New Medicine Recommendation

DIFICLIR 200 mg film-coated tablets (fidaxomicin)

Indication: Treatment of Clostridium difficile infections (CDI) also known as C. difficile-associated diarrhoea (CDAD) in adults

Recommendation:

Amber level 0 Fidaxomicin should be initiated by a microbiologist or under microbiologist recommendation.

Fidaxomicin (Dificlir®) to be considered as an option for use following a first or second relapse. i.e. as second or third line therapy.

Fidaxomicin to also be considered for patients with severe CDI who are considered to be at high risk for recurrence as per the Public Health England Guidance. e.g. elderly patients with multiple comorbidities who are receiving concomitant antibiotics and those not responding to oral vancomycin.

Suitable for prescribing in primary care following recommendation or initiation by a specialist.

Little or no specific monitoring required.

Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.

Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence:

- A formal commissioning policy is required as fidaxomicin was added to the PBR Tariff Excluded Drugs List as a CCG commissioned drug from the 1st April 2019.
- PHE guidance suggests that for **severe** CDI, fidaxomicin should be considered for patients who are considered at high risk for recurrence and also those patients who are not responding to oral vancomycin (125mg qds).
- PHE guidance also states that fidaxomicin should be preferred for patients with recurrent CDI, whether mild, moderate or severe, although the efficacy of fidaxomicin in patients with multiple recurrences is unclear.
- The evidence used to support the PHE guidance, NICE evidence summary and SMC/AWMSG recommendations is two phase III, multi centred, randomised, double blind trials with almost identical designs and essentially similar results.
- In both studies fidaxomicin was found to be non-inferior to vancomycin with regard to clinical cure. However, recurrence rates were significantly lower and sustained response

significantly higher in the fidaxomicin groups, based on modified intention-to-treat (ITT) and per protocol (PP) analysis.

- A post hoc analysis found that in the absence of concomitant antibiotic use during the treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar. However, fidaxomicin was significantly more effective than vancomycin in achieving clinical cure in the presence of concomitant antibiotic therapy.

Details of Review

Name of medicine (generic & brand name)**: Fidaxomicin (Dificlir)**[1]

Strength(s) and form(s): 200 mg film-coated tablets

Dose and administration:

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

BNF therapeutic class / mode of action:

Infection: Antibacterials (other)

Licensed indication(s)

Fidaxomicin is indicated in adults for the treatment of Clostridium difficile infections (CDI) also known as C. difficile-associated diarrhoea (CDAD)

Proposed use (if different from, or in addition to, licensed indication above):

As per licenced indication (limited clinical data is available on the use of fidaxomicin in severe or life threatening Clostridium Difficile infection).

Course and cost:

200mg twice daily for 10 days = 20 tablets = £1,350 (Drug Tariff, September 2019)

Current standard of care/comparator therapies:

Public Health England guidance prefers vancomycin or fidaxomicin to metronidazole for patients with severe cases of C Difficile .[5]

Vancomycin

Clostridium difficile infection (first use) – 125mg every 6 hours for 10 days; increased if necessary to 500mg every 6 hours for 10 days, (increased dose if severe or complicated infection).

Vancomycin 125mg capsules x 28 =£132.49 (Drug Tariff, September 2019).

- 125mg q6h for 10 days = 40 capsules = £189.27

Vancomycin 250mg capsules x 28 = £146.38 (Drug Tariff, September 2019)

- 500mg q6h for 10 days = 80 capsules = £418.23

Clostridium difficile infection (multiple recurrences) - 125mg every 6 hours for 10 days, followed by, either tapering the dose (until 125mg daily) or a pulse regimen (125-500mg every 2-3 days for at least 3 weeks).

Relevant NICE guidance:

NICE Evidence summary: Clostridium difficile infection: fidaxomicin. Published: 13 July 2012.[2]

SMC 791/12[3]- fidaxomicin (Dificlir®) is accepted for restricted use within NHS Scotland. SMC restriction: Treatment of adults with a first CDI recurrence on the advice of local microbiologists or specialists in infectious diseases.

AWMSG 847[4] - Fidaxomicin (Dificlir®) is recommended as an option for restricted use within NHS Wales. Fidaxomicin (Dificlir®) should be restricted for use in the following subpopulations within its licensed indication for the treatment of adults with Clostridium difficile infections (CDI), also known as C. difficile-associated diarrhoea (CDAD): - Patients with severe CDI; - Patients with recurrence of CDI. Fidaxomicin (Dificlir®) should be prescribed on the advice of a consultant microbiologist, consistent with Health Protection Agency guidance.

Public Health England: Updated guidance on the management and treatment of Clostridium difficile infection (2013).[5] The guidance advises that:

- Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics.
- The use of oral vancomycin or fidaxomicin in preference to metronidazole in patients with severe C Difficile infection.
- In severe C Difficile infection cases not responding to oral vancomycin 125 mg qds, oral fidaxomicin (200mg bd) should be considered.
- Fidaxomicin should be preferred for patients with recurrent CDI, whether mild, moderate or severe, because of their increased risk of further recurrences.

Background and context

Clostridium difficile infection (CDI) is the most important cause of hospital-acquired diarrhoea.. Clostridium difficile is a spore-forming, anaerobic, gram-positive rod. CDI is caused by an overgrowth of C. difficile in the colon most commonly associated with previous antibiotic use which eradicates or disrupts the gut flora, allowing C. difficile to proliferate. Antibiotics commonly linked to CDI include cephalosporins, fluoroquinolones, clindamycin, ampicillin, and amoxicillin, but almost any antibiotic can cause CDI. C. difficile can also persist as spores in the stools leading to frequent recurrences after successful initial treatment.

It is estimated that approximately 40,000 cases among inpatients are potentially underdiagnosed each year in Europe[6]. The recurrence of CDI is estimated to occur in approximately 20-30% of cases.[7]

CDI ranges from mild to severe diarrhoea to, more unusually, severe inflammation of the bowel (known as pseudomembranous colitis). People who have been treated with broad spectrum antibiotics, people with serious underlying illnesses, and older people are at greatest risk – more than 80% of CDIs reported are in people aged over 65 years

Mild cases of CDI associated with treatment with broad spectrum antibiotics may recover after stopping the causative antibiotic therapy, although this approach is not straightforward in clinical practice given the concern that symptoms may worsen. Conservative treatment often is not sufficient for moderate to more severe cases and targeted antibiotic therapy is required, historically this was most commonly with oral metronidazole or vancomycin. Both drugs have, in most cases, been effective in treating CDI, but about a quarter of patients who initially respond to these agents have a clinical recurrence.

Fidaxomicin is the first in a new class of macrocyclic antibiotics, with a very narrow spectrum of antibacterial activity mainly directed against CDI, that is poorly absorbed from the gastrointestinal tract (and is therefore not suitable for treating systemic infections).

Public Health England guidance recommends metronidazole as first line therapy in mild to moderate CDI, but vancomycin in severe cases; with fidaxomicin being considered in severe cases not responding to oral vancomycin and in those patients with severe CDI who are considered at high risk of recurrence – these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics. The guidance also recommends that after a first recurrence, fidaxomicin should be preferred for patients with recurrent CDI, whether mild, moderate or severe, because of their increased risk of further recurrences. The efficacy of fidaxomicin in patients with multiple CDI recurrences is unclear.[5]

Summary of evidence

Summary of efficacy data in proposed use:

Historically, CDI has been treated with either Metronidazole or Vancomycin but approximately 25% of patients adequately treated with either metronidazole or vancomycin experience recurrences.[8]

The evidence for fidaxomicin is based on two, multi centred, randomised, double blind trials with almost identical designs and essentially similar results. These trials assessed the non-inferiority of fidaxomicin (200mg twice daily) with vancomycin (125mg four times daily) for 10 days in patients aged 16 years or older with mild to severe CDI. Mild to severe CDI was defined as more than three bowel movements in the 24 hours before randomisation and the presence of either C Difficile toxin (A or B).

One study (Louie et al)[9] included patients in North America only. The other (Cornely et al)[10] included patients in Europe (approximately 40% of the total) as well as North America. In the Louie et al study 46% patients and in the Cornely et al study 54% were 65 years or older.

The primary endpoint in both studies was clinical cure, defined as resolution of diarrhoea and no further need for treatment. The proportion of patients who were cured but subsequently had recurrence during a 4-week or 30-day follow-up was also investigated, as was the total proportion of patients who did not have a recurrence during the follow up period (termed sustained response or global cure). Both were secondary outcomes. Non-inferiority was pre-specified for the primary end-point with a margin of 10%. Clinical failure was the persistence of diarrhoea and the need for additional therapy for treatment. Recurrence was defined as a re-establishment of diarrhoea within 30 days post treatment, to an extent that was greater than the frequency noted on the last day of study medication with the demonstration of either Toxin A or B (or both) of C. Difficile.

In both studies fidaxomicin was found to be non-inferior to vancomycin with regard to clinical cure. However, recurrence rates were significantly lower and sustained response significantly higher in the fidaxomicin groups, based on modified intention-to-treat (ITT) and per protocol (PP) analysis.

A reduced risk of recurrence was not observed in the subgroup of patients with the virulent ribotype 027 strain of C difficile. Within the Cornely et al. study, the ribotype 027 strain accounted for 10% of patients in Europe and 46% of patients in the USA and Canada.

A post hoc analysis found that in the absence of concomitant antibiotic use during the treatment phase, clinical cure rates for fidaxomicin and vancomycin were similar. However, fidaxomicin was significantly more effective than vancomycin in achieving clinical cure in the presence of concomitant antibiotic therapy[11]

Study 101.1.C.003 (Louie et al)

A total of 629 patients were enrolled, with 623 receiving study drug (323 on vancomycin and 300 on fidaxomicin). Overall 54 patients (22 patients [7.3%] in the fidaxomicin group and 32 patients [9.8%] in the vancomycin group) withdrew from the study.

Study 101.1.C.004 (Cornely et al)

A total of 535 patients were enrolled, with 524 receiving study drug (260 on vancomycin and 264 on fidaxomicin). Overall 79 patients (45 patients [16.7%] in the fidaxomicin group and 34 patients [12.8%] in the vancomycin group) withdrew from the study. Overall, 39.5% of patients who received study drug in this trial were enrolled in European sites.

Summary of clinical cure rates at end of therapy for the pooled phase 3 studies[12]

	Louie et al			Cornely et al			Both studies pooled		
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI[1] n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI[1] n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI[3] n/N (%)
PP pop[n]	244/265 (92.1)	254/283 (89.8)	2.3	198/216 (91.7)	213/235 (90.6)	1.0	442/481 (91.89)	467/518 (90.15)	1.74
95% CI[2]	(88.1,94.8)	(85.6,92.8)	(-2.6,7.1)	(87.1,94.7)	(86.1,93.8)	(-4.3,6.3)	(89.02,94.07)	(87.20,92.49)	(-1.84,5.28)
mITT Pop[n]	253/287 (88.2)	265/309 (85.8)	2.4	221/252 (87.7)	223/257 (86.8)	0.9	474/539 (87.94)	488/566 (86.22)	1.72
95% CI[2]	(83.8,91.4)	(81.4,89.2)	(-3.1,7.8)	(83.0,91.2)	(82.0,90.4)	(-4.9,6.7)	(84.84,90.48)	(83.06,88.87)	(-2.25,5.67)

[1]The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates.
[2] 2-sided 95% point estimate confidence interval surrounding the cure rate.
[3] 2-sided 95% CI around the difference in response rates.

In both studies the recurrence rate was significantly lower in the fidaxomicin groups compared to the vancomycin groups. The 95% CIs did not contain the value of zero, indicating superiority of fidaxomicin over vancomycin in the risk of recurrence. Analysis of time to recurrence showed that patients treated with fidaxomicin experienced recurrence of CDI later than patients treated with vancomycin (estimated 10% of vancomycin-treated patients had recurrence by Day 8 post-dose versus 20 days for fidaxomicin-treated patients p = 0.003).

Summary of CDI Recurrence Rates in the Phase 3 Studies[12]

	Louie et al			Cornely et al			Both studies pooled		
	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI n/N (%)	Fidaxomicin n/N (%)	Vancomycin n/N (%)	Difference 95%CI n/N (%)
PP pop[n]	28/211 (13.3)	53/221 (24.0)	-10.7	23/140 (12.8)	46/182 (25.3)	-14.2	51/391 (13.04)	99/403 (24.57)	-11.52
95% CI	(9.3,18.6)	(18.8, 30.1)	(-17.9, -3.3)	(8.6,18.5)	(19.5, 32.1)	(--21.4, -6.8)	(9.99, 16.85)	(20.53, 29.10)	(-16.83, -6.09)
P-value			0.004			<0.001			<0.001
mITT Pop[n]	39/253 (15.4)	67/265 (25.3)	-9.9	28/221 (12.7)	60/223 (26.9)	-14.2	67/474 (14.14)	127/488 (26.02)	-11.89
95% CI	(11.5,20.4)	(20.4,30.9)	(-16.6, -2.9)	(8.9,17.8)	(21.5,33.1)	(-21.4, -6.8)	(11.22,17.65)	(22.25,30.19)	(-16.83, -6.84)
P-value			0.005			<0.001			<0.001

In line with this, the global cure rate in patients treated with fidaxomicin was statistically and clinically superior to patients treated with vancomycin.

The activity of fidaxomicin on recurrence was most pronounced in the initial two weeks after completing therapy, when only 7.4% of patients treated initially with fidaxomicin experienced a recurrence compared with 19.3% of those treated initially with vancomycin (p<0.001). In the following two-week period, the recurrence rates were similar: 6.6% for those originally treated with fidaxomicin compared with 8.1% for those treated with vancomycin (p=0.402). Thus, these results

indicate that fidaxomicin reduces the risk for relapses (early recurrence, < 2 weeks from end of treatment) while there was a similar rate of late recurrences (probable re-infections) in both treatment arms. Early recurrences (within 2 weeks) were more likely to be relapses of the primary infection, whilst late recurrences (within 4 weeks) were more likely to be reinfection.[8]

Caution is required when translating the results of these studies to routine clinical practice in accordance with Public Health England guidance[5] which recommends different treatments according to severity. Many patients included in the study had mild to moderate CDI (approximately 60%). For these patients, Public Health England guidance recommends initial treatment with metronidazole and not vancomycin. No clinical trials have compared the efficacy or safety of fidaxomicin with metronidazole. Of the approximately 40% of patients who were classified as having severe CDI, vancomycin would be an appropriate first-line treatment.

There is limited experience of using fidaxomicin in seriously ill patients, with only eight patients in the combined licensing studies diagnosed with pseudomembranous colitis. Experience is also limited in patients with severe comorbidities (for example, renal or hepatic impairment, inflammatory bowel disease). In such patients there is a possibility of greater systemic absorption. Caution is needed in these patients when using fidaxomicin in view of the uncertain benefits and risks.

As discussed earlier, only one study included European participants, and the prevalence of different C difficile strains differed between the two studies. For example, the more virulent ribotype 027 strain was more prevalent in North America than in Europe. Although overall results for both trials were essentially the same, because a high proportion of the strains from European patients were not identified, it was not possible to associate the outcome of results with strain.

A systematic review published in 2011 concluded that no antimicrobial agent is clearly superior for the initial cure of CDI, but that recurrence is less frequent with fidaxomicin than vancomycin.[13]

NICE have also concluded that fidaxomicin may have advantages in reducing the rate of recurrence and that local decision makers should take into account the potential benefits alongside the medical need, the risks of treatment and the relatively high cost of fidaxomicin in comparison with other CDI treatments.

Other efficacy data:

C.Difficile has minimal ability to develop spontaneous resistance to fidoxamicin in vitro and in clinical studies. In vitro, the resistance frequency for fidaxomicin against C.Difficile was 2.8×10^{-8} at four and eight times the MIC, which was similar to both vancomycin and metronidazole. This feature was also confirmed in strains from the Phase III clinical trials, where over the course of treatment no resistance to fidaxomicin developed.[8]

Summary of safety data:

The most common adverse reactions are vomiting, nausea and constipation.

Table of Adverse Events from SPC[1]

MedDRA system organ class	Common	Uncommon	Frequency not known
Immune system disorders		rash, pruritus	hypersensitivity reactions (angioedema, dyspnea)
Metabolism and nutrition disorders		decreased appetite	
Nervous system disorders		dizziness, headache, dysgeusia	
Gastrointestinal disorders	vomiting, nausea, constipation	abdominal distention, flatulence, dry mouth	
Hepatobiliary disorders		alanine aminotransferase increased	

Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100)

Some patients with hypersensitivity reactions reported a history of allergy to macrolides. Fidaxomicin should be used with caution in patients with a known macrolide allergy.

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.

Co-administration of potent P-glycoprotein inhibitors such as cyclosporine, ketoconazole, erythromycin, clarithromycin, verapamil, dronedarone and amiodarone is not recommended.

In the pooled phase 3 studies, a total of 38 and 36 deaths occurred among patients treated with vancomycin and fidaxomicin, respectively. The most common cause of death was sepsis, which was the cause of death for 7 patients (4 in the vancomycin group and 3 in the fidaxomicin group): followed by respiratory failure in 6 patients (2 versus 4), and pneumonia in 5 patients (2 versus 3). None of the deaths were considered to be related to administration of the study drug.

Strengths and limitations of the evidence:

Strengths

- Two multicentre, randomised controlled trials with similar results
- Active comparator
- Large patient numbers

Limitations

- Lack of validated severity scoring index systems.
- Patients with mild to severe CDI were included. Approximately 60% had mild-moderate – for these patients PHE recommends initial treatment with metronidazole and not vancomycin.
- Data from several important sub groups e.g. patients with pseudomembranous colitis, patients with multiple recurrences of CDI, patients with IBD and patients with impaired renal and impaired hepatic function, are missing
- Patients with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months) were excluded from the studies – not reflective of clinical practice.

- No data on repeated treatment with fidaxomicin
- No comparison with metronidazole.
- Only one study included European participants and the prevalence of different C. difficile strains differed between the two studies.

Summary of evidence on cost effectiveness:

SMC accepted that there was an economic case to justify the use of fidaxomicin in patients with first CDI recurrence. However, for the population of patients with severe CDI, a convincing economic case for fidaxomicin was not demonstrated.

AWMSG have recommended fidaxomicin as an option for restricted use as follows:

- Patients with severe CDI
- Patients with recurrence of CDI

The cost of fidaxomicin 200mg twice daily for 10 days is £1,350 (Drug Tariff, September 2019).

The equivalent cost of vancomycin: 125mg q6h for 10 days = 40 (125mg) capsules = £189.27, 500mg q6h for 10 days = 80 (250mg) capsules = £418.23.

If a patient is prescribed fidaxomicin instead of vancomycin for the treatment of CDI then there would be a significant cost impact of between £931.77 - £1,160.73 for a 10 day course.

According to Public Health England data, the rate of all CDI cases per 100,000 population, per year was 24 in 2017/18.[14]

For the 1.76 million population of Lancashire and South Cumbria, this would equate to 422 cases of CDI. If all these patients were treated with fidaxomicin instead of vancomycin then this would equate to an increase of between £393,206 and £489,828 per year.

Recent figures available from NHS England[15] would suggest that in 2018-19 this figure has increased to 485 cases within LSCMMG.

Prescribing and risk management issues:

n/a

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Fidaxomicin is the first in a new class of macrocyclic antibiotics

Financial implications of the intervention:

If routine prescribing of fidaxomicin was routine in all patients with C Difficile infection, the cost pressure would be between £393,206 and £489,828 per year. The cost when used following a first or second relapse would be significantly less.

Service Impact Issues Identified:

N/A

Equality and Inclusion Issues Identified:

N/A

Cross Border Issues Identified:

GMMMG - Fidaxomicin (Dificlir®) may be considered as an option for use following a first or second relapse. i.e. as second or third line therapy. Fidaxomicin should be initiated by a microbiologist or under microbiologist recommendation.

Fidaxomicin may also be considered for patients with severe CDI who are considered to be at high risk for recurrence as per the Public Health England Guidance. e.g. elderly patients with multiple comorbidities who are receiving concomitant antibiotics.

Fidaxomicin is classed as GREEN+ drug on the GMMMG RAG list as suitable for prescribing by a GP on the advice of a microbiologist.

Pan Mersey - Pan Mersey APC recommends that Fidaxomicin should only be prescribed on the advice of a consultant microbiologist or consultant in infectious diseases.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

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