New Medicine Assessment

Rifaximin as second line antibacterial treatment for the treatment of Small Intestinal Bacterial Overgrowth

Recommendation: RED

Medicine is supplied by the hospital for the duration of the treatment course.

Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Red medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use. If however, a primary care prescriber has particular specialist knowledge or experience of prescribing a particular drug for a particular patient it would not always be appropriate for them to expect to transfer that prescribing responsibility back to secondary care. There should be a specific reason and a specific risk agreement, protocol and service set up to support this

Primary care prescribers may prescribe RED medicines in exceptional circumstances to patients to ensure continuity of supply while arrangements are made to obtain on going supplies from secondary care.

Summary of supporting evidence:

- The studies show that rifaximin is well tolerated and has a degree of efficacy in treating patients with Small Intestinal Bacterial Overgrowth (SIBO) as indicated by the normalisation of breath tests and relief of symptoms associated with SIBO.
- One study showed that rifaximin was not effective in eradicating SIBO in patients without irritable bowel syndrome.[11]
- One study showed that rifaximin was less effective than metronidazole in eradicating SIBO in patients with blind loop syndrome.5
- SIBO eradication in the trials appears to be greater with the higher Rifaximin doses

Details of Review

Name of medicine (generic & brand name)**:**

Rifaximin (Targaxan, Xifaxanta)

Strength(s) and form(s):

Targaxan (550mg tablet)

Xifaxanta (200mg tablets)

Dose and administration:

Unlicensed indication / dose requested.

Requesting clinician has stated 550mg three times per day i.e. total daily dose of 1650mg.

However, the maximum dose in the majority of trials is 1600mg per day i.e. 400mg, 600mg, 600mg.

BNF therapeutic class / mode of action

Antimycobacterials – rifaximin is a rifamycin which is poorly absorbed from the gastro-intestinal tract and should not therefore be used to treat systemic infections.

Licensed indication(s):

Rifaximin is available as two separate medicinal products with different licensed indications:

Targaxan is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Xifaxanta is indicated for the treatment of travellers' diarrhoea that is not associated with any of: Fever, Bloody diarrhoea, Eight or more unformed stools in the previous 24 h, Occult blood or leucocytes in the stool.

Xifaxanta may shorten the duration of diarrhoea when this is associated with non-invasive strains of E.coli

Proposed use

For the treatment of small intestinal bacterial overgrowth (SIBO) in patients who have failed to respond to either Co-amoxiclav, or Metronidazole plus cefalexin or trimethoprim / sulfamethoxazole.

Current standard of care/comparator therapies:

- Co-amoxiclav 625mg twice a day
- Metronidazole 400 mg three times per day; plus Cefalexin 500 mg three or four times per day
- Metronidazole 400 mg three times per day; plus Co-trimoxazole 960mg tablet twice per day

Relevant NICE guidance:

N/A

Background and context

A new product request was received by ELMMB from a consultant gastroenterologist for Rifaximin fort the treatment of Small Intestinal Bacterial Overgrowth. However, due to the unlicensed specialist nature of the request ELMMB felt it appropriate that this application be considered by LSCMMG.

SIBO is defined as the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal symptoms. These bacteria are usually coliforms, which are typically found in the colon and include predominantly Gram negative aerobic and anaerobic species that ferment carbohydrates producing gas.[1]

Evidence suggests that abdominal pain, bloating, gas, distension, flatulence and diarrhoea are the most common symptoms and prevalent in more than two thirds of patients. In severe cases, nutritional deficiencies including vitamin B12, vitamin D and iron deficiencies can occur, but in most cases these are subtle or undetectable.[1]

There is no common agreement concerning the choice, dosing and duration of antibiotic therapy. Broad spectrum antibiotics which affect enteric aerobes and anaerobes are used. There are no controlled trials to guide the duration of treatment or management of recurrent SIBO and recommendations are commonly based on clinical experience.

The goals of treatment for SIBO are:

- Correct the underlying cause

- Provide nutritional support if necessary
- Treat the overgrowth

Treatment aimed at correcting the underlying cause includes dietary, surgical and medical therapies. Strict adherence to diet may lead to symptom improvement in patients with coeliac disease and bacterial overgrowth. Surgical revision of altered small bowel anatomy maybe beneficial in patients with SIBO secondary to small bowel diverticulosis, fistulas or strictures. Medications should be reviewed to determine if they are playing a role in the development of symptoms.

Antibiotics reduce or eliminate the bacterial overload and reverse the mucosal inflammation associated with overgrowth and malabsorption. A variety of antibiotics have been used in the treatment of SIBO, most with little supporting evidence. Ideally, antibiotic therapy would be based on bacterial culture and sensitivity data. However, this approach is impractical in the clinical setting.[2]

Until the end of 1990s, only systemic antimicrobials were used, whose adverse events (AEs) and detrimental effects on gut microbiota are now well known. Poorly absorbed antibiotics, unlike systemic ones, allow localised targeting of enteric pathogens and are associated with minimal risk of systemic toxicity or AEs. The restricted use of drugs only for enteric-infections should also reduce the development of widespread resistance, especially of enterobacteria, a major limitation of current antibiotics.

The optimal duration of antibiotic therapy is not known and most trials employed a 7-10 day course. Some studies have incorporated cyclic antibiotic regimens e.g. 10 days / month, although there is no data to support this approach as being more effective than a single course.[3]

Rifaximin is a product of synthesis experiments designed to modify the parent compound, rifamycin, in order to achieve low gastrointestinal absorption while retaining good antibacterial activity. Both experimental and clinical pharmacology have clearly shown that this compound is a poorly absorbed antibiotic with a broad spectrum of antibacterial activity, covering Gram-positive and Gram-negative microorganism, both aerobes and anaerobes.[12]

Summary of evidence

Summary of efficacy data in proposed use:

Rifaximin vs chlortetracycline in the short term treatment of small intestinal bacterial overgrowth[4]

This was a small, randomised, double-blind controlled trial in order to compare the efficacy and tolerability of rifaximin to those of tetracycline, which at the time (2000) was considered the first-choice drug.

In 21 patients affected by small intestinal bacterial overgrowth, fasting, peak and total H_2 excretion after ingestion of 50 g glucose and severity of symptoms were evaluated before and after a 7-day course of rifaximin, 1200 mg/day (400 mg three times a day), patient number =10, or chlortetracycline, 1 g/day (333 mg three times a day), patient number = 11.

Fasting, peak and total H_2 excretion decreased significantly in the group of patients treated with rifaximin (11.2 ±12.9 to 3.1 ±3.6ppm, 51.2 ± 55.3 to 18.9 ± 20.0ppm and 372 ± 354 to 118 ± 118ppm for fasting excretion, peak excretion and total excretion respectively) whereas chlortetracycline did not modify these parameters. The H_2 breath test normalized in 70% of patients after rifaximin and in 27% of patients after chlortetracycline.

On entry to the study and 3 days after the end of treatment, a global symptom score was calculated for each patient by the sum of each symptom score (intensity of abdominal pain, bloating, diarrhoea, anorexia, lassitude and borborygmi). The improvement in symptoms was significantly higher in patients treated with rifaximin (1.1 vs 0.2, $P<0.05$).

Conclusion: Rifaximin is a promising, easily-handled and safe drug for the short-term treatment of small intestinal bacterial overgrowth

Dose of rifaximin used = 400mg three times daily for 7 days.

Absorbable vs non-absorbable antibiotics in the treatment of small intestine bacterial overgrowth in patients with blind loop syndrome[5]

The aim of this study was to evaluate the efficacy of absorbable vs. non-absorbable antibiotics in patients with blind loop syndrome.

A group of small intestine bacterial overgrowth patients (n=21) with total gastrectomy(n=6) or gastrojejunostomy (n=15) and blind loop underwent a therapeutic trial comparing rifaximin to metronidazole. Seven patients underwent a course of rifaximin (400mg three times a day for 7 days) followed by a course of metronidazole (250mg twice daily for 7 days) on recurrence of symptoms. To compare the effect of the drugs, another two groups of patients underwent two consecutive courses of rifaximin or metronidazole. Hydrogen breath test after glucose administration and symptom severity measurement were performed.

Before and the day after the conclusion of each course of treatment, the H_2 glucose breath test was performed. Both drugs reduced breath H_2 excretion but a much better improvement was achieved after metronidazole.

Before and after each course of treatment, presence and severity of abdominal pain, bloating, flatulence and diarrhoea were evaluated. Symptom improvement was higher after metronidazole.

Conclusion: Metronidazole is more effective than rifaximin for the treatment of small intestine bacterial overgrowth associated with the presence of a blind loop i.e. in a group of patients with blind loop a non-absorbable antibiotic, rifaximin, showed a lower therapeutic efficacy than an absorbable antibiotic, metronidazole.

Dose of rifaximin used = 400mg three times daily for 7 days

Rifaximin dose finding study for the treatment of small intestinal bacterial overgrowth[6]

A prospective, randomised, parallel-group, dose-finding study assessed the efficacy, safety and tolerability of different doses of rifaximin for SIBO eradication. Eligible patients were randomly assigned to receive a 7-day course of rifaximin 600 mg, 800 mg or 1200 mg daily. The study included adult patients (>18 years) with positivity to Glucose Breath Test (GBT)[a] for various gastrointestinal symptoms, the most common being bloating, abdominal discomfort and diarrhoea. Exclusion criteria were use of antimicrobial agents within the previous 3 months, hypersensitivity to rifamycin- and/or tetracycline-like antibiotics, pregnancy or breast-feeding, evidence of major concomitant diseases (including tumours, hepatic and/or renal insufficiency). Total blood cell count, liver and kidney function were evaluated at enrolment and 3 days after the end of treatment. GBT was reassessed 1 month after the end of therapy. The primary endpoint was GBT normalisation rates; secondary endpoints were compliance and incidence of side effects using the three different rifaximin regimens.

A total of 90 consecutive patients diagnosed with SIBO were enrolled and randomised by a 1:1:1 fashion to the three therapy regimens. Across groups, the mean age ranged from 31 ± 14 to 34 ± 12 years and the percentage of men enrolled ranged from 23% to 30%. Compliance was higher than 95% in all groups. No drop-outs were reported. In both the Intention-To-Treat (ITT) and Per-Protocol (PP) analyses, SIBO eradication was significantly higher in the 1200 mg group (60%) compared with patients in the 600 mg (17%; $p< 0.001$) or 800 mg groups (27%; $p<0.01$); no significant differences were observed in the 600 mg and 800 mg groups in terms of GBT normalization rate. In terms of safety, no abnormalities in total blood cell count, liver or kidney function were observed 3 days after the end of treatment. The occurrence of adverse events (AEs) during the study was similar in the 3 groups (3, 4, 4, respectively); the most common AEs were weakness (n = 5), headache (n=2) and constipation (n = 2).

Dose of rifaximin used = 600-1200mg daily

High dosage rifaximin for the treatment of small intestinal bacterial overgrowth[7]

[a] GBT positivity defined as the presence of an increase in H_2 excretion >12 parts per million (p.p.m.) over the baseline value within 2h from ingestion of the glucose solution

The aim of this prospective, parallel-group, randomised trial was to assess efficacy, safety and tolerability of rifaximin 1600 mg compared to 1200 mg/day for small intestinal bacterial overgrowth treatment.

Eighty consecutive small intestinal bacterial overgrowth patients were enrolled. Diagnosis of small intestinal bacterial overgrowth based on the clinical history and positivity to H_2/CH_4 glucose breath test. Patients were randomized in two 7-day treatment groups: rifaximin 1600mg (group 1); rifaximin 1200mg (group 2). Glucose breath test was reassessed 1 month after. Compliance and side-effect incidence were also evaluated.

One drop-out was observed in group 1 and two in group 2. Glucose breath test normalization rate was significantly higher in group 1 compared to group 2 both in intention-to-treat (80% vs. 58%; $P < 0.05$) and per protocol analysis (82% vs. 61%; $P < 0.05$). No significant differences in patient compliance and incidence of side effects were found between groups.

Conclusion: Rifaximin 1600 mg/day showed a significantly higher efficacy for small intestinal bacterial overgrowth treatment compared to 1200 mg with similar compliance and side-effect profile.

Doses of rifaximin used = 1200mg or 1600mg (split into three doses / day)

Efficacy of rifaximin, a nonabsorbed oral antibiotic, in the treatment of small bacterial overgrowth[8]

A prospective, open-label study investigated the efficacy and safety of rifaximin 800 mg daily for 28 days in relieving symptoms and normalising GBT in patients with SIBO.

Enrolled patients underwent GBT for gastrointestinal symptoms related to different diagnoses. Consecutive adult patients (>18 years) with positivity to GBT were included. Exclusion criteria were use of antimicrobial agents within previous 4 weeks and pregnancy or breast-feeding. The primary objective was symptom relief or improvement; the secondary objective was GBT normalisation rates. Symptom assessment and GBT were performed before and after 4 weeks of therapy. A global symptom score was calculated by the sum of each symptom score

A total of 20 consecutive SIBO patients (mean age 47.8 years [range 19 to 85]; 4 males) presenting with diarrhoea (n=14, 70%), bloating plus gas (n=3, 15%) and/or constipation (n=3, 15%) as the dominant symptom were enrolled and given rifaximin treatment. After treatment, improvement of global symptom score > 50% was reported by 75% of patients (15/20), of whom 12/14 patients with diarrhoea and 3/6 of patients with bloating plus gas and/or constipation. GBT eradication was achieved by 50% of patients (6 in the diarrhoea and 4 in the other group). No AEs were reported.

Dose of rifaximin used = 800mg daily

Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole[9]

A prospective, randomised, controlled study, evaluated the efficacy and safety of rifaximin 1200 mg daily versus metronidazole 750 mg daily for 7 days in patients with SIBO. Enrolled patients underwent a GBT for various chronic gastrointestinal symptoms, including bloating, abdominal pain, flatulence and diarrhoea within at least the previous 6 months. Consecutive adult patients (>18 years of age) with positivity to GBT were included. Exclusion criteria were use of antimicrobial agents within the previous 3 months, hypersensitivity to antibiotics, pregnancy or breast-feeding, tumours, hepatic and/or renal insufficiency. GBT was reassessed 1 month after the end of therapy. The primary endpoint was GBT normalisation rates; secondary endpoints were compliance and incidence of side effects in the two groups.

A total of 142 patients were enrolled and randomly assigned to receive rifaximin (n=71) or metronidazole (n=71) for 7 days. Patients' demographic and clinical characteristics were similar between the groups: median age: 34.5 years (range 25-46 years); 37.5% males; 42% irritable bowel syndrome (IBS). 135 out of 141 patients completed the study therapeutic regimens; 5 drop-outs occurred in the metronidazole group (one due to inability to attend study appointments, and 4 due to AEs) and 1 drop-out in the rifaximin group (due to inability to attend study appointments). In the ITT analysis, GBT normalisation was achieved in 63.4% (45/71) versus 43.7% (31/71) of patients in the rifaximin compared to the metronidazole group ($P<0.05$; OR: 1.50; 95% CI: 1.14-4.38). No statistically significant differences were found in the PP analysis. One drop-out was recorded in the rifaximin group (unable to attend) compared to 5 drop-outs in the metronidazole group, 4 of which were due to AEs. The overall incidence of AEs was 15.5% (22/142), and was significantly higher in

the metronidazole compared to the rifaximin arm: 22.5% (16/71) versus 8.5% (6/71; OR: 1.59; 95% CI: 1.15-8.61). The AEs seen in the metronidazole group included nausea/vomiting, taste disturbance, diarrhoea, bloating, abdominal pain, loss of appetite, skin rush and constipation. The 6 AEs observed in the rifaximin group were constipation, bloating and nausea/vomiting, all of which were mild.

Dose of rifaximin used = 1200mg daily

Meta – analysis: antibiotic therapy for small intestinal bacterial overgrowth[10]

This was a systematic review and meta-analysis comparing the clinical effectiveness of antibiotic therapies in the treatment of symptomatic patients with documented SIBO.

Four databases (PubMed, Web of Science, Embase, Cochrane) were searched to identify clinical trials comparing effectiveness of: (i) different antibiotics, (ii) different doses of the same antibiotic and (iii) antibiotics compared with placebo. Data were independently extracted according to predetermined inclusion and exclusion criteria. Study quality was independently assessed. The primary outcome was normalisation of post-treatment breath testing. The secondary outcome was post-treatment clinical response.

Of 1356 articles identified, 10 met inclusion criteria. Due to the small number of studies that were appropriate for meta-analysis, sensitivity analyses were not possible.

Most studies were open-label, randomised trials. Five studies included adults with symptoms of SIBO, 2 included patients with Crohn's disease, 1 included patients with formally diagnosed irritable bowel syndrome, 1 included subjects with celiac disease, and 1 included children with chronic abdominal pain. The mean sample size per study was 63 subjects (range 14 to 142), and mean number per treatment arm was 30 (range 7 to 71).

Only two antibiotics were evaluated in more than one study. Pre-enrolment restrictions varied. Testing for eradication was performed between 3 and 30 days after completing the treatment course.

Rifaximin was the most commonly studied antibiotic (eight studies) with overall breath test normalisation rate of 49.5% (95% confidence interval, CI 44.0-55.1) (44.0%-55.1%) then (46.7%-55.5%), then (4.6%-17.8%). The rate of breath test normalization was determined for each study. Because numerous different antibiotic comparisons were studied, we calculated the pooled rate of breath test normalization for different antibiotics. For rifaximin, this was calculated across varying doses: low-dose (600–800 mg per day), medium-dose (1200 mg per day), and high-dose (1600–1650 mg per day). Data from individual studies were pooled and weighted by sample size. The mean rate of breath test normalization was calculated along with the 95% confidence interval.

Metronidazole was used in two studies, with a combined breath test normalization rate of 51.2% (95% CI 40.1–62.1). Ciprofloxacin had the highest rate of breath test normalization (100%, 95% CI 76.8–100.0), but this was based on a single study with only 14 subjects in each treatment arm. For all antibiotic regimens combined, breath test normalization occurred in 51.1% (95% CI 46.7–5.5). Conversely, only 9.8% (95% CI 4.6–17.8) of placebo-treated subjects among 4 studies had breath test normalization.

Antibiotic efficacy varied by antibiotic regimen and dose. Antibiotics were more effective than placebo, with a combined breath test normalisation rate of 51.1% (95% CI 46.7-55.5) for antibiotics compared with 9.8% (95% CI 4.6-17.8) for placebo. Meta-analysis of four studies favoured antibiotics over placebo for breath test normalisation with an odds ratio of 2.55 (95% CI 1.29-5.04). Clinical response was heterogeneously evaluated among six studies, but tended to correlate with breath test normalisation.

Conclusion: Antibiotics appear to be more effective than placebo for breath test normalisation in patients with symptoms attributable to SIBO, and breath test normalisation may correlate with clinical response. Studies were limited by modest quality, small sample size and heterogeneous design. Additional higher quality clinical trials of SIBO therapy are warranted

Doses of rifaximin used from 600mg – 1650mg / day

Rifaximin for small intestinal bacterial overgrowth in patients without irritable bowel syndrome[11]

A prospective, open-label study assessed the efficacy and safety of rifaximin 1200 mg daily for 10 days for treatment of SIBO in non-IBS patients.

Enrolled patients underwent lactulose-H_2 breath testing (LBT) for gastrointestinal symptoms, such as bloating and flatulence. Consecutive adult patients (>18 years) with positivity to LBT[b] were included. Exclusion criteria were chronic recurrent abdominal pain or fulfilment of the Rome III criteria for IBS; use of antimicrobial agents during the previous 6 months; current use of laxatives or promotility agents; intake of bowel preparation for colonoscopy or capsule endoscopy within 30 days; presence of pancreatic exocrine or renal insufficiency; active malignancy and hepatic failure; pregnancy, breast-feeding or pre-menopause with no use of contraceptive; and hypersensitivity to the antibiotics belonging to rifamycin and/or tetracycline group. The primary objective was LBT normalisation rates. Safety was also assessed. LBT was reassessed 2 weeks after end of therapy.

Of the 53 non-IBS patients enrolled, 22 patients were found positive to LBT and received rifaximin treatment, however, only 19 patients (age 56.5 ± 17.6 years; 36.8% males) were included in the final analysis set, as 3 did not attend the follow-up visit. LBT normalisation was observed in 42.1% of patients (8/19); patients' demographic and clinical characteristics were similar between rifaximin responders and non-responders. Compared to baseline, the mean peak hydrogen excretion was not significantly reduced with rifaximin treatment (13.7 ± 2.8 vs 10.3 ± 7.3 ppm, p=0.06). No AEs were reported.

Dose of rifaximin used = 1200mg daily.

Systematic review with meta – analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth[12]

This was a systematic review and meta-analysis to summarise evidence about the efficacy and safety of rifaximin to eradicate SIBO in adult patients.

MEDLINE, EMBASE, CCRCT, Scopus and Web of Science were searched from inception to March 16, 2015 for RCTs and observational studies. Furthermore, abstract books of major European, American and Asian gastroenterological meetings were also examined.

Thirty-two studies involving 1331 patients were included (these included non – randomised trials). The overall eradication rate according to intention-to-treat analysis was 70.8% (95% CI: 61.4-78.2; I2 = 89.4%) and to per protocol analysis 72.9% (95% CI: 65.5-79.8; I2 = 87.5%). Meta-regression identified three covariates (drug dose, study design and co-therapy) independently associated with an increased eradication rate. The overall rate of adverse events was 4.6% (95% CI: 2.3-7.5; I2 = 63.6%). In the subset of studies (n= 10) allowing the analysis, improvement or resolution of symptoms in patients with eradicated SIBO was found to be 67.7% (95% CI: 44.7-86.9; I2 = 91.3%).

Doses of rifaximin used ranged from 600 mg/day to 1600 mg/day, and duration of treatment ranged from 5 to 28 days

Conclusion: Rifaximin treatment seems to be effective and safe for the treatment of SIBO. However, the quality of the available studies is generally poor. Well-designed RCTs are needed to substantiate these findings and to establish the optimal regimen.

Doses of rifaximin used from 600mg – 1600mg / day

Summary of safety data:

Undesirable effects for Rifaximin 550mg (Targaxan)

Adverse reactions listed by MedDRA system organ class and frequency category.

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Infections and infestations		Clostridial infection, urinary tract infection, candidiasis	Pneumonia, cellulitis, upper respiratory tract infections, rhinitis	

[b] LBT positivity defined as an increase >10 ppm over the baseline level in H_2 excretion

Blood and lymphatic system disorders		Anaemia		Thrombocytopenia
Immune system disorders				Anaphylactic reactions, angioedemas, hypersensitivity
Metabolism and nutrition disorders		Anorexia, hyperkalaemia	Dehydration	
Psychiatric disorders	Depression	Confusional state, anxiety, hypersomnia, insomnia		
Nervous system disorders	Dizziness, headache	Balance disorders, amnesia, convulsion, attention disorders, hypoesthesia, memory impairment		
Vascular disorders		Hot flush	Hypertension, hypotension	Presyncope, syncope
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Pleural effusion	Chronic obstructive pulmonary disease	
Gastrointestinal disorders	Abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites	Abdominal pain, oesophageal varices haemorrhage, dry mouth, stomach discomfort	Constipation	
Hepatobiliary disorders				Liver function tests abnormalities
Skin and subcutaneous tissue disorders	Rashes, pruritus			Dermatitis, eczema
Musculoskeletal and connective tissue disorders	Muscle spasms, arthralgia	Myalgia	Back pain	
Renal and urinary disorders		Dysuria, pollakiuria	Proteinuria,	
General disorders and administration site conditions	Oedema peripheral	Oedema, pyrexia	Asthenia	
Investigations				International normalised ratio abnormalities
Injury, poisoning and procedural complications		Fall	Contusions, procedural pain	

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (frequency cannot be estimated from the available data).

Strengths and limitations of the evidence:

Strengths:

- Drug appears to be effective in a high proportion of treated patients
- Drug covers gram-positive and gram-negative organisms, both aerobes and anaerobes
- Adverse events are minimal; drug has low gastrointestinal absorption
- Provides an option in patients unable to tolerate systemic antibacterials due to systemic adverse events

Limitations:

- Proposed use is for an unlicensed indication
- Small clinical trials
- Lack of comparator trials
- Lack of blinding and allocation concealment in all trials
- Non-standardised outcome measures

Summary of evidence on cost effectiveness:

Drug Tariff Prices (March 2020)[13]

- Rifaximin 200mg tablet (Xifaxanta) £15.15 for 9 tablets
- Rifaximin 550mg tablet (Targaxan) £259.23 for 56 tablets
- Co- amoxiclav 625mg tablets £2.50 for 21 tablets
- Metronidazole 400 mg tablets £3.97 for 21 tablets
- Cefalexin 500 mg capsules £2.15 for 21 capsules
- Cefalexin 500mg tablets £2.86 for 21 tablets
- Co-trimoxazole 960mg tablets £23.48 for 100 tablets

For 7day course at maximum dose

- Rifaximin 1650mg / day i.e. 550mg three times daily, 21 tablets = £97.21
- Rifaximin 1600mg / day i.e. 8 x 200mg tablets, 56 tablets = £94.27
- Co-amoxiclav 625mg twice daily, 14 tablets = £1.67
- Metronidazole 400mg three times daily, 21 tablets = £3.97 PLUS Cefalexin 500mg three times daily, 21 capsules / tablets = £2.15 / £2.86. Total cost = £6.12 / £6.83
- Metronidazole 400mg three times daily, 21 tablets = £3.97 PLUS Co-trimoxazole 960mg twice a day, 14 tablets = £3.29. Total cost = £7.26

Prescribing and risk management issues:

N/A

Commissioning considerations:

Productivity, service delivery, implementation:

Potential for reduced primary care appointments for treatment & reduced hospital outpatient follow-up as symptoms will be well controlled.

Anticipated patient numbers and net budget impact:

Numbers of patients affected and hence budgetary impact to be determined – unclear at present.

Innovation, need, equity:

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