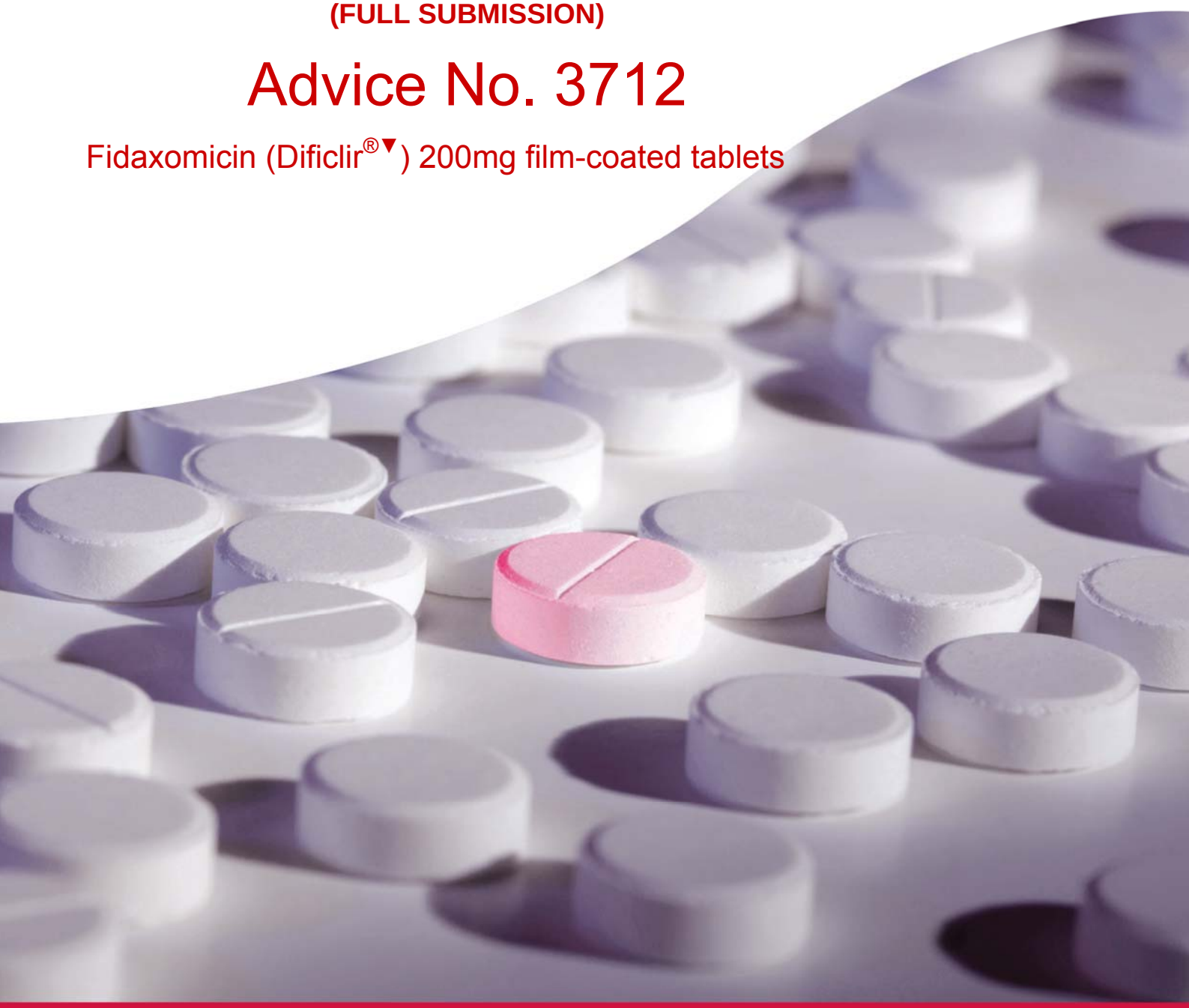
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 3712

Fidaxomicin (Dificlir®▼) 200mg film-coated tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3712
Fidaxomicin (Dificlir®▼) 200 mg film-coated tablets

This assessment report is based on evidence submitted by Astellas Pharma Ltd on 1 June 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Fidaxomicin (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[2].
Dosing	The recommended dose in adults and elderly patients is 200 mg (one oral tablet) administered twice daily (once every 12 hours) for ten days with or without food. The safety and efficacy of fidaxomicin in children aged below 18 years has not yet been established[2].
Marketing authorisation date	5 December 2011[2].

2.0 DECISION CONTEXT

2.1 Background

Clostridium difficile infection (CDI) is one of the commonest causes of diarrhoea following antibiotic therapy, especially in patients over 65 years[3]. Of the 1,900 CDI cases that occurred in Wales between October 2010 and September 2011, 326 were hospital in-patients aged 2–65 years, while 1,574 were > 65 years[1,4]. *C. difficile* can cause illness when broad-spectrum antibiotics disturb the balance of naturally occurring bacteria in the gut, allowing *C. difficile* to multiply and produce toxins A and B[3]. CDI symptoms typically occur in the first week of antibiotic treatment, but can be delayed until several weeks after treatment has been completed[3]. These symptoms often include diarrhoea (mild to severe) and, unusually, life-threatening inflammation of the intestines; other symptoms include fever, loss of appetite, nausea and abdominal pain or tenderness[5]. Experts contacted by the applicant company estimate that severe CDI can be seen in 10% of Welsh cases[1].

CDI treatment consists of stopping all antibiotics that are not required and using metronidazole or vancomycin to treat the infection[3]. Current guidelines advise the use of metronidazole as first-line treatment of non-severe CDI and during first recurrence of non-severe disease; vancomycin use is recommended in patients with a severe index case, in patients with a severe first recurrence, and in patients with a second recurrence of CDI (irrespective of severity)[6,7].

Fidaxomicin is a novel narrow-spectrum antibiotic that targets *C. difficile* and other Gram-positive bacteria and has bactericidal properties (with minimal activity versus the normal bowel flora) through inhibition of RNA polymerase[8]. This effect on RNA transcription leads to inhibition of spore and toxin production by *C. difficile*. In

December 2011, fidaxomicin received marketing authorisation for the treatment of CDI in adults[2]. The applicant company has highlighted the use of fidaxomicin in the following patient groups:

- Patients with a severe CDI
- Patients with a first recurrence of CDI[1].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Vancomycin
- Metronidazole.

The applicant company has used vancomycin as the main comparator in the submission, as it is the treatment of choice for recurrent or severe CDI, as specified by current guidance, except for the first non-severe recurrence where oral metronidazole is recommended[1,6,7].

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence. Evidence summaries: new medicines (ESNM) 1. *Clostridium difficile* infection: fidaxomicin (2012)[9].
- Department of Health. Updated guidance on the diagnosis and reporting of *Clostridium difficile* (2012)[10].
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Treatment guidance document for *Clostridium difficile* infection (2009)[6].
- Department of Health. *Clostridium difficile* infection: how to deal with the problem (2008)[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Comparative effectiveness

The company submission highlights two closely related phase III studies comparing the effectiveness of fidaxomicin and vancomycin[1]. The submission also includes a phase IIa study evaluating a range of fidaxomicin doses[11], which is of limited relevance to the comparison of fidaxomicin, vancomycin and metronidazole, and is therefore not discussed further. An indirect comparison of fidaxomicin and metronidazole is also presented[1].

3.1.1 Direct comparison of fidaxomicin and vancomycin

Studies 101.1.C.003 and 101.1.C.004 were multicentre, double-blind, randomised, non-inferiority studies to compare the safety and efficacy of fidaxomicin with vancomycin in adult patients with *C. difficile*-associated diarrhoea of varying severity[12,13]. Patients were randomised (1:1) to receive oral fidaxomicin (200 mg twice-daily) or vancomycin (125 mg four times per day) for 10 days, followed by a 30-day follow-up period[12,13].

Eligible patients had a diagnosis of CDI, defined as a change in bowel habits with more than three unformed stools in the 24 hours before randomisation and presence of *C. difficile* toxin type A or B within 48 hours of randomisation. Patients that had previously received fidaxomicin or had more than one occurrence of CDI within the three months prior to study initiation were excluded from the studies, as were patients with life-threatening or fulminant CDI, toxic megacolon or a history of ulcerative colitis or Crohn's disease[1,12,13].

The primary efficacy endpoint was clinical cure in the per protocol (PP) and modified intent to treat population (mITT; comprising patients with confirmed CDI who underwent randomisation and received at least one dose of study medication). Clinical cure was defined as the resolution of diarrhoea (i.e. three or fewer unformed stools for two consecutive days), remaining well before the time of study medication discontinuation and requiring no further CDI therapy as of the second day after the end of the course of therapy. If symptoms persisted and further treatment was required, this was classed as a primary failure. The secondary endpoints were rate of CDI recurrence during the four weeks following the end of therapy (in both studies) and rate of clinical cure without recurrence (sustained cure rate; study 101.1.C.004 only). For both studies the time to resolution of diarrhoea was included as an exploratory endpoint, defined as the number of days from the start of treatment until the earliest resolution of diarrhoea[12,13].

Table 1 illustrates several endpoint analyses and subgroup evaluations. Analysis of the primary endpoint (clinical cure) demonstrates that the criteria for non-inferiority were met. Both studies favoured fidaxomicin, with a difference of 2.4% in study 101.1.C.003 (95% confidence interval [CI]: -3.1%, 7.8%) for the mITT analysis and 2.3% (95% CI: -2.6%, 7.1%) for the PP analysis, while study 101.1.C.004 demonstrated a difference of 0.9% (95% CI: -4.9%, 6.7%) and 1.0% (95% CI: -4.3%, 6.3%) respectively. An analysis of pooled data also demonstrated non-inferiority, with a difference of 1.7% in both the ITT and PP populations. In both studies, the fidaxomicin treatment group exhibited a significantly lower recurrence rate and increased rate of sustained cure[12,13].

In patients with first recurrence or severe CDI, the rate of clinical cure in the fidaxomicin treatment group was comparable or slightly lower than that of vancomycin treated patients (see Table 1). However, rates of recurrence and sustained cure were slightly improved in the fidaxomicin group when compared with vancomycin-treated patients[12,13].

Table 1. Overview of endpoint analyses from pooled analysis of studies 101.1.C.003 and 101.1.C.004[1,8].

	Fidaxomicin	Vancomycin	Difference (95% CI)
Primary endpoint: clinical cure rate			
Modified intent to treat population (mITT)	474/539 (87.9%)	488/566 (86.2%)	1.7% (-2.2, 5.7)
Per protocol population (PP)	442/481 (91.9%)	467/518 (90.2%)	1.7% (-1.8, 5.3)
Secondary and ancillary analyses			
Recurrence rate (mITT)	67/474 (14.1%)	127/488 (26.0%)	-11.9% (-16.8, -6.8)
Recurrence rate (PP)	51/391 (13.0%)	99/403 (24.6%)	-11.5 (-16.8, -6.1)
Sustained cure rate (mITT)	407/539 (75.5%)	361/566 (63.8%)	11.7% (6.3, 17.0)
Sustained cure rate (PP)	378/481 (78.6%)	344/518 (66.4%)	12.2% (6.7, 17.6)
Subgroup analyses			
Severe CDI subgroup* (mITT population)			
Clinical cure rate	168/202 (83.1%)	180/211 (85.3%)	-
Recurrence rate	24/168 (14.3%)	48/180 (26.7%)	-
Sustained cure rate	144/202 (71.3%)	132/211 (62.6%)	-
First recurrence subgroup (mITT population)			
Clinical cure rate	79/88 (89.8%)	80/90 (88.9%)	-
Recurrence rate	16/79 (20.2%)	26/80 (32.5%)	-
Sustained cure rate	63/88 (71.6%)	54/90 (60.0%)	-

* Severe CDI defined as a white blood cell count of ≥ 15,001 per mm^3 or by the presence of ≥10 unformed bowel movements per day[1,12].

3.1.2 Indirect treatment comparison of fidaxomicin and metronidazole

As there were no data directly comparing metronidazole to fidaxomicin, an indirect treatment comparison has been included in the company submission to evaluate the relative efficacy of the two treatments with regard to clinical cure and recurrence rate in patients with CDI[1]. The comparison utilised data from studies 101.1.C.003 and 101.1.C.004, in addition to a study conducted by Zar et al[14], which evaluated in-patients with mild/moderate/severe toxin-positive CDI who were randomised to receive vancomycin (125 mg four times per day) or metronidazole (250 mg four times per day) for 10 days, with a follow-up of 21 days. Of the subjects enrolled, 40/71 (56%) patients receiving vancomycin and 41/79 (52%) metronidazole-treated subjects had non-severe CDI, where severe disease was defined as matching two or more of the following criteria within 48 hours of enrolment: age > 60 years, temperature > 38.3°C, albumin level < 2.5 mg/dl and peripheral white blood cell count > 15,000 cells/mm^3. The endpoints for the study included clinical cure (defined as resolution of diarrhoea by day six of treatment and no presence of *C. difficile* toxin A at days six and ten) and recurrence rate (defined as recurrence of *C. difficile* toxin A-positive diarrhoea by day 21 after initial cure). The vancomycin treatment group demonstrated increased rates of clinical cure and lower recurrence rates than the metronidazole treatment group (97% versus 84% and 7% versus 14% respectively) and this was reflected in non-severe CDI patients (98% versus 90% and 5% versus 8% respectively)[14].

The company has utilised an adjusted indirect comparison by Bucher and colleagues, and Table 2 illustrates the main outcomes of this comparison between the studies. The odds ratio for clinical cure or recurrence favoured fidaxomicin in non-severe CDI patients but was not statistically significant[1].

Table 2. Summary of the main outcomes of the indirect treatment comparison in patients with non-severe CDI[1].

Outcome	Treatment comparison	Odds ratio [95% CI]
Clinical cure	Fidaxomicin versus metronidazole	6.13 [0.56, 66.82]
	Fidaxomicin versus vancomycin	1.45 [0.63, 3.36]
	Metronidazole versus vancomycin	0.24 [0.03, 2.22]
Recurrence rate	Fidaxomicin versus metronidazole	0.30 [0.04, 1.99]
	Fidaxomicin versus vancomycin	0.49 [0.32, 0.74]
	Metronidazole versus vancomycin	1.63 [0.26,10.37]

The three studies utilised in this adjusted indirect comparison differed with regard to inclusion and exclusion criteria, markers to determine severe CDI and definitions for the primary and secondary endpoints[12–14]. Further, the study by Zar et al was smaller in comparison to the vancomycin/fidaxomicin studies and did not report an ITT analysis. The applicant company suggests that this study is also unlikely to have included patients with the more virulent 027 *C. difficile* strain (due to the timing of the study 1994–2002)[1], which comprised 38.1% and 33.2% of the patient population in studies 101.1.C.003 and 101.1.C.004[12,13]. Due to these differences in methodology and patient population, the findings of the adjusted indirect comparison should be interpreted with caution.

In addition, the study by Zar et al demonstrates that the vancomycin treatment group achieved superior rates of clinical cure and recurrence when compared with metronidazole[14]. By contrast, a recent Cochrane review, which included the study by Zar et al, established that no statistically significant differences in efficacy were found between vancomycin and metronidazole[15].

3.2 Comparative safety

Safety was assessed using studies 101.1.C.003 and 101.1.C.004[12,13]. In these phase III trials, the overall incidence of treatment-emergent adverse events (AEs) was comparable between fidaxomicin and vancomycin (187/300 [62.3%] versus 195/323 [60.4%] during study 101.1.C.003 and 186/264 [70.5%] versus 177/260 [68.1%] during study 101.1.C.004)[1,8]. Additionally, the incidence of serious AEs in both studies was similar between the two treatment groups (145/564 [25.7%] fidaxomicin-treated patients and 135/583 [23.2%] vancomycin-treated patients in a pooled analysis of the phase III studies)[8]. Discontinuation of treatment due to AEs was low in both phase III studies with no apparent difference between treatment groups (< 10% across treatment groups). In the pooled analysis a total of 38 and 36 deaths occurred among patients treated with vancomycin and fidaxomicin, respectively; none of these were considered to be treatment related[8].

In the pooled analysis, the AEs observed more frequently (≥ 2% difference) in fidaxomicin-treated patients were abdominal pain (5.7% versus 3.1%) and constipation (3.7% versus 1.7%). The most frequent treatment-related AEs included nausea (15 [2.7%] in the fidaxomicin group and 20 [3.4%] vancomycin-treated patients) and dizziness (5 [0.9%] versus 1 [0.2%] respectively)[8].

3.2 AWTTC critique

- The applicant company has highlighted the use of fidaxomicin in the following patient groups: patients with severe CDI and patients with a first recurrence of CDI[1].
- The company submission includes an indirect comparison between fidaxomicin and metronidazole[1]. While a common approach to the lack of direct head-to-head comparison data, an indirect comparison has inherent limitations (see Section 3.1.2). In addition, the dose of metronidazole (250 mg four times daily) used in the study by Zar et al[14] is different to that recommended for treatment of CDI in current UK and European guidelines (400–500 mg three times daily)[6,7].
- The clinical studies 101.1.C.003 and 101.1.C.004 did not provide comprehensive data regarding the use of fidaxomicin in several subgroups of patients, such as patients with pseudomembranous colitis or inflammatory bowel disease and impaired renal or hepatic function. As absorption from the gastrointestinal tract or exposure may differ in these patients, the efficacy and safety profile may be different in these populations. Additionally, the studies included only patients with no more than one episode of CDI within three months before study initiation and so did not provide evidence in patients with multiple recurrences of CDI. At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) also concluded that no data on repeated treatment with fidaxomicin are available and the potential emergence of resistance in the clinical setting is unknown[8]. However, CHMP also noted that fidaxomicin belongs to a novel antibiotic class, which it considered important from an antibiotic resistance perspective, as it limits the risks for cross-resistance[8].
- The company has suggested that adherence may be better with fidaxomicin[1], as it is administered less frequently[1,2] than metronidazole[16] and vancomycin[17]. However, no evidence has been submitted to support this conclusion.
- The phase III studies evaluating the efficacy of fidaxomicin defined severe CDI as a white blood cell count of ≥ 15,001 per mm^3 or the presence of ≥ 10 unformed bowel movements per day, which is not the same as the criteria in current use in the UK[6,7]. Using the classification of severe CDI defined in guidelines relevant to Welsh patients, the proportion of severe CDI cases included in the trial is 25% (rather than 37% of patients using study definition)[1].

However, post hoc analyses demonstrate similar results regardless of which definition was used[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis of fidaxomicin 200 mg oral tablets taken twice daily compared against vancomycin 125 mg oral tablets taken four times daily, which is intended to reflect first-line treatment for severe and first recurrence of CDI[1]. As fidaxomicin is licensed for all severities of CDI, the lack of a comparison against metronidazole, which is used in the treatment of non-severe index and the first recurrence of non-severe disease[6,7], limits the company's supporting evidence for fidaxomicin to a subset of the licensed indication where metronidazole is not considered an appropriate treatment, i.e. all severe CDI, or after first recurrence.

The analysis is based on a Markov model with five health states in addition to death. Patients enter the model with CDI (index case or first recurrent), from where they may be clinically cured with initial treatment, be cured but then experience recurrence, experience initial treatment failure but then be cured with the use of high dose vancomycin, or fail to achieve cure even with high dose vancomycin and so receive tapered vancomycin followed by last resort treatment with 14 days of rifampicin treatment. For non-severe first recurrences following a severe index case, metronidazole is used as the treatment of choice in both comparator pathways. Within each health state, patients may experience CDI complications. The model cycle length is ten days, to reflect the recommended treatment duration for fidaxomicin as used in the pivotal trials[12,13]. The model has a one-year analytical time horizon.

Treatment efficacy is modelled using the pooled direct comparative data, for the relevant subpopulations of the two phase III fidaxomicin pivotal trials in which vancomycin was used as the active comparator. Resource use data are derived from Welsh health statistics, expert opinion and extrapolation from other sources[1]. Cardiff and Vale University Health Board reports an excess length of stay (LOS) associated with CDI of 27 days, which is used to estimate LOS for recurrence episodes (15.8 days) based on the ratio of LOS for index and recurrent episodes derived from English Hospital Episodes Statistics (HES) data for 2010/11. Non-drug costs are based on published unit costs data[18], and drug costs are based on list prices in BNF 63[19]. Given the model time horizon, no discounting is applied to costs or effects.

4.1.2 Results

Table 3. Company-reported results of the base case analysis.

	Severe			First recurrence		
	Fidaxomicin	**Vancomycin**	**Difference**	**Fidaxomicin**	**Vancomycin**	**Difference**
Medication costs	£2,502	£454	£2,048	£3,566	£651	£2,916
Hospitalisation costs	£14,715	£16,825	-£2,110	£15,829	£19,556	-£3,727
Primary care costs	£144	£162	-£18	£153	£185	-£31
Cost of complications	£6	£5	£0	£5	£6	-£1
Total costs	£17,367	£17,446	-£79	£19,553	£20,397	-£844
Total QALYs	0.714	0.703	0.011	0.709	0.690	0.019
ICER (£/QALY gained)	Fidaxomicin dominates vancomycin in severe and first recurrence CDI*					

* Fidaxomicin is both more effective and less costly than vancomycin.
ICER: incremental cost-effectiveness ratio; LYG: Life-year gained; QALY: Quality-adjusted life-year gained.

In the company base case analyses of patients with severe and first recurrence CDI, fidaxomicin is estimated to be both more effective and less costly than vancomycin over a one-year time horizon. The main driver for the difference in effectiveness is the modelled impact of fidaxomicin on CDI recurrence, while the differences in costs are mainly driven by the modelled differences in hospital LOS associated with recurrence.

One-way sensitivity and threshold analyses are reported for the most influential parameters. The base case ICER is sensitive to changes in the assumed odds ratio for recurrence of CDI with fidaxomicin. In the severe CDI subgroup, the ICER increases to £20,000-£30,000 per QALY gained when the odds ratio for first recurrence increases from 0.456 in the base case analysis to 0.592-0.636. Increasing the odds ratio for further recurrence from 0.528 in the base case analysis to 0.654 generates ICERs of £30,000 per QALY gained and £27,000 per QALY gained for the index severe CDI subgroup and the first recurrence CDI subgroup, respectively. The model is also sensitive to the assumed hospital LOS following recurrence: ICERs in excess of £20,000 and £30,000 per QALY gained were generated when the LOS following recurrence was reduced to 13.7 and 12.9 days in the index severe CDI subgroup, or 10.7 and 9.9 days in the first recurrence CDI group, respectively. In probabilistic sensitivity analyses, which take account of combined parameter uncertainty, the probability of fidaxomicin having an ICER below £20,000 per QALY gained was reported to be 53% in severe index CDI and 64% in patients with a first recurrence of CDI. The probabilities of the ICER being below £30,000 per QALY gained were 56% and 67%, respectively. Fidaxomicin was dominant over vancomycin in 46% of simulations for the severe CDI subgroup and 59% of simulations for the first recurrent CDI group.

4.1.3 AWTTC critique

Strengths of the economic evidence include:

- Direct comparative data are used to model efficacy for fidaxomicin versus vancomycin.
- The model structure accounts for the potentially recurrent nature of CDI infection and the choice of the cycle length and time horizon is justified.

- A wide range of sensitivity analyses have been conducted to explore the impact of key assumptions.

Limitations of the economic evidence include:

- AWTTC appraises medicines within their licensed indications and requested comparison of fidaxomicin against vancomycin and metronidazole. The company has provided analyses only against vancomycin. The company submission implies it is positioning fidaxomicin as a treatment for severe CDI and recurrence of any degree of severity, but the exclusion of metronidazole as a comparator means evidence is available only in support of fidaxomicin where metronidazole is not a viable treatment option.
- The estimates of cost-effectiveness are driven mainly by the assumed relative reductions in recurrence of CDI and the assumed length of hospital stay associated with recurrence of CDI, which appear to be subject to significant uncertainty.
- The proportions of the two pivotal trial populations with severe CDI and with first recurrence are small (approximately 37% and 16%, respectively, using the trial-based definitions of severe CDI) and the trials do not appear to have been powered to detect differences between the comparators in these subgroups. The definition used in the trials for severe CDI is not in line with the definition used in guidelines relevant to a Welsh population[7] (using the guideline definition, the proportion of patients in the trial with severe CDI is around 25%), although post hoc analyses demonstrate similar results irrespective of definition used.
- The pivotal trials demonstrated fidaxomicin was statistically superior to vancomycin at preventing recurrence of CDI in the subgroup with severe index CDI, but not in the subgroup with recurrent CDI. The 95% CI around the recurrence odds ratios are wide, reflecting the uncertainty in the point estimates derived from subgroup analyses. The company has assumed fidaxomicin to have the same relative efficacy in multi-recurrent cases as in single recurrent cases, although evidence in these circumstances is noted by CHMP to be lacking[8]. The model is very sensitive to the odds ratios for recurrence in both subgroups, with plausible values well within the 95% CI range generating ICERs in excess of £20,000–£30,000 per QALY.
- The probabilistic sensitivity analyses, which consider the combined uncertainty across multiple parameters, demonstrate considerable collective uncertainty around the base case cost-effectiveness estimates.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified two recently published conference abstracts. The first reports on a study assessing the cost-effectiveness of fidaxomicin compared to vancomycin for the treatment of CDI from a USA hospital perspective using decision modelling and efficacy data from one of the two pivotal trials[20]. The authors concluded that vancomycin was more cost-effective compared to fidaxomicin and that fidaxomicin only dominated vancomycin in two-way sensitivity analysis assuming an unlikely clinical cure rate of 97%. The second study examined the cost-effectiveness of fidaxomicin, vancomycin and metronidazole for the treatment of CDI, also from a USA payer perspective using decision modelling[21]. The authors concluded that vancomycin was the most cost-effective option at a willingness to pay < $22,000 per additional cure, and fidaxomicin the most cost-effective above this threshold. Metronidazole was not found to be a cost-effective option compared to either fidaxomicin or vancomycin. The two studies did not specify any particular patient group in terms of severity or history of recurrence. It is also difficult to extrapolate from these results to NHS Wales due to the

different health care settings and funding systems. The sponsors of the studies are unclear, and as few details are provided within the abstracts, a detailed critique is not possible.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on surveillance data from Wales that reportedly show the incidence of CDI decreasing by 25% between 2010 and 2011[4], and the rate of recurrences observed in the vancomycin arms of the fidaxomicin pivotal trials, the company estimates that the total number of patients with CDI (both new cases and early recurrences) will be between 1,425–1,700 in year 1, falling to 451–1,156 in year 5. The percentage of patients with severe CDI is estimated to be 12.2%, based on a retrospective chart review study conducted in the US[22], while the percentage of patients with first recurrence is estimated to be 26%, as observed in the fidaxomicin pivotal studies[12,13]. The number of patients predicted to be eligible for treatment with fidaxomicin is, therefore, estimated to be 544–629 in year 1 decreasing to 172–442 in year 5, due to the decreasing incidence which is assumed to continue over the next five years. Costs used in the budget impact analysis are based on the economic model. The company assumes market share of 10% year 1 rising to 50% in year 5. Hence, the total number of patients anticipated to receive fidaxomicin is estimated to be 54–65 in year 1 rising to 86–221 in year 5.

5.1.2 Results

The company anticipates cost savings from the use of fidaxomicin instead of vancomycin, as detailed in Table 4. The company has also highlighted potential cost savings related to reduced risk of transmission to other patients, and reduced risk of outbreaks, as a result of fewer recurrence episodes. These have not been included in the budget impact estimates.

Table 4. Company-reported costs associated with use of fidaxomicin for the treatment of CDI.

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients (licensed indication)	1,425–1,700	1,069–1,360	802–1,156	601–1,156	451–1,156
Number of patients (subpopulation highlighted in company submission)	544–649	408–520	306–442	230–442	172–442
Uptake (%)	10%	20%	30%	40%	50%
Treated patients	54–65	82–104	92–133	92–177	86–221
Net costs					
Primary care	-£1,472– -£2,037	-£2,208– -£3,264	-£2,484– -£4,162	-£2,489– -£5,549	-£2,327– -£6,937
Secondary & tertiary care	-£174,703– -£208,424	-£262,055– -£333,992	-£294,812– -£425,839	-£295,454– -£567,786	-£276,185– -£709,732
Staffing/Infrastructure	Not included				
Personal social services	Company reports N/A				
Medication costs	£143,547– £171,254	£215,320– £272,428	£242,235– £349,896	£242,763– £466,527	£226,932– £583,139
Overall net cost for whole population	-£32,628– -£38,926	-£48,942– -£62,377	-£55,060– -£79,531	-£55,180– -£106,042	-£51,581– -£132,552

The company has provided sensitivity analyses to assess the impact of varying the excess LOS for severe CDI and for a recurrence, which are the main cost drivers of the economic model. Using a range of excess LOS explored in the economic model (20.07 days to 29.85 days for severe CDI; 12.24 to 18.46 for recurrent CDI), the year 1 net budget impact may range from additional costs of around £7,000 to cost savings of around £71,000. In year 5 the net budget impact may range from additional costs of around £11,000 to cost savings of £250,000.

5.1.3 AWTTC critique

- The company used Welsh-specific CDI incidence data to estimate the overall number of cases of CDI, taking account of the recent decreases in incidence as a result of infection control measures in recent years. However, the range of estimated number of patients to be treated appears subject to some uncertainty.
- The percentage of patients with severe CDI is based on a USA study conducted several years ago during a period of increased CDI incidence and, hence, the proportion of patients with severe CDI may differ currently in Wales.
- The anticipated market uptake is a key component of the estimated cost savings and is a source of uncertainty.
- The cost savings anticipated in the base case budget impact model are derived from the economic model. The limitations and uncertainties in the main cost drivers in the economic model also apply to the budget impact estimates
- Given the aforementioned limitations, there is considerable uncertainty in the budget impact estimates provided by the company.

5.2 Comparative unit costs

The table below provides example comparative costs for CDI treatments. Vancomycin and metronidazole regimens are as reported in CDI treatment guidelines[7].

Table 4. Examples of cost per CDI treatment course for index episodes and first recurrence.

Drugs	Example regimens[†]	Cost per course
Fidaxomicin (Dificlir®) 200 mg capsules	200 mg twice daily for 10 days	£1,350
Vancomycin (Vancocin® Matrigel®) 125 mg capsules	125 mg four times daily for 10–14 days	£126.16–£176.62
Metronidazole (Non-proprietary) 200, 400 and 500 mg tablets	400–500 mg every 8 hours (1200–1500 mg daily) for 10–14 days	£1.86–£61.96

[†]Example regimens based on the licensed regimen for fidaxomicin and the recommended regimens for vancomycin and metronidazole as stated for index episodes and first CDI recurrence in UK guidelines[7].
Costs based on BNF[19] and MIMS[23] list prices as of 18 July 2012.
This table does not imply therapeutic equivalence of the stated drugs and doses.
See all relevant Summaries of Product Characteristics for full dosing details[2,16,17].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC are of the opinion that, if recommended, fidaxomicin (Dificlir®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed by specialist recommendation.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months but post-hoc analysis of existing data is being conducted at present.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 29 June 2012
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1. Additional clinical information

Table 1A. Overview of endpoint analyses from studies 101.1.C.003 and 101.1.C.004.

	101.1.C.003[8,12,24]			101.1.C.004[8,13,25]			Pooled[1,8]		
	Fidaxomicin	Vancomycin	Difference (95% CI)	Fidaxomicin	Vancomycin	Difference (95% CI)	Fidaxomicin	Vancomycin	Difference (95% CI)
Primary endpoint: clinical cure rate									
Modified intent to treat population (mITT)	253/287 (88.2%)	265/309 (85.8%)	2.4% (-3.1, 7.8)	221/252 (87.7%)	223/257 (86.8%)	0.9% (-4.9, 6.7)	484/539 (87.9%)	488/566 (86.2%)	1.7% (-2.2, 5.7)
Per protocol population (PP)	244/265 (92.1%)	254/283 (89.8%)	2.3% (-2.6, 7.1)	198/216 (91.7%)	213/235 (90.6%)	1.0% (-4.3, 6.3)	442/481 (91.9%)	467/518 (90.2%)	1.7% (-1.8, 5.3)
Secondary and ancillary analyses									
Recurrence rate (mITT)	39/253 (15.4%)	67/265 (25.3%)	-9.9% (-16.6, -2.9)	28/221 (12.7%)	60/223 (26.9%)	-14.2% (-21.4, -6.8)	67/474 (14.1%)	127/488 (26.0%)	-11.9% (-16.8, -6.8)
Recurrence rate (PP)	28/211 (13.3%)	53/221 (24.0%)	-10.7% (-17.9, -3.3)	23/180 (12.8%)	46/182 (25.3%)	-12.5 (-20.3, -4.4)	51/391 (13.0%)	99/403 (24.6%)	-11.5 (-16.8, -6.1)
Sustained cure rate (mITT)	214/287 (74.6%)	198/309 (64.1%)	10.5% (3.1, 17.7)	193/252 (76.6%)	163/257 (63.4%)	13.2% (5.2, 20.9)	407/539 (75.5%)	361/566 (63.8%)	11.7% (6.3, 17.0)
Sustained cure rate (PP)	206/265 (77.7%)	190/283 (67.1%)	10.6% (3.1, 17.9)	172/216 (79.6%)	154/235 (65.5%)	14.1% (5.9, 22.1)	378/481 (78.6%)	344/518 (66.4%)	12.2% (6.7, 17.6)
Subgroup analyses									
Severe CDI subgroup (mITT population)									
Clinical cure rate	92/112* (82.1%)	109/123* (88.6%)	-	48/63† (76.2%)	43/61† (70.5%)	-	168/202* (83.1%)	180/211* (85.3%)	-
Recurrence rate	12/92* (13.0%)	29/109* (26.6%)	-	4/48† (8.3%)	14/43† (32.6%)	-	24/168* (14.3%)	48/180* (26.7%)	-
Sustained cure rate	80/112* (71.4%)	80/123* (65.0%)	-	44/63† (69.8%)	29/61† (47.5%)	-	144/202* (71.3%)	132/211* (62.6%)	-
First recurrence subgroup (mITT population)									
Clinical cure rate	42/48 (87.5%)	48/54 (88.9%)	-	37/40 (92.5%)	32/36 (88.9%)	-	79/88 (89.8%)	80/90 (88.9%)	-
Recurrence rate	9/42 (21.4%)	15/48 (31.3%)	-	7/37 (18.9%)	11/32 (34.4%)	-	16/79 (20.2%)	26/80 (32.5%)	-
Sustained cure rate	33/48 (68.8%)	33/54 (61.1%)	-	30/40 (75.0%)	21/36 (58.3%)	-	63/88 (71.6%)	54/90 (60.0%)	-

* Severe CDI defined as a white blood cell count of ≥ 15,001 per mm^3.or by the presence of ≥10 unformed bowel movements per day[1,12].
† Severe CDI defined as meeting any one or more of the European Society of Clinical Microbiology and Infectious Diseases criteria which includes > 15,000 white blood cells per microlitre, serum creatinine concentration > 1·5 mg/dl, or body temperature > 38·5°C[6,13].