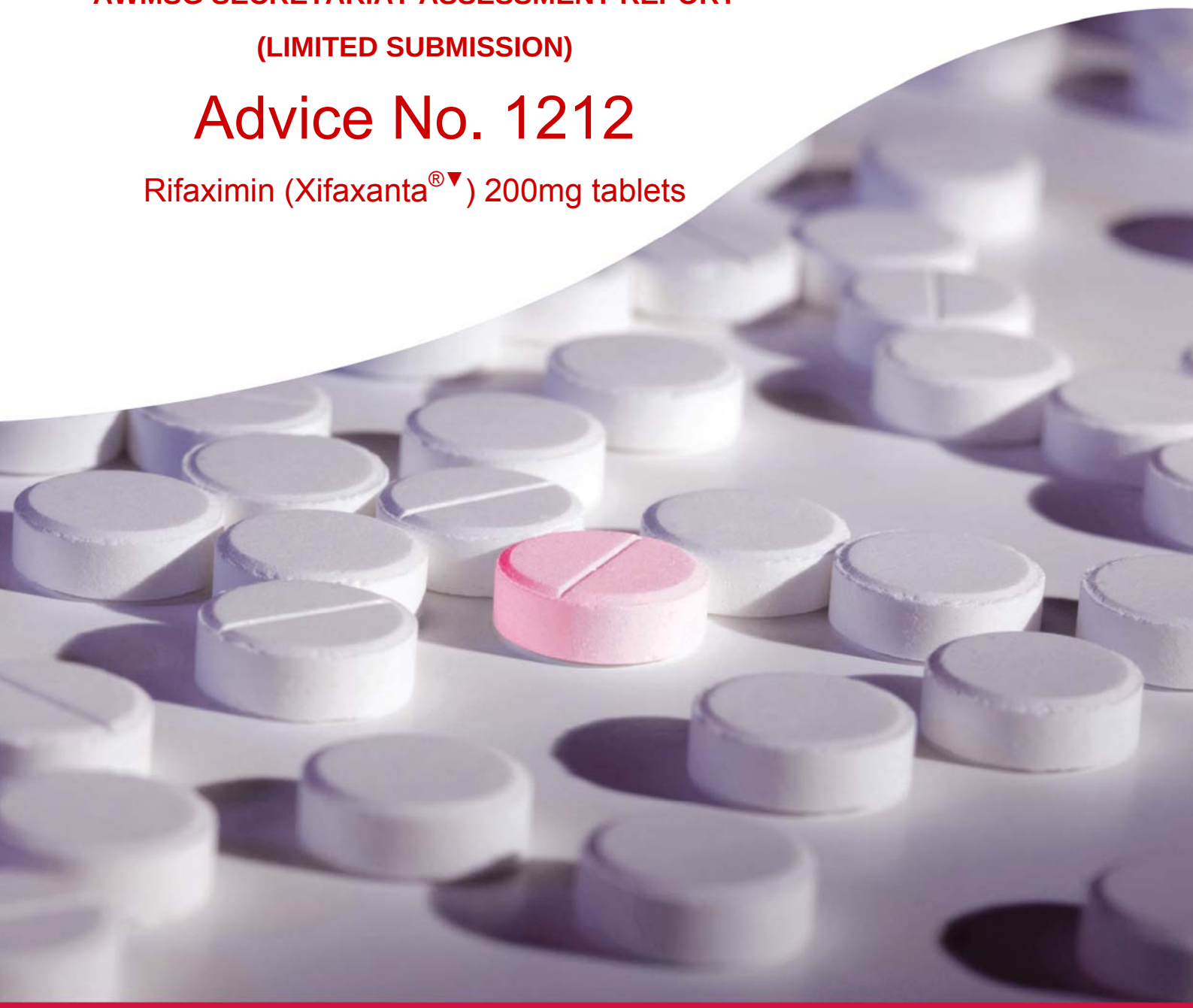
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1212

Rifaximin (Xifaxanta®▼) 200mg tablets



AWMSG Secretariat Assessment Report – Advice No. 1212
Rifaximin (Xifaxanta®▼) 200 mg tablets

This assessment report is based on evidence from a limited submission by Norgine Pharmaceuticals Ltd on 23 December 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Rifaximin (Xifaxanta®▼) is indicated for the treatment of travellers' diarrhoea that is not associated with any of the following: • fever; • bloody diarrhoea; • eight or more unformed stools in the previous 24 hours; • occult blood or leucocytes in the stool. Rifaximin may shorten the duration of diarrhoea when this is associated with non-invasive strains of *Escherichia coli*[2].
Dosing	The recommended dose of 200 mg should be taken every eight hours for three days (a total of nine doses). Rifaximin must not be used for more than three days even if symptoms continue and a second course of treatment must not be taken. The safety and efficacy of rifaximin in children (aged less than 18 years) has not been established[2].
Marketing authorisation date	2 December 2010[1].
UK launch date	15 September 2011[1].

2.0 DECISION CONTEXT

2.1 Background

Travellers' diarrhoea, affects 20–50% of individuals travelling from developed to developing countries, and is defined as at least three loose to watery stools in 24 hours, with or without one or more symptoms of abdominal cramps, fever, nausea, vomiting, or blood in the stool[3]. The incidence is affected by a wide range of factors including age, eating or drinking habits (travellers' diarrhoea is usually contracted from contaminated food or water), country visited and the season of visit[4]. Bacteria appear to be responsible for up to 85% of cases of travellers' diarrhoea[5]. The most frequent cause is enterotoxigenic *E. coli*, which may be part of the normal gut flora in the local population[6]. Other bacterial causes include enteroaggregative *E. coli*, as well as multiple species of *Campylobacter*, *Salmonella*, and *Shigella*[3].

Travellers' diarrhoea is usually a mild and self-limiting illness with symptoms not normally persisting beyond five days, but in 10% of cases symptoms last more than one week and in 2% of cases symptoms last for longer than a month[3,4]. Serious complications of travellers' diarrhoea include haemolytic uraemic syndrome, Guillain Barré syndrome and post-infectious arthropathies with any invasive bacteria[7]. It is reported that greater than 10% of patients affected by travellers' diarrhoea may go on to develop postinfectious irritable bowel syndrome.

Following anti-diarrhoeal agents and fluid replacement, the treatment of travellers' diarrhoea includes empirical oral antibiotic treatment for moderate to severe cases[7]. A single dose of an antibiotic, or up to three days of treatment, can be expected to improve the condition within 20–36 hours, shortening symptoms by one to two days compared with placebo[3,4]. A fluoroquinolone antibiotic such as ciprofloxacin is usually prescribed; an alternative is azithromycin for cases where ciprofloxacin is contraindicated, or in countries (such as Thailand) where quinolone resistance is prevalent[3,8]. Another alternative is rifaximin, a broad-spectrum antibiotic that (unlike azithromycin and ciprofloxacin) undergoes virtually no absorption from the gut into the plasma[2,9].

Figures for the numbers of travellers' diarrhoea cases requiring treatment after return to Wales are not available. The company have estimated a figure of 6205 cases per year in Wales, approximately 500 of which would be eligible for treatment with rifaximin (see Section 5.0 for details)[1].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership (WMP)[*] were ciprofloxacin and azithromycin. It should be noted that azithromycin is not licensed in the UK for the treatment of travellers' diarrhoea.

2.3 Guidance and related advice

- Hill DR, Ryan ET. Management of travellers' diarrhoea (2008)[3].
- Prodigy clinical topic. Diarrhoea- prevention and advice for travellers - management[8].
- National Travel Health Network and Centre. Health information for overseas travel (2010)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission compared rifaximin and ciprofloxacin for treatment of travellers' diarrhoea using evidence from two randomised controlled trials; these are discussed in Section 3.1. Evidence was also included comparing rifaximin with loperamide[10], trimethoprim/sulfamethoxazole[11] (co-trimoxazole; not routinely used to treat travellers' diarrhoea in Wales) and placebo[12]. Although supportive, these studies are not directly relevant to this submission and will not be discussed further.

3.1 The effectiveness of rifaximin in comparison with ciprofloxacin

Two studies have compared the effectiveness of rifaximin and ciprofloxacin for the treatment of travellers' diarrhoea: one study by DuPont and colleagues published in 2001[5] and one Taylor and colleagues[9] published in 2006.

The study by DuPont and colleagues was conducted in Mexico (where adult students from the United States were recruited) and Jamaica (where participants were international tourists). To be eligible, subjects had to have passed three or more unformed stools in the past 24 hours, have been ill for less than 72 hours, and to have at least one other additional symptom of enteric infection (nausea, vomiting, abdominal cramps/pain, tenesmus, dysentery or faecal urgency). Exclusion criteria included the use of more than two doses of antidiarrhoeal medication in the 24 hours before enrolment, any dose of symptomatic therapy in the two hours before enrolment, and use of any antimicrobial drug active against enteric bacterial pathogens in the week before enrolment[5].

[*] In April 2012 the Welsh Medicines Partnership became part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

A total of 187 subjects were enrolled (163 in Mexico and 24 in Jamaica) and were randomised to three days of treatment with either 400 mg rifaximin (n = 93) twice daily or 500 mg ciprofloxacin (n = 94) twice daily. The study period was five days, during which time subjects kept a diary of clinical symptoms and signs, and the time and form of all stools passed[5].

At baseline, treatment arms were comparable in terms of pretreatment symptoms and demographics. The primary endpoint was the time to last unformed stool (TLUS), defined as the interval between initiation of therapy and passage of the last unformed stool. For the intention to treat population, median TLUS was 25.7 hours (95% confidence interval [CI] 20.9–38.0) for rifaximin-treated subjects and 25.0 hours (95% CI 18.5–35.2) for ciprofloxacin-treated subjects. A pre-planned statistical analysis showed that the treatment groups were equivalent with respect to TLUS. Of the secondary efficacy endpoints, no significant differences between treatment arms was observed for the number of unformed stools passed on each day of the study, number of subjects whose condition improved on day one or day two[*], number of subjects whose treatment failed[†], or the number of subjects who achieved bacteriological cure[‡]. For the measured clinical symptoms after initiation of therapy (also a secondary endpoint), nausea was significantly less common in rifaximin-treated than ciprofloxacin-treated subjects on day two (18% versus 34% respectively, p = 0.012) and day three of the study period (10% versus 23% respectively, p = 0.009). Tenesmus was significantly more common in rifaximin-treated than ciprofloxacin-treated subjects on day one of the study period (p = 0.016, no subject numbers provided); the authors of the published trial state that tenesmus was also more common in the rifaximin arm at baseline, but no figures are provided to corroborate this[5].

The study by Taylor and colleagues was conducted at seven travel clinics in India, Peru, Guatemala and Mexico. Inclusion and exclusion criteria were as stated for the study by DuPont, with the exception of the use of antidiarrhoeal agents: subjects were excluded if they had used more than two doses of such an agent in the past eight hours. Recruited subjects (n = 399) were all travellers, but no breakdown of country of origin was disclosed. Subjects were randomised to treatment with 200 mg rifaximin three times daily (n = 197), 500 mg ciprofloxacin twice daily and placebo once daily (n = 101) or placebo three times daily (n = 101)[9].

The primary efficacy endpoint was TLUS, defined as for the study by DuPont et al. There was no significant difference in median TLUS for the rifaximin (32.0 hours) and ciprofloxacin (28.8 hours) treatment arms (p = 0.35). Median TLUS for the placebo treatment arm was 65.5 hours, which was significantly different from both the rifaximin and ciprofloxacin treatment arms (p = 0.0014 and p = 0.0003, respectively)[9]. Of the secondary efficacy endpoints, there was no significant difference between rifaximin and ciprofloxacin for the proportion of subjects with improvements in diarrhoeal syndrome, or the proportion of subjects with wellness (defined as no watery stools and no more than two soft stools in a 24 hour interval with no other clinical symptoms except for mild excess gas/flatulence, or no unformed stools in a 48 hour interval with no fever, with or without other clinical symptoms). However, ciprofloxacin was superior to rifaximin in terms of the number of unformed stools passed per unit time (6.2 and 8.8 [units not specified] respectively, p < 0.0004) and the proportion of subjects who failed treatment (7.4% and 13.4% respectively, p = 0.05).

[*] Improvement was defined as a reduction by at least 50% in the number of unformed stools passed during a 24 hour period, in comparison with the number of unformed stools passed in the 24 hours immediately prior to study enrolment.

[†] Treatment failure was defined as (i) clinical deterioration or worsening of clinical symptoms after at least 24 h of therapy, in comparison with pretreatment symptoms and number of stools passed; (ii) failure of clinical symptoms to abate after at least 24 h of therapy; or (iii) illness continuing after 120 h.

[‡] Bacteriologic cure was defined as a negative post-treatment stool examination for the etiologic organism identified before treatment.

A pre-planned subgroup analysis for subjects with invasive pathogens was conducted. This reported a lower median TLUS for ciprofloxacin than rifaximin (24.4 and 43.7 hours, respectively), although it should be noted that patient numbers in this subgroup were small (22 rifaximin-treated subjects, 7 ciprofloxacin-treated subjects) and no statistical analysis was reported.

In both of the studies discussed above, the number of subjects experiencing an adverse event was similar in the rifaximin and ciprofloxacin treatment arms over the five-day study period (DuPont et al: 33% and 36% respectively; Taylor et al: 26.6% and 24.0% respectively). In the study by Taylor et al, placebo was also found to have a similar adverse event rate (25.0%) to rifaximin and ciprofloxacin. In all cases, the adverse event profile was similar across all treatment arms.

3.2 AWTTC critique

- On the basis of results from two randomised controlled trials, rifaximin appears to have comparable effectiveness to ciprofloxacin for the treatment of diarrhoea caused by non-invasive pathogens.
- No evidence has been provided comparing the effectiveness of rifaximin with azithromycin in this indication (which represents unlicensed use of azithromycin), and a literature search by AWTTC has not identified any supporting evidence on this topic.
- The studies included have focussed on traveller's diarrhoea in Central and South America; data on individuals visiting the Middle East, Asia and Africa is limited[7].
- In contrast to fluoroquinolone antibiotics used to treat travellers' diarrhoea, there is evidence that rifaximin does not appear to induce resistance in enteric flora[1,7]. Additionally it is reported that rifaximin does not induce cross-resistance to other antibiotics used to treat travellers' diarrhoea[13].
- Both the studies discussed in Section 3.1 included cases of diarrhoea caused by both invasive and non-invasive pathogens. In the clinical assessment at the time of marketing authorisation, the Medicines and Healthcare products Regulatory Agency (MHRA) suggest that rifaximin may provide comparable efficacy to ciprofloxacin only in patients with diarrhoea due to non-invasive pathogens[14]. This is reflected in the licensed indication and Summary of Product Characteristics (SPC). Rifaximin is not recommended for use in cases likely to be associated with potentially invasive pathogens such as *Campylobacter*, *Salmonella*, and *Shigella*[15].
- Rifaximin was first marketed in Italy in 1987[9], and therefore post-marketing adverse drug reactions would be expected to complement the short-term safety results reported from the studies described in Section 3.1. However, the MHRA noted that although there appear to be no major safety issues with rifaximin, the number of post-marketing adverse drug reaction reports received is very small, suggesting under-reporting of adverse drug reactions[14].
- Rifaximin is not systemically absorbed from the gut following oral administration, which has been suggested to lower the risk of adverse events compared to systemically absorbed antibiotics[1,9]. It should be noted that the trials discussed above show similar rates of adverse events for rifaximin and ciprofloxacin; however, these studies only provided evidence in relation to the safety profile during and immediately after treatment.
- Ciprofloxacin has the potential to interact with a number of other medicinal products[16]. By contrast, the systemic drug interaction potential with rifaximin is low[2].
- Rifaximin is recommended as an alternative choice to ciprofloxacin and azithromycin in regions where *E. coli* predominates such as Latin America and Africa[3].
- Fluoroquinolones are a predisposing class of drug associated with development of antibiotic-associated *Clostridium difficile* diarrhoea and colitis; however rifaximin exhibits a low potential for producing major alterations to the intestinal flora[5].

- Ciprofloxacin should be used with caution in epileptic patients; both azithromycin and ciprofloxacin should be used with caution in patients with risk factors for QT prolongation[15]. Rifaximin may provide an alternative treatment for these patients.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

Applicant companies are not required to submit evidence on cost-effectiveness for a limited submission, and literature searches by AWTTC identified no relevant studies.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Context and methods

The company submission presents a simple estimate of the total annual cost of rifaximin for the treatment of adult patients with travellers' diarrhoea in NHS Wales[1]. It is assumed that only the costs of rifaximin prescribing for patients who return to Wales from a high risk area and present with symptoms of non-invasive diarrhoea will fall on NHS Wales; any prescribing of rifaximin before travel would be on a private prescription-basis. The company estimates that around 333,400 people travel from Wales to high risk areas each year, reportedly based on UK population estimates of travellers to high risk areas (company data on file – not verified). Of these, 12,410 (3.72%) are assumed to seek medical care in Wales for gastrointestinal (GI) complaints, based on rates observed in a published cohort study of US travellers to developing countries[17]. The company then assumes that 50% of GI complaints will be due to travellers' diarrhoea, of which 80% will occur in adults. Of these, it is assumed only 10% will have non-invasive diarrhoea, as those presenting for treatment after returning to Wales are likely to have had the illness for more than 3–4 days, and illness is therefore more likely to be due to an invasive organism. Based on the assumption of one prescription per year, the company estimates that rifaximin will therefore be prescribed to 496 people each year, at a total cost to NHS Wales of £7,520. Assuming these 496 patients would normally be treated with generic ciprofloxacin, the use of rifaximin instead would cost an additional £7,424 per year. Assuming that all 496 patients would normally be treated with azithromycin, the use of rifaximin would instead cost an additional £5,872 year.

5.2 AWTTC critique

Due to a reported lack of data on the number of people with travellers' diarrhoea in Wales, the company has employed a wide range of assumptions. Estimates of rates of travellers' diarrhoea are based on one published cohort study, conducted among US travellers over 20 years ago. How this study was selected as being the most appropriate from the literature to inform estimates, and the reliability of those estimates, is unclear. Subsequent estimates of the proportion of patients meeting the licensed indication for rifaximin appear to be based on assumed values.

The company submission provides brief comparative efficacy data against ciprofloxacin, but no data are presented against azithromycin. Furthermore, the efficacy data largely relate to acute treatment of diarrhoea (less than 72 hours since onset), rather than persistent diarrhoea suggested by the company in its budget impact analysis as being the likely use of rifaximin in Wales. As noted by the company, persistent diarrhoea may be invasive and warrant the use of laboratory tests to establish the cause. It is not clear whether rifaximin, which is not absorbed and is not licensed for use in invasive diarrhoea[2], would be the first choice treatment of such diarrhoea in routine practice. Collectively, the estimate of the number of patients potentially eligible for treatment with rifaximin in Wales, and the associated budget impact, is subject to considerable uncertainty.

5.3 Comparative unit costs

Table 1 provides comparative unit costs for empirical treatment of travellers' diarrhoea. The SPC for ciprofloxacin suggests one day of empirical treatment for severe travellers' diarrhoea[16]; however, Prodigy guidelines suggest up to three days of treatment[8], which is costed below.

Table 1. Examples of drug acquisition costs for the treatment of travellers' diarrhoea in adults.

Medicine	Example regimen	Cost per treatment episode
Rifaximin (Xifaxanta®) 200 mg tablets	200 mg every 8 hours for 3 days	£15.15
Ciprofloxacin (non-proprietary) 500 mg tablets	500 mg twice daily for up to 3 days*	Up to £0.61
Ciprofloxacin (Ciproxin®) 500 mg tablets	500 mg twice daily for up to 3 days*	Up to £7.49
Azithromycin (non-proprietary)† 500 mg tablets	500 mg once daily for 3 days†	£3.30
Azithromycin (Zithromax®)† 250 mg capsules	500 mg once daily for 3 days†	£10.74

**Up to three days treatment period assumed based on empirical treatment advice on Prodigy guidelines[8].*
†Not licensed for treatment of travellers' diarrhoea.
Costs are based on BNF[15] and NHS electronic drug tariff[18] list prices as of 20 January 2012.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that Rifaximin (Xifaxanta®▼) may be suitable for prescribing by all prescribers within NHS Wales for the above indication.

6.2 Ongoing studies

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

6.3 AWMSG review

This ASAR will be considered for review in July 2015.

6.4 Evidence search

Date of evidence search: 4 January 2012.
Date range of evidence search: No date limits were applied to database searches.

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