Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

fidaxomicin 200mg film-coated tablets (Dificlir®) SMC No. (791/12)

Astellas Pharma Ltd

08 June 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fidaxomicin (Dificlir®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of adults with *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD).

SMC restriction: Treatment of adults with a first CDI recurrence on the advice of local microbiologists or specialists in infectious diseases.

Fidaxomicin demonstrated non-inferiority to another antibiotic in the clinical cure of *Clostridium difficile* infection and superiority in reducing recurrence.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC for first-line use in adults with severe CDI.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Fidaxomicin 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.

Dosing Information

200mg orally twice daily (every 12 hours) for ten days. Fidaxomicin can be taken with or without food.

Product availability date

1st June 2012

Summary of evidence on comparative efficacy

Clostridium difficile is an anaerobic Gram-positive bacterium that is thought to exist asymptomatically in the colons of up to 3% of healthy adults and 35% of hospital inpatients. The main cause of symptomatic *C. difficile* infection (CDI) is concomitant use of systemic antibiotics which disrupts normal gastrointestinal flora allowing *C. difficile* overgrowth. CDI recurrence is due to either re-infection or relapse from germinating spores in the gut and the risk is increased in the presence of reduced immunity and continuing disruption of gastrointestinal flora.

Fidaxomicin is a novel bactericidal macrocyclic antibiotic that that inhibits bacterial ribonucleic acid (RNA) polymerase. It is effective against *C. difficile* with limited activity against other Gram-positive bacteria. It exerts its activity mainly in the gastrointestinal tract and has low systemic absorption. The submitting company has requested that SMC considers fidaxomicin when positioned for use in the first-line treatment of adults with severe CDI and in adults with a first CDI recurrence (of any severity).

The evidence supporting the licensed indication is from two similar double-blind, randomised active-controlled phase III non-inferiority studies with a combined total of 1,164 patients.[1,2] Inclusion criteria were age ≥16 years, diagnosis of CDI defined as diarrhoea (a change in bowel habits, with more than three unformed bowel movements [UBM] in the 24-hour period before randomisation) and a positive stool toxin result obtained within 48 hours before randomisation. Patients were allowed to have received up to four doses of metronidazole or vancomycin in the previous 24 hours. Patients were excluded if the CDI was life-threatening or fulminant, if toxic megacolon was present or if they had experienced more than one episode of CDI within the previous three months.

Study definitions of CDI severity were: mild CDI: 4 to 5 UBM per day or white blood cell count (WBC) ≤12,000/mm^3; moderate CDI: 6 to 9 UBM per day or WBC 12,001 to 15,000/mm^3; severe CDI: ≥10 UBM or WBC ≥15,001/mm^3.

Randomisation was stratified depending on whether the CDI was the first or second episode in the previous 3 months and patients were randomised equally to receive 10 days treatment with oral fidaxomicin 200mg every 12 hours or oral vancomycin 125mg every 6 hours. Study medications were masked (over-encapsulated) and patients in the fidaxomicin group received two doses of placebo as part of the dosage schedule in order to maintain blinding.

The primary outcome in both studies was clinical cure rate at end of treatment, defined as the resolution of diarrhoea (≤3 UBM for 2 consecutive days), maintained for the treatment duration and with no further need (in the opinion of the investigator) for treatment from the second day after the end of the treatment course. Patients with a substantial reduction in the number of unformed stools at the end of treatment but who had residual mild abdominal discomfort were considered to have achieved clinical cure, if no new anti-infective therapy for CDI was required within 2 days of study treatment completion. The primary endpoint was analysed in the modified intention-to-treat (mITT) and per protocol (PP) populations. The mITT population included all randomised patients who received at least one dose of study medication. The PP population included those patients in the mITT population who received treatment for ≥3 days (and ≥8 days in the case of patients who achieved clinical cure), had documented adherence to the protocol, and had an end-of-therapy evaluation.

The primary endpoint of clinical cure rate at end of treatment for fidaxomicin versus vancomycin in the PP population was 92% (244/265) versus 90% (254/283), treatment difference 2.3 (-2.6 to 7.1), in the first study, and 92% (198/216) versus 91% (213/235), treatment difference 1.0 (95% CI: -4.3 to 6.3), in the second study. In both studies, the difference in cure rates between treatments was within the prespecfied margin of 10% and non-inferiority was achieved in the PP population. This was confirmed in the mITT population in which the clinical cure rates for fidaxomicin versus vancomycin were 88% (253/287) versus 86% (265/309), treatment difference 2.4 (95% confidence interval [CI]: -3.1 to 7.8), in the first study, and 88% (221/252) versus 87% (223/257), treatment difference 0.9 (95% CI: -4.9 to 6.7), in the second study.

In both studies, there were no significant differences between fidaxomicin and vancomycin in clinical cure rates in the pre-specified subgroups of patients with severe CDI or with prior CDI.

Patients who met the criteria for clinical cure were monitored for recurrence, defined as a new episode of diarrhoea (>3 UBM in 24 hours), a positive stool toxin test, and need for retreatment within 30 days of treatment completion. The recurrence rate was significantly reduced in patients receiving fidaxomicin compared with vancomycin: 15% (39/253) versus 25% (67/265), treatment difference -9.9 (95% CI: -16.6 to -2.9), in the first study, and 13% (28/221) versus 27% (60/223), treatment difference –14·2 (95% CI: –21·4 to –6·8), in the second study.

In the subgroup of patients with severe CDI, recurrence rates in the first and second studies for fidaxomicin compared with vancomycin were 13% (12/92) versus 27% (29/109) and 16% (12/76) versus 27% (19/71), respectively; significant for the first study (and the pooled results), but not for the second study. In both studies there was no significant difference in recurrence rates in the subgroup of patients with prior CDI.

In patients infected with the aggressive NAP1/BI/027 strain of CDI, there was no significant difference in recurrence rates between fidaxomicin and vancomycin (mITT): 27% (16/59) versus 21% (14/67) in the first study and 22% (12/54) versus 38% (19/50) in the second study.

The improvement in recurrence rate produced by fidaxomicin in the mITT population corresponded to a significantly higher sustained cure (resolution of diarrhoea without recurrence)) in patients receiving fidaxomicin compared with vancomycin: 75% (214/287) versus 64% (198/309), treatment difference 10.5 (95% CI: 3.1 to 17.7), in the first study and 77% (193/252) versus 63% (163/257), treatment difference 13.2 (95% CI: 5.3 to 21.0), in the second study.

Table 1: Pooled efficacy data from two pivotal studies[1, 2, 3]

	Fidaxomicin % (n/N)	Vancomycin n/N (%)
Clinical cure rate		
All (mITT population)	88% (474/539)	86% (488/566)
Severe CDI (study definition)	83% (168/202)	85% (180/211)
Severe CDI (ESCMID definition)	76% (102/135)	75% (108/144)
Prior CDI (in previous 3 months)	90% (79/88)	89% (80/90)
NAP1/BI/027 strain of CDI	81% (113/140)	82% (117/143)
Recurrence rate		
All eligible *	14% (67/474)	26% (127/488)
Severe CDI (study definition)*	14% (24/168)	27% (48/180)
Severe CDI (ESCMID definition)*	14% (14/102)	30% (33/108)
Prior CDI (in previous 3 months)	20% (16/79)	32% (26/80)
NAP1/BI/027 strain of CDI	25% (28/113)	28% (33/117)

ESCMID= European Society of Clinical Microbiology and Infectious Diseases, *= significant difference between treatment groups

Summary of evidence on comparative safety

Fidaxomicin exerts its antibacterial effect locally in the gastrointestinal tract and has low systemic absorption. Infection-induced gastrointestinal inflammation may increase fidaxomicin absorption and subsequent adverse events. Current evidence on safety is limited and there is no evidence for use of repeated courses of fidaxomicin.

In the pooled pivotal studies, treatment-related adverse events were reported in 11% of all patients with no significant difference in frequency between the fidaxomicin and vancomycin groups. These were primarily gastrointestinal symptoms: nausea, vomiting, diarrhoea, and abdominal pain.

Fidaxomicin is a substrate of P-glycoprotein (P-gp) and may be a mild to moderate inhibitor of intestinal P-gp.

Summary of clinical effectiveness issues

Although there has been a significant reduction in the incidence of CDI in Scotland in the past few years largely due to improved antimicrobial stewardship, it is still considered to be a substantial health problem. Fidaxomicin has a marketing authorisation for the treatment of CDI infections but the submitting company has requested that SMC considers its use in a narrower patient population, namely for the first-line treatment of adults with severe CDI and adults with a first CDI recurrence (of any severity).

The two pivotal studies demonstrated that fidaxomicin is non-inferior to vancomycin for clinical cure and superior to vancomycin in preventing recurrence of CDI. However fidaxomicin did not reduce CDI recurrence compared with vancomycin in patients with prior CDI (a population included in the company's proposed positioning). There was also no improvement over vancomycin in patients with the aggressive NAP1/BI/027 strain of CDI. This strain was present in a higher proportion of study patients (26%) than would be expected in patients with CDI in Scotland (between 3% and 9% in 2010, Health Protection Scotland surveillance data).

The study population differs from the company's proposed positioning in terms of number of CDI episodes as patients may have previously experienced CDI earlier than the 3 months pre-randomisation. It is not known if this would affect the effectiveness of fidaxomicin relative to vancomycin.

The study definition of disease severity differed from European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Scottish guidance definitions. A post hoc analysis of pooled data from the studies was conducted using the ESCMID classification of severe CDI: fever; marked leucocytosis and increased serum creatinine. According to this definition approximately 25% of the mITT patient population were classified as severe CDI, compared with 37% using the study definition. However results of this analysis were comparable to the main study results.

Evidence in seriously ill patients with CDI is limited due to the pivotal studies' exclusion criteria. Only five patients receiving fidaxomicin had a diagnosis of pseudomembranous colitis.

In Scotland, patients with CDI are likely to be older than the study population. The mean age of patients in the pivotal studies was 60 to 64 years whereas in Scotland the highest incidence of CDI is in those in their 70s and 80s. In 2010, the total number of new cases in patients aged 15 to 64 years was 692 compared with 2,219 in those over 64 years. Subgroup analyses of recurrence rates in the pooled studies demonstrated that the benefit of fidaxomicin over vancomycin in older patients was similar to that in the whole study population.

Fidaxomicin has a narrower spectrum of antibacterial activity than vancomycin and is thought to have less collateral impact on non-pathogenic gastrointestinal bacteria.

An indirect comparison of fidaxomicin versus metronidazole was conducted using adjusted indirect comparison methodology (Bucher) with the vancomycin arms as a common comparator. The relative efficacy of fidaxomicin versus metronidazole was reported for non-severe CDI, as current treatment guidelines recommend the use of metronidazole in first non-severe recurrence. The pivotal fidaxomicin studies and one metronidazole study were included. There was no difference in clinical cure and recurrence rates between fidaxomicin and metronidazole; however, the odds of sustained cure were significantly higher for fidaxomicin than metronidazole. The indirect comparison has a number of limitations in terms of internal validity (heterogeneity between studies and the confidence intervals for two of the reported outcomes were wide indicating a high level of uncertainty). In addition, there were limitations in terms of external validity, as the studies included patients treated for first occurrence of CDI and not just first non-severe recurrence of CDI, the target population. Also the metronidazole dose differed to that recommended in current guidelines. Although a number of metronidazole studies were identified during the literature search, only one was used in the indirect comparison because it was the only study that reported efficacy by disease severity. Expert statistical advice sought by SMC considered that a mixed treatment comparison, utilising all studies, may have resulted in a more robust indirect comparison.

SMC clinical expert advice indicated that treatment options for CDI are limited and highlighted specific challenges in managing patients with the more severe and recurrent forms of the infection. They suggested that fidaxomicin would be a useful additional treatment option for CDI but should be reserved for use in patients with recurrent or severe disease.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing fidaxomicin with vancomycin in patients with CDI. The economic analysis focused on the use of fidaxomicin as first-line treatment for adults with severe CDI and adults with a first CDI recurrence. These subgroups were selected on the basis that avoiding recurrent disease is important in patients with severe disease and patients at high risk of recurrence. The comparator treatment was oral vancomycin based on Scottish guidelines which recommend vancomycin for patients with severe disease and any non-severe recurrence beyond the first one. Metronidazole was also included in the model for patients where their first recurrence is non-severe.

A one-year Markov model was used based on the primary clinical endpoints of the clinical studies. Patients entered the model in the CDI health state and were treated with either fidaxomicin or vancomycin for 10 days. After treatment patients either moved to the "CDI- cured" health state or "failed to respond" health state. Patients who did not respond to initial treatment were assumed to sequence through increased doses of vancomycin, a vancomycin taper regimen, and intravenous immunoglobulin or rifampicin until a response was achieved.

The clinical data used in the model were taken from a pooled analysis of the two pivotal phase III studies comparing fidaxomicin and vancomycin. Data on the recurrence rates from the subgroups of patients with severe disease and patients who had prior CDI were used. In the subgroup analyses, the lower recurrence rate with fidaxomicin treatment was significant in the severe CDI subgroup only. The cure rate was assumed to be equal in both arms of the model based on the pivotal studies where non-inferiority was demonstrated.

The utility values were taken from a study where the quality of life of patients with CDI was estimated based on the utility associated with being hospitalised with CDI. These utility values were then adjusted based on some assumptions. The key resource use included in the model was excess length of stay (LOS) due to CDI and the estimates used were taken from an assessment of Hospital Episodes Statistics (HES) data for 2006 – 2011. The HES data indicated that mean excess LOS was 19.3 days for an index episode of CDI and 12.2 days for a recurrence.

The submitting company estimated the following base case results for the severe CDI and first CDI recurrence subgroups:

Subgroup	Incremental cost	Incremental quality-adjusted life year (QALY)	Cost per QALY
Severe CDI	£171	0.01	£16,529
First CDI recurrence	-£391	0.019	Fidaxomicin dominant

There were some limitations with the analysis:

- There are weaknesses with the clinical data used in the model. In particular, the patients in the subgroup analyses do not fully match the positioning proposed by the submitting company and the difference in the recurrence rate was not statistically significant in the first recurrence group.
- Threshold analyses showed that the results were particularly sensitive to the recurrence rates

with relatively small changes resulting in the incremental cost-effectiveness ratio (ICER) increasing to over £30K per QALY. In the severe CDI subgroup, the ICER increased to £30K when the odds ratio of experiencing a first recurrence in the fidaxomicin arm increased to 0.525 (from 0.456). Similarly, the ICER increased to £30K when the odds ratio of experiencing a second recurrence increased to 0.573 (from 0.528) in the severe group and 0.624 in the first recurrence group.

- The probability of experiencing a third or subsequent recurrence was based on the study recurrence rates and then adjusted using a published study where the odds ratio of a subsequent recurrence in patients who have experienced at least two recurrences was estimated to be 3.87. This study is relatively old (from 1997) but the company argued it is still relevant, particularly as there are no alternative studies measuring subsequent recurrence rates in CDI. However, it should be noted that the results were sensitive to relatively small changes in this parameter.
- The excess LOS estimates used in the model were derived from HES data from 2006 to 2011 inclusive. Given the rate of CDI in Scotland has reduced during this time period, it may be more appropriate to use data from the most recent year only. In addition, it is not clear that the excess LOS estimates based on the HES data can be attributed entirely to CDI as there will be other factors which influence the length of stay in hospital. Therefore, the excess LOS due to CDI may have been overestimated. The company provided an additional sensitivity analysis using the data from 2010/11 only which resulted in the ICERs increasing to £48K and £10K in the severe CDI and first recurrence groups respectively.

While the ICER is sensitive to the recurrence rates and the LOS data used in the model, SMC considered that the economic case in the population of patients with first CDI recurrence was demonstrated. This is largely due to the lower base case ICER in this subgroup which allowed for greater changes in the model parameters before the ICER increased to above acceptable thresholds. In addition, when the most recent LOS data were used the ICER was increased to around £10K in this subgroup. As such, the economic case was considered demonstrated in patients with a first CDI recurrence.

For the population of patients with severe CDI, however, the base case ICER was higher with considerable uncertainty such that the true ICER was likely to remain above acceptable limits. The economic case in this patient population was therefore not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from National Concern for Healthcare Infections (NCHI).

Additional information: guidelines and protocols

NHS National Services Scotland Guidance on Prevention and Control of *Clostridium difficile* Infection (CDI) in Healthcare Settings in Scotland September 2009. It includes treatment recommendations for first and second episodes of CDI:

If possible, discontinue any non-CDI antimicrobial treatment in patients and any anti-motility agents and gastric acid suppressant agents. Treatment is based on assessment of symptoms and the following disease severity markers:

- Temperature >38.5^{o}C
- major risk factors (hospitalisation in intensive care unit, immunosuppression)

- Suspected pseudomembranous colitis, toxic megacolon, ileus
- Colonic dilatation in computerised tomography (CT) scan/abdominal X-ray >6cm
- WBC >15 cells/mm^3
- Creatinine >1.5 x baseline

Treatment

No severity markers: oral metronidazole 400 or 500mg three times daily for ten to fourteen days. If no improvement after five days, switch to oral vancomycin 125mg four times daily for ten to fourteen days.

For ≥2 severity markers: oral vancomycin 125mg four times daily for ten to fourteen days. If ileus is present, add intravenous metronidazole 500mg three times daily until it is resolved.

Additional information: comparators

Oral vancomycin is the relevant comparator for first-line treatment of severe CDI and for a severe first recurrence of CDI. Oral metronidazole is the relevant comparator for a mild or moderate first recurrence of CDI.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Fidaxomicin	Orally 200mg twice daily for 10 days	1,350
Vancomycin	Orally 125mg four times daily for 7 to 10 days	88 to 126
Metronidazole	Orally 800mg (first dose) then 400mg three times daily for 7 days	1.52

Doses are for general comparison and do not imply therapeutic equivalence. Costs for vancomycin and metronidazole from eVadis on 30. March 2012. Cost for fidaxomicin from submitting company.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,161 in year 1 and 255 in year 5. The reduced number of eligible patients is based on the assumption that the rates of CDI will continue to fall in line with Scottish Government targets. Assuming a market share of 10% in year 1 (116 patients) and 50% in year 5 (128 patients), the gross impact on the medicines budget was estimated at £382K in year 1 and £422K in year 5. Assuming displacement of vancomycin, the net medicines budget impact was estimated to be £352K in year 1 and £388K in year 5. These budget impact estimates do not reflect the SMC restriction to use in patients with a first CDI recurrence only.

References

The undernoted references were supplied with the submission. The one shaded grey is additional to those supplied with the submission.

1. Louie TJ, Miller MA, Mullane KA et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection N Engl J Med 2011 364: 422-31.

2. Cornely OA, Crook DW, Esposito R et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial Lancet Infectious Diseases 2012 12 281-9

3. European Medicines Agency European Public Assessment Report Dificlir 2011 EMA/857570/2011

This assessment is based on data submitted by the applicant company up to and including 11 May 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.