority review of this submission was requested by the manufacturer and granted by the Common Drug Review (CDR).

Summary of CDEC Considerations:
The Committee considered the following information prepared by CDR: a systematic review of double-blind, RCTs of fidaxomicin, a critique of the manufacturer's pharmacoeconomic evaluation, and a patient group submission regarding the important outcomes and issues to patients.

Patient Input Information
The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input:

- Patient groups stated that antibiotics for the treatment of *C. difficile,* such as metronidazole and vancomycin, have limited effectiveness and that broad-spectrum antibiotics can also increase a patient's risk for re-infection and prolonged suffering.
- Patient groups indicated that the longer an individual is ill with *C. difficile*, the greater the strain on caregivers. Unresolved infection also increases the risk of spreading the infection to caregivers, and family or individuals, within an institutionalized setting.
- Patient groups expect that the use of fidaxomicin will result in faster treatment times, improved quality of life, and less patient anxiety surrounding hospital visits.

Clinical Trials
The systematic review included two 40-day double-blind, non-inferiority RCTs (study 003 [N = 629] and study 004 [N = 535]) that compared fidaxomicin with vancomycin in the treatment of adult patients with symptomatic *C. difficile* infection (change in bowel habits with more than three unformed bowel movements in the 24 hours before randomization and *C. difficile* toxin A or B detected in the stool).

Both studies randomized patients (stratified on the basis of having either a single prior episode within three months or no prior occurrence within the last three months) to 10-day regimens of oral fidaxomicin 200 mg administered every 12 hours, with intervening matching doses of placebo, or oral (capsules) vancomycin 125 mg administered every six hours. Patients were followed for an additional four weeks to assess *C. difficile* infection recurrences and treatment adverse events. Premature study withdrawal (before the 40-day visit) was less than 10% and there were no notable differences in the frequency of premature study withdrawal between the fidaxomicin and vancomycin groups.

Limitations of the two trials include the lack of a direct comparison between fidaxomicin and metronidazole for the treatment of mild to moderate *C. difficile* infection. The clinical cure end point in both trials has not been validated and it was not consistent with definitions of *C. difficile* treatment used in Canadian clinical practice. Similarly, the definition of disease severity was not the same as that specified in clinical guidelines, although it is uncertain how this might have affected the conclusions. There is some uncertainty about the conclusions regarding the efficacy of fidaxomicin for *C. difficile* infection recurrence, as the recurrence rate was a secondary outcome and the duration of the post-treatment follow-up period in the trials was likely the minimum period in which to identify recurrences. Patients who had severe, complicated disease, as well as those who suffered from inflammatory bowel diseases or who required continuation of other antibiotics beyond seven days, were excluded from both studies.

Data is also lacking for fidaxomicin use in patients with multiple recurrences of *C. difficile* infection.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, resolution of symptoms, recurrence, total and serious adverse events, and withdrawal due to adverse events.

Clinical cure rate was the primary outcome in both trials. Clinical cure was defined as less than or equal to three unformed bowel movements for two consecutive days and remaining well before the time of study medication discontinuation, with no further need for *C. difficile* infection therapy as of the second day after completion of the study medication. A non-inferiority design was used to assess the efficacy of fidaxomicin compared with vancomycin for clinical cure, where the non-inferiority margin was –10%. If the lower limit of the 95% confidence interval (CI) was greater than 0, fidaxomicin would have been considered superior to vancomycin. Global cure was defined as the resolution of diarrhea (i.e., clinical cure) without recurrence.

Neither study was designed to compare fidaxomicin and vancomycin for mortality, emergent colectomy, nor complications associated with *C. difficile* infection; however, these end points were reported as safety data. Complications were defined as the number of patients who developed toxic megacolon, septic shock, or a bowel perforation during the study. Resolution of symptoms included the percentage of patients with clinical cure or failure, time to resolution of symptoms, and recurrence of *C. difficile* colitis. Quality of life was not assessed in either of the included studies.

Results

Efficacy

- In study 003, 6.5% of vancomycin patients and 5.3% of fidaxomicin patients died during the 40-day study period. Similarly, 6.5% and 7.6% of patients treated with vancomycin and fidaxomicin respectively died in study 004. The leading causes of death among both groups were sepsis/septic shock, cardiovascular events, and cancer.
- There was no difference between fidaxomicin and vancomycin for the proportion of patients achieving clinical cure after 10 days of treatment. Based on the per-protocol population, the percentage difference (fidaxomicin – vancomycin) was 2.3% (95% CI, –2.6 to 7.1) in study 003 and 1.0% (95% CI, –4.3 to 6.3) in study 004. The results were similar for the modified intention to treat populations. Non-inferiority was demonstrated in both studies according to pre-established criteria.
- Fidaxomicin was shown to be superior to vancomycin in the secondary analysis of *C. difficile* infection recurrence: in study 003, the percentage difference was –10.7% (95% CI: –17.9 to –3.3) in the per-protocol population; in study 004 it was –12.5% (95% CI: –20.3 to –4.4) in the in the per-protocol group; the results were the same for the mITT populations.
- In both studies, the proportion of patients with global (sustained) cure was higher in the fidaxomicin group versus the vancomycin group over the 28-day follow-up period, regardless of the analysis population used.
- The median time to resolution of diarrhea was not different between the fidaxomicin and vancomycin groups.
- The time to recurrence of *C. difficile* colitis was significantly longer for fidaxomicin than vancomycin.

- Subgroup analyses did not show any marked difference between treatment groups for clinical cure rates, but for recurrences and global cure rates, there was a statistically significant benefit for fidaxomicin-treated patients with advanced age and non-NAP1/BI/027 strains.
- For patients treated with concomitant systemic antibiotics and patients with cancer, recurrence rates tended to favour fidaxomicin; however, a statistically significant difference between treatments was reported only for study 004 for patients treated with concomitant systemic antibiotics and patients with cancer, and in the per protocol but not the mITT population of study 003 for patients with cancer (significance test results were not reported for this subgroup in study 004).
- For patients with a prior episode of *C. difficile* infection at baseline or the NAP1/BI/027 strain, the fidaxomicin group did not demonstrate superiority in recurrence rate or global cure when compared with vancomycin.
- Emergency colectomy and complications associated with *C. difficile* infection were relatively rare in both studies, occurring in less than 1% of the trial populations.

Harms (Safety and Tolerability)

- Serious adverse events occurred in approximately one quarter of patients in both treatment groups and in both studies (ranges: 22.3% to 24.1% vancomycin; 25.0% to 26.5% fidaxomicin). Fidaxomicin-treated patients experienced more blood disorders (namely neutropenia, leukopenia), vascular disorders, and adverse events related to the System Organ Class investigations (increased blood uric acid and decreased lymphocyte count), as well as hyponatremia, hypophosphatemia, and hyperkalemia.
- The frequency of adverse events was similar between groups, although there was a higher frequency in study 004 (68.1% vancomycin; 70.5% fidaxomicin) than in study 003 (60.4% vancomycin; 62.3% fidaxomicin). The most frequent adverse events in both groups were nausea, hypokalemia, vomiting, abdominal pain, and headache.
- Withdrawals due to adverse events in studies 003 and 004 occurred in less than 10% of patients in both treatment groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis that compared fidaxomicin with vancomycin in patients with an initial or first recurrent episode of *C. difficile* infection over a one-year time horizon. Patients could experience up to three additional recurrences with retreatment throughout the year; however, patients would only receive fidaxomicin for treatment of the initial episode of *C. difficile* infection and first recurrence, and vancomycin for subsequent recurrences. Data on clinical cure, first recurrence rates, and time-to-resolution of diarrhea were obtained from clinical study 003 and study 004. Quality-of-life data were obtained from physician interviews, and supplemented with published literature. The manufacturer reported that fidaxomicin compared with vancomycin is associated with a cost per QALY of $50,260.

CDR noted the following limitations with the manufacturer's analysis:

- The cost-effectiveness estimates were extremely sensitive to input parameters estimating recurrence rates. The incremental effectiveness was small (0.011 QALYs in the base case). Consequently, any changes in the relative risk of recurrence or total costs were amplified when dividing by the small benefits. If real world recurrence rates for patients treated with fidaxomicin are even marginally higher than the estimate used in the model, the incremental cost-effectiveness ratio could be substantially higher than reported by the manufacturer.
- There is no clinical evidence to support the assumption of a maintained reduction in recurrence rates with fidaxomicin compared with vancomycin beyond the first recurrence.
- Metronidazole was not included as a comparator, although it is considered a standard of care for mild-to-moderate *C. difficile* infection, as per clinical practice guidelines.

Based on CDR reanalyses, when more conservative estimates of the effects of fidaxomicin beyond the first recurrence were considered, the incremental cost per QALY of fidaxomicin compared with vancomycin exceeded $90,000.

At the recommended doses, fidaxomicin (200 mg twice daily for 10 days; $2,200) is more expensive compared with vancomycin (125 mg to 500 mg four times per day for seven to 10 days; $158 to $900) and metronidazole (250 mg four times per day or 500 mg three times per day for 10 to 14 days; $2 to $30).

Evidence Gaps:

The Committee noted that there is an absence of evidence regarding the safety and efficacy of fidaxomicin in the treatment of the following patient populations:

- patients with multiple recurrences of *C. difficile* infection
- patients with severe, complicated *C. difficile* infection
- patients with underlying inflammatory bowel diseases and *C. difficile* infection.

Other Discussion Points:

The Committee noted the following:

- Fidaxomicin does not have a recurrence benefit compared with vancomycin for the NAP1/BI/027 strain that is currently associated with increased morbidity and mortality in Canada.
- Fidaxomicin has not been compared with metronidazole, an agent commonly used as the first-line treatment for mild to moderate *C. difficile* infection.
- The post-treatment follow-up period in the trials (28 days) was a limitation, as this is likely the minimum period in which to identify recurrences.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

November 21, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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