

# Pouchitis: rifaximin

## Evidence summary

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[nice.org.uk/guidance/esuom30](https://www.nice.org.uk/guidance/esuom30)

## Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

One small randomised controlled trial (RCT) and 2 small non-comparative observational studies provide limited evidence that rifaximin alone or in combination with ciprofloxacin can improve symptoms or induce remission in people with pouchitis that is refractory to other antibiotics. One small non-comparative observational study provides limited evidence that rifaximin monotherapy can help maintain remission in people with chronic pouchitis that has responded to other antibiotics.

**Regulatory status:** off label.

The topic was prioritised because there was noted to be a high volume of requests from the NHS for information about this use of rifaximin, variation in clinical practice and uncertainty about the balance of risks and benefits when rifaximin is used for pouchitis.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>• Rifaximin 400 mg 3 times daily for 4 weeks induced clinical remission in 2 out of 8 people compared with 0 out of 9 people given placebo. No patients obtained complete remission (1 RCT).</li> <li>• 16 out of 18 and 7 out of 8 people with refractory chronic pouchitis obtained complete remission or improvement after treatment with rifaximin 1 g twice daily plus ciprofloxacin 500 mg twice daily for 2 weeks (2 non-comparative observational studies).</li> <li>• 33 out of 51 people with chronic pouchitis, who were treated with rifaximin 200–1800 mg daily after induction of remission with other antibiotics, stayed in remission for 3 months or longer (1 non-comparative observational study).</li> </ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Rifaximin is contraindicated in people with intestinal obstruction.</li> <li>• <i>Clostridium difficile</i>-associated diarrhoea has been reported with the use of rifaximin. The potential association of rifaximin treatment with <i>Clostridium difficile</i>-associated diarrhoea and pseudomembranous colitis cannot be ruled out.</li> </ul>
<p><b>Patient factors</b></p> <ul style="list-style-type: none"> <li>• Common adverse events associated with rifaximin (occurring in more than 1 in 100 people) include dizziness and headaches, pruritus and rashes, and abdominal symptoms of pain, distension, nausea and vomiting, diarrhoea or constipation. Other adverse effects affecting most systems of the body have been observed less frequently.</li> </ul>	<p><b>Resource implications</b></p> <ul style="list-style-type: none"> <li>• Rifaximin costs £15.15 for 9×200 mg tablets and £259.23 for 56×550 mg tablets.</li> <li>• A course of rifaximin 400 mg 3 times daily for 4 weeks costs £282.80.</li> <li>• A course of rifaximin 1 g twice daily plus ciprofloxacin 500 mg twice daily for 2 weeks costs £238.75.</li> <li>• Three months' prophylaxis with rifaximin 200–1800 mg daily costs £141.40 to £1272.60.</li> </ul>

## Key points

Rifaximin is an oral rifamycin antibiotic that is poorly absorbed by the gastrointestinal system. It has wide antibacterial action against most Gram-negative and Gram-positive aerobic and anaerobic bacteria associated with gastrointestinal infection.

Rifaximin is available as 2 licensed products, both of which are licensed for use in people aged 18 years and older:

- [Targaxan 550 mg film-coated tablets](#) for the reduction in recurrence of episodes of overt hepatic encephalopathy.
- [Xifaxanta 200 mg film-coated tablets](#) for the treatment of travellers' diarrhoea.

Rifaximin is not licensed for treating refractory pouchitis or maintaining remission in people with chronic pouchitis and its use for these indications is off-label.

Pouchitis is defined in the European Crohn's and Colitis Organisation (ECCO) publication [European evidence-based consensus on the management of ulcerative colitis: special situations](#) as non-specific inflammation of the ileal reservoir (pouch). It affects up to 50% of people 10 years after ileal pouch-anal anastomosis (IPAA) for ulcerative colitis, although the cumulative incidence of pouchitis in people with an IPAA for familial adenomatous polyposis is much lower. Symptoms of pouchitis include pelvic discomfort, abdominal cramps and urgency, tenesmus, increased stool frequency and liquidity, and faecal incontinence. There may also be rectal bleeding, fever or other systemic symptoms. The Pouchitis Disease Activity Index (PDAI) incorporates symptoms, endoscopy and histological findings. The range of possible scores is 0–18, with a score of 7 or more indicating pouchitis and higher scores indicating worse disease.

The [ECCO consensus document](#) states that single antibiotic treatment with a 2-week course of either metronidazole or ciprofloxacin is the first-line treatment of choice for acute pouchitis, and combination therapy may also be used. Up to 10% of people develop chronic pouchitis with symptoms lasting longer than 4 weeks. Chronic pouchitis is often treated with combined antibiotic treatment, and other possible treatments include oral or topical budesonide or infliximab. None of these drugs is licensed specifically for treating pouchitis. The consensus document states that a probiotic food supplement can be effective for maintaining antibiotic-induced remission and for preventing pouchitis within the first year after surgery. Surgery can be considered as a last resort for people whose pouchitis does not respond to other treatment options.

Limited research has examined rifaximin for the treatment of pouchitis. [Isaacs et al. \(2007\)](#) reported a double-blind placebo-controlled RCT examining 4 weeks' treatment with rifaximin (400 mg 3 times daily) for acute or chronic active pouchitis (n=18). Among the 17 participants in the study who had at least 1 post-baseline efficacy evaluation, all of those in the rifaximin group (8/8) and nearly all of those in the placebo group (8/9) had received previous antibiotic treatment. Of these 17 people, 2 of the 8 people in the rifaximin group and no one in the placebo group obtained clinical remission at the end of the 4 weeks' treatment (PDAI score of less than 7 points and a decrease from baseline PDAI score of 3 points). This was not statistically significant (p=0.211) but the study was underpowered. No one in the study obtained complete remission (PDAI score of 0).

Two small, non-comparative observational studies reported rates of remission (PDAI score of 0) or improvement (PDAI score reduction of at least 3 points) after treatment with rifaximin 1 g twice daily in combination with ciprofloxacin 500 mg twice daily for 2 weeks for chronic pouchitis that was not responsive to at least 4 weeks' treatment with other antibiotics (usually metronidazole or ciprofloxacin monotherapy). The study by [Gionchetti et al. \(1999\)](#) included 18 adults, of whom 6 obtained remission with treatment and 10 had an improvement in their condition. The study by [Abdelrazeq et al. \(2005\)](#) included 8 adults: after treatment, 5 of them remained in remission for at least 6 months and a further 2 had an improvement in their condition.

[Shen et al. \(2008\)](#) reported experience with rifaximin for maintenance treatment after antibiotic-induced remission in 51 people with antibiotic-dependent pouchitis, at a daily dose of 200 mg up to a maximum 1800 mg for up to 24 months. At 3 months, 33 were still in remission. Four of these people later relapsed at between 3 and 12 months. Antibiotic induction regimen, symptom score after induction and rifaximin dose were not predictive of maintaining remission.

In the RCT by [Isaacs et al. \(2007\)](#), adverse events were experienced by 6 of the 8 people in the rifaximin group and 5 of the 10 people in the placebo group (statistical significance not reported). One case of each of the following adverse events was experienced by people in the rifaximin group: flatulence, frequent bowel movements, proctalgia, rectal haemorrhage, thirst, candida, upper respiratory tract infection, cluster headache and headache. In the study by [Shen et al. \(2008\)](#), 1 person discontinued rifaximin because of a transient facial rash. No adverse events were reported in the 2 other non-comparative observational studies.

Rifaximin is contraindicated in people with intestinal obstruction. The summaries of product characteristics for [Targaxan](#) and [Xifaxanta](#) state that *Clostridium difficile*-associated diarrhoea has been reported with the use of rifaximin. The potential association of rifaximin treatment with *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis cannot be ruled out. The effects on gut flora may also lead to reduced effectiveness of oral contraceptives, and additional

contraceptive precautions are recommended. Despite limited systemic absorption, there may also be reddish discolouration of the urine.

Common adverse events associated with rifaximin (occurring in more than 1 in 100 people) include dizziness and headaches, pruritus and rashes, and abdominal symptoms of pain, distension, nausea and vomiting, diarrhoea or constipation. Other adverse events affecting most systems of the body have been observed less frequently.

The 4 published studies provide limited evidence about rifaximin in the care of people with pouchitis. Large, double-blind RCTs are needed to better assess the safety and efficacy of rifaximin for the treatment of acute or chronic pouchitis and pouchitis refractory to other antibiotics, or for maintenance of antibiotic-induced remission.

#### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Overview for healthcare professionals

### *Regulatory status of rifaximin*

Rifaximin is available as 2 licensed products, both of which are licensed for use in people aged 18 years and older:

- Targaxan 550 mg film-coated tablets for the reduction in recurrence of episodes of overt hepatic encephalopathy.
- Xifaxanta 200 mg film-coated tablets for the treatment of travellers' diarrhoea.

Rifaximin is not licensed for the treatment of pouchitis and its use for this indication is off-label. In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using rifaximin outside its authorised indications.

## Evidence statements

- There is limited published research examining rifaximin for the treatment of pouchitis, including only 1 small randomised controlled trial (RCT).
- [Isaacs et al. \(2007\)](#) (n=18) reported a double-blind placebo-controlled RCT examining 4 weeks' treatment with rifaximin (400 mg 3 times daily) for active pouchitis (acute or chronic). Among the 17 people who had at least 1 post-baseline efficacy evaluation, all of those in the rifaximin group (8/8) and nearly all of those in the placebo group (8/9) had received previous antibiotic treatment. Of these 17 people, 2 of the 8 people in the rifaximin group and no one in the placebo group obtained clinical remission at 4 weeks (Pouchitis Disease Activity Index [PDAI] score of less than 7 points and a decrease from baseline PDAI score of 3 points). This was not statistically significant (p=0.211) but the study was underpowered. No one in the study obtained complete remission (PDAI score of 0).
- Two small, non-comparative observational studies reported rates of remission (PDAI score of 0) or improvement (PDAI score reduction of at least 3 points) after treatment with rifaximin 1 g twice daily in combination with ciprofloxacin 500 mg twice daily for 2 weeks for chronic pouchitis that was not responsive to at least 4 weeks' treatment with other antibiotics (usually metronidazole or ciprofloxacin monotherapy). The study by [Gionchetti et al. \(1999\)](#) included 18 adults, of whom 6 obtained remission with treatment and 10 had an improvement in their condition. The study by [Abdelrazeq et al. \(2005\)](#) included 8 adults: after treatment, 5 of them remained in remission for at least 6 months and a further 2 had an improvement in their condition.
- [Shen et al. \(2008\)](#) reported experience with rifaximin for maintenance treatment after antibiotic-induced remission in 51 people with antibiotic-dependent pouchitis, at a daily dose of 200 mg up to a maximum 1800 mg for up to 24 months. At 3 months, 33 were still in remission. Four of these people later relapsed at between 3 and 12 months. Antibiotic induction regimen, symptom score after induction and rifaximin dose were not predictive of maintaining remission.
- In the RCT by [Isaacs et al. \(2007\)](#), adverse events were experienced by 6 of the 8 people in the rifaximin group and 5 of the 10 people in the placebo group (statistical significance not reported). One case of each of the following adverse events was experienced by people in the

rifaximin group: flatulence, frequent bowel movements, proctalgia, rectal haemorrhage, thirst, candida, upper respiratory tract infection, cluster headache and headache. In the study by [Shen et al. \(2008\)](#), 1 person discontinued rifaximin because of a transient facial rash. No adverse events were reported in the 2 other non-comparative observational studies.

- Rifaximin is contraindicated in people with intestinal obstruction. The summaries of product characteristics for [Targaxan](#) and [Xifaxanta](#) state that *Clostridium difficile*-associated diarrhoea has been reported with the use of rifaximin. The potential association of rifaximin treatment with *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis cannot be ruled out. The effects on gut flora may also lead to reduced effectiveness of oral contraceptives, and additional contraceptive precautions are recommended. Despite limited systemic absorption, there may also be reddish discolouration of the urine.
- Common adverse events associated with rifaximin (occurring in more than 1 in 100 people) include dizziness and headaches, pruritus and rashes, and abdominal symptoms of pain, distension, nausea and vomiting, diarrhoea or constipation. Other adverse events affecting most systems of the body have been observed less frequently.
- The 4 published studies provide limited evidence about rifaximin in the care of people with pouchitis. Large, double-blind RCTs are needed to better assess the safety and efficacy of rifaximin for the treatment of acute or chronic pouchitis and pouchitis refractory to other antibiotics, or for maintenance of antibiotic-induced remission.

## Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

## Efficacy

Limited research has examined rifaximin for the treatment of pouchitis. [Isaacs et al. \(2007\)](#) reported a double-blind placebo-controlled RCT examining 4 weeks' treatment with rifaximin (400 mg 3 times daily) for acute or chronic active pouchitis (n=18). Among the 17 people who had at least 1 post-baseline efficacy evaluation, all of those in the rifaximin group (8/8) and nearly all (8/9) of those in the placebo group had received previous antibiotic treatment. Of these 17 people, 2 of the 8 people in the rifaximin group and no one in the placebo group obtained clinical remission at the end of the 4 weeks' treatment (PDAI score of less than 7 points and a decrease from baseline PDAI score of 3 points). This was not statistically significant (p=0.211) but the study was underpowered. No one in the study obtained complete remission (PDAI score of 0).

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[Shen et al. \(2008\)](#) reported experience with rifaximin for maintenance treatment after antibiotic-induced remission in 51 people with antibiotic-dependent pouchitis, at a daily dose of 200 mg up to a maximum 1800 mg for up to 24 months. At 3 months, 33 were still in remission. Four of these people later relapsed at between 3 and 12 months. Antibiotic induction regimen, symptom score after induction and rifaximin dose were not predictive of maintaining remission.

## Safety

In the RCT by [Isaacs et al. \(2007\)](#), adverse events were experienced by 6 of the 8 people in the rifaximin group and 5 of the 10 people in the placebo group (statistical significance not reported). One case of each of the following adverse events was experienced by people in the rifaximin group: flatulence, frequent bowel movements, proctalgia, rectal haemorrhage, thirst, candida, upper respiratory tract infection, cluster headache and headache. In the study by [Shen et al. \(2008\)](#), 1 person discontinued rifaximin because of a transient facial rash. No adverse events were reported in the 2 other non-comparative observational studies.

Rifaximin is contraindicated in people with intestinal obstruction. The summaries of product characteristics for [Targaxan](#) and [Xifaxanta](#) state that *Clostridium difficile*-associated diarrhoea has been reported with the use of rifaximin. The potential association of rifaximin treatment with *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis cannot be ruled out. The effects on gut flora may also lead to reduced effectiveness of oral contraceptives, and additional contraceptive precautions are recommended. Despite limited systemic absorption, there may also be reddish discolouration of the urine.

Common adverse events associated with rifaximin (occurring in more than 1 in 100 people) include dizziness and headaches, pruritus and rashes, and abdominal symptoms of pain, distension, nausea and vomiting, diarrhoea or constipation. Other adverse events affecting most systems of the body have been observed less frequently.



## Cost

The current NHS cost of rifaximin (excluding VAT; costs taken from [Drug Tariff](#), February 2014) is:

- £15.15 for 9×200 mg tablets (Xifaxanta)
- £259.23 for 56×550 mg tablets (Targaxan).

## Relevance to NICE guidance programmes

This use of rifaximin is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued clinical guidelines on conditions that may be associated with surgical construction of an ileoanal pouch:

- [Ulcerative colitis: management in adults, children and young people](#) (NICE clinical guideline 166)
- [Colorectal cancer: the diagnosis and management of colorectal cancer](#) (NICE clinical guideline 131).

NICE guidance is in development for a licensed indication for rifaximin:

- [Rifaximin for the maintenance treatment of hepatic encephalopathy](#) (NICE technology appraisal guidance, publication date to be confirmed).

## Intervention and alternatives

Rifaximin is an oral rifamycin antibiotic that is poorly absorbed by the gastrointestinal system (less than 1%). It has wide antibacterial action against most Gram-positive and Gram-negative aerobic and anaerobic bacteria associated with gastrointestinal infection.

Two licensed products are available, with marketing authorisation held by Norgine:

- [Targaxan 550 mg film-coated tablets](#) are licensed for the reduction in recurrence of episodes of overt hepatic encephalopathy in people aged 18 years and older at a dose of 550 mg twice daily. The summary of product characteristics notes that clinical benefit in this indication was established from a controlled study in which participants in the study were treated for 6 months.

- [Xifaxanta 200 mg film-coated tablets](#) are licensed for treating travellers' diarrhoea that is not associated with fever, bloody diarrhoea, 8 or more unformed stools in the previous 24 hours or occult blood or leucocytes in the stool. For this indication, rifaximin is given at a dose of 200 mg every 8 hours for a total of 9 doses. It is not recommended in people aged younger than 18 years.

Rifaximin is not licensed for the treatment of pouchitis and its use for this indication is off-label.

## Condition

Management of some colorectal diseases may sometimes necessitate removal of the entire colon and rectum (proctocolectomy). This procedure is most commonly performed in people with ulcerative colitis; other indications include colorectal cancer and familial adenomatous polyposis. A pouch may be formed from the terminal ileum, which is attached to the anus so as to maintain normal passage of stool through the anus rather than through a permanent external ileostomy. This is called ileal pouch-anal anastomosis (IPAA).

Pouchitis is defined in the European Crohn's and Colitis Organisation (ECCO) publication [European evidence-based consensus on the management of ulcerative colitis: special situations](#) as non-specific inflammation of the ileal reservoir (pouch). It is reported to affect up to 50% of people in the 10-year period after IPAA for ulcerative colitis, although the cumulative incidence of pouchitis in people with an IPAA for familial adenomatous polyposis is much lower.

The [ECCO consensus document](#) states that symptoms of pouchitis include pelvic discomfort, abdominal cramps and urgency, tenesmus (a feeling of needing to evacuate the bowels), increased stool frequency and liquidity, and faecal incontinence. There may also be rectal bleeding, fever or other systemic symptoms. Diagnosis of pouchitis relies on evaluation of symptoms and endoscopy ('pouchoscopy') with biopsy of the pouch mucosa. The Pouchitis Disease Activity Index (PDAI), which incorporates symptoms, endoscopy and histological findings, has been developed to standardise diagnostic criteria and assess severity. The range of possible scores is 0–18, with higher scores indicating worse disease. Pouchitis is termed 'active' when symptoms, endoscopy and histological findings are present, and is indicated by a total PDAI score of 7 or more. Active pouchitis is further divided into acute or chronic, depending on the duration of symptoms. The [ECCO consensus document](#) defines chronic pouchitis as symptom duration of more than 4 weeks. Up to 10% of people will develop chronic pouchitis needing long-term treatment.

The [ECCO consensus document](#) states that pouchitis recurs in more than 50% of people who have experienced it and can comprise infrequent episodes (less than once a year), a relapsing course

(1–3 episodes a year) or a continuous course. Complications of pouchitis include abscesses, fistulae, stenosis of the pouch–anal anastomosis and, rarely, adenocarcinoma of the pouch.

### *Alternative treatment options*

The [ECCO consensus document](#) states that the optimum treatment of acute pouchitis is not clearly defined and that the evidence base is limited. Antibiotics are the mainstay of treatment, and pouchitis responds to metronidazole or ciprofloxacin in most people. Single antibiotic treatment with either drug is normally the first-line treatment of choice. If pouchitis becomes chronic, combined antibiotic treatment can be effective. Other possible treatments include oral or topical budesonide or infliximab. None of these drugs is licensed specifically for treating pouchitis.

The [ECCO consensus document](#) states that, once antibiotic-induced remission has been achieved, a highly concentrated probiotic food supplement (VSL#3) can be effective for maintaining remission. It can also be effective in preventing pouchitis within the first year after surgery. Surgery can be considered as a last resort for people whose pouchitis does not respond to other treatment options.

### **Evidence review: efficacy**

Limited research has examined rifaximin for the treatment of pouchitis. Four relevant studies that have been published in full were identified: 1 small placebo-controlled randomised controlled trial (RCT) of rifaximin for the treatment of active pouchitis (n=18); 2 non-comparative observational studies of rifaximin plus ciprofloxacin for the treatment of chronic pouchitis refractory to previous treatment (n=18 and n=8); and 1 non-comparative observational study of rifaximin maintenance therapy after antibiotic-induced remission (n=51).

### *Randomised controlled trial*

[Isaacs et al. \(2007\)](#) conducted a double-blind, placebo-controlled trial at 10 US sites between May 2003 and April 2004; the trial included 18 people with active pouchitis (acute or chronic).

The study recruited adults (aged 18 years and older) with a history of a total colectomy with ileal-pouch anal anastomosis (IPAA) for ulcerative colitis, and who had active pouchitis (Pouchitis Disease Activity Index [PDAI] score of 7–18 points). Pouchitis was defined as acute if symptoms had not been treated with antibiotics or other medical therapy within the previous 30 days, and chronic if antibiotics or other medical therapy for pouchitis had been given within the previous 30 days. Extensive exclusion criteria included infectious, ischaemic, or immunological diseases with

gastrointestinal involvement; significant hepatic or renal disease; or unstable cardiovascular or pulmonary disease. Concomitant treatment with antibiotics, probiotics, sulfasalazine, olsalazine, balsalazide, mesalamine, rectal short-chain fatty acids, rectal glutamine, loperamide or diphenoxylate was not permitted after study enrolment. Concomitant therapy with rectal or oral corticosteroids was not permitted within 2 weeks of enrolment, and concomitant therapy with immune-modifying drugs was not permitted within 3 months of enrolment.

Participants were randomised to 4 weeks' treatment with rifaximin 400 mg 3 times daily (n=8) or placebo 3 times daily (n=10). It is unclear if allocation was concealed.

The primary outcome was clinical remission at 4 weeks (PDAI score of less than 7 points and a decrease from baseline PDAI score of 3 points). Secondary outcomes included complete remission (PDAI score of 0), symptomatic improvement (decrease from baseline PDAI clinical sub-score of 2 points), endoscopic improvement (decrease from baseline PDAI endoscopic subscore of 2 points), and health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Analysis was based on the modified intention-to-treat population (all randomised participants who had a baseline efficacy evaluation, took at least 1 dose of the study medication, and had at least 1 post-baseline efficacy evaluation). This excluded 1 person from the placebo group who withdrew without having any post-baseline assessments. Among the remaining 17 people (mean age 41 years), there was no significant difference in baseline characteristics between the rifaximin and placebo groups. The mean PDAI score at baseline was 10.6 in the rifaximin group and 9.2 in the placebo group. All people in the rifaximin group and nearly all (8/9) of those in the placebo group had received previous antibiotic treatment. Seven people in each group had received 5-aminosalicylates, 4 of the 8 people in the rifaximin group had received non-steroidal anti-inflammatory drugs (1/9 in the placebo group), and 2 of the 8 people had received probiotics (1/9 in the placebo group).

Two people in the placebo group withdrew before 4 weeks because of lack of efficacy and their treatment was counted as ineffective, using a 'last observation was carried forward' approach. Clinical remission was obtained in 2 of the 8 people in the rifaximin group, both of whom had had acute pouchitis, compared with none of the placebo group. However, this difference was not statistically significant ( $p=0.211$ ). No one in the study obtained complete remission. There were also no statistically significant differences in any of the secondary outcomes.

## *Observational studies*

### **Rifaximin plus ciprofloxacin for chronic pouchitis**

Gionchetti et al. (1999) reported the experience of 18 adults with chronic treatment-resistant (refractory) pouchitis who were treated with the combination of ciprofloxacin and rifaximin at 1 institution in Bologna, Italy.

Chronic pouchitis was defined as the presence of symptoms for more than 4 weeks and the need for treatment with antibiotics or anti-inflammatory drugs for more than 15 days each month to control symptoms. Treatment resistance was defined as non-response to at least 4 weeks' treatment with antibiotics: metronidazole 1.2 g once daily (12 people), amoxicillin/clavulanic acid 1 g twice daily (4 people) or ciprofloxacin 500 mg twice daily (2 people).

The 18 people (10 male, median age 33 years) had a median PDAI score of 11 (range 9–17). The reasons why they had had IPAA surgery were not given. The first episode of pouchitis had been a median of 27 months before the study (range 4–72 months), and the current episode of pouchitis had lasted for a median of 2 months (range 0.5–4.5 months).

All participants in the study received combination treatment with rifaximin 1 g twice daily plus ciprofloxacin 500 mg twice daily for 15 days. By the end of this period, 6 of the 18 people had obtained remission of pouchitis (PDAI score of 0), and a further 10 had an improvement in PDAI score of at least 3 points. The authors stated that the 2 people whose condition did not respond were not the 2 who had previously not obtained a beneficial effect from ciprofloxacin treatment.

Abdelrazeq et al. (2005) reported the experience of 8 people who underwent IPAA at York Hospital, UK, between 1988 and 2003 and who developed chronic refractory pouchitis that was treated with a combination of rifaximin and ciprofloxacin.

The 8 adults (aged 20–50 years, 6 male) had a median PDAI score was 12 (range 9–18). The reasons why they had had IPAA surgery were not given. They all had chronic active pouchitis (symptom duration of more than 4 weeks, or pouchitis that required more than 2 weeks' treatment each month to control symptoms) that was refractory (non-responsive to at least 4 weeks' treatment with metronidazole or ciprofloxacin or immediately relapsing upon stopping or reducing antibiotics). They were treated with rifaximin 1 g twice daily plus ciprofloxacin 500 mg twice daily for 2 weeks.

After treatment, 5 of the 8 people remained in remission for at least 6 months (PDAI score of 0) and a further 2 of the 8 people had an improvement in PDAI score of at least 3 points. In 2 of these 7 people who obtained a benefit from rifaximin, pouchitis recurred at 6 and 8 months, but responded again to further courses of the same treatment combination. At median 30-month follow-up, all 7 people had satisfactory pouch function.

The 1 person whose pouchitis did not respond to the treatment combination was also reported to have had no response to systemic steroids, immunosuppressive therapy and hyperbaric oxygen therapy. Their pouch was subsequently removed surgically.

### Rifaximin as maintenance therapy

Shen et al. (2008) reported the experience of adults with antibiotic-dependent pouchitis who had undergone IPAA for ulcerative colitis and who attended the Pouchitis Clinic of The Cleveland Clinic, Ohio, USA between July 2004 and June 2006.

The 53 adults (mean age 46–47 years) all had current symptoms and met both of the following criteria:

- Antibiotic-dependent pouchitis, defined as 4 or more episodes per year, each of which responded to a 2-week course of ciprofloxacin or metronidazole but recurred soon after treatment ended.
- Frequent episodes of pouchitis needing long-term treatment (at least 16 weeks) for remission maintenance with continuous, low-dose antibiotics or frequent pulse therapy with antibiotics.

People with antibiotic-refractory pouchitis (pouchitis not responsive to a 2–4-week course of ciprofloxacin or metronidazole) or with concurrent cuffitis (inflammation of the rectal cuff), irritable pouch syndrome or Crohn's disease of the pouch were not included in this group.

Active pouchitis was defined as a modified PDAI (mPDAI) score of 6 or more (mPDAI includes symptomatic and endoscopic, but not histological, criteria; total possible score 12). To induce remission, participants were given either single or combination treatment (at the clinician's discretion) with: ciprofloxacin 1000 mg daily; metronidazole 1000 mg or 1500 mg daily; tinidazole 1000 mg daily; or rifaximin 600 mg, 800 mg or 1200 mg daily for 2 weeks.

Of the 53 people who received induction with either single or combination antibiotics, 51 obtained remission after 2 weeks (mPDAI score less than 6) and began maintenance treatment with rifaximin for up to 24 months at a starting dose of 200 mg daily. Symptoms, adverse events and

treatment compliance were assessed every 1–3 months. If there was partial response, the rifaximin dose was increased up to a maximum 1800 mg daily. Treatment was discontinued if active pouchitis recurred despite dose increases, or if the person chose to stop treatment.

After 3 months, 33 of the 51 people (65%) were still in remission, and the remainder (18/51) had relapsed. The 33 people in whom remission was maintained for 3 months had no symptomatic or endoscopic evidence of relapse between the end of induction and the 3-month assessment (0 point change on both symptom and endoscopy scores of the mPDAI). People who relapsed had a median increase of 3 points in both symptom and endoscopy scores between the end of induction and 3 months.

Four of the 33 people in whom remission was maintained had symptom recurrence after 3–12 months, but 26 of the 33 people continued rifaximin for at least 6 months, 19 for at least 12 months, 5 for at least 18 months and 2 for at least 24 months.

The majority of these people (23/33) received rifaximin 200 mg daily for the entire maintenance period. Ten people needed dose escalation during the maintenance period to 400 mg (3/33), 600 mg (3/33), 800 mg (2/33), 1200 mg (1/33) or 1800 mg daily (1/33). Similarly, the majority of those who relapsed had received 200 mg daily (11/18). Antibiotic induction regimen, symptom score after induction and rifaximin dose were not predictive of maintaining remission.

## Evidence review: safety

### *Summary of product characteristics*

Rifaximin is contraindicated in people with intestinal obstruction. The summaries of product characteristics for both [Targaxan](#) and [Xifaxanta](#) state that, as with nearly all antibacterial agents, *Clostridium difficile*-associated diarrhoea has been reported with rifaximin. The potential association of rifaximin treatment with *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis cannot be ruled out.

The effects on gut flora may also lead to reduced effectiveness of oral contraceptives, and additional contraceptive precautions are recommended. Despite limited systemic absorption, there may also be reddish discolouration of the urine.

Common adverse events associated with rifaximin (occurring in more than 1 in 100 people) include dizziness and headaches, and abdominal symptoms of pain, distension, nausea and vomiting, diarrhoea or constipation. Studies of [Targaxan](#) (for its licensed indication: reduction in recurrence

of episodes of overt hepatic encephalopathy) have also commonly reported depression, dyspnoea, pruritus and rashes, and arthralgia. Studies of *Xifaxanta* (for its licensed indication: treatment of travellers' diarrhoea) have commonly reported pyrexia. Other adverse events affecting most systems of the body have been observed but were uncommon (fewer than 1 in 100), rare (fewer than 1 in 1000) or an unknown frequency.

### *Adverse events observed in studies*

In the RCT by [Isaacs et al. \(2007\)](#), all 18 randomised participants were included in the safety analyses. A similar proportion of people in both study groups experienced adverse events: 6 of the 8 people in the rifaximin group and 5 of the 10 people in the placebo group (statistical significance not reported). One case of each of the following adverse events was experienced by people in the rifaximin group: flatulence, frequent bowel movements, proctalgia, rectal haemorrhage, thirst, candida, upper respiratory tract infection, cluster headache and headache. There were no withdrawals because of adverse events in either group, and no serious adverse events in either group.

In the study by [Gionchetti et al. \(1999\)](#), there were no adverse events and no changes in laboratory measures (including full blood count and blood chemistry) in the 18 people who took rifaximin plus ciprofloxacin.

In the study by [Abdelrazeq et al. \(2005\)](#), no side effects and no significant changes from baseline values in any of the laboratory tests examined were observed in the 8 people who took rifaximin plus ciprofloxacin.

In the study by [Shen et al. \(2008\)](#), rifaximin was well tolerated when used for maintenance for up to 24 months. One person discontinued rifaximin 2 weeks after starting treatment because of a transient facial rash. No other adverse effects were reported.

## **Evidence review: economic issues**

### **Cost**

The current NHS cost of rifaximin (excluding VAT; costs taken from [Drug Tariff](#), March 2014) is:

- £15.15 for 9×200 mg tablets (*Xifaxanta*)
- £259.23 for 56×550 mg tablets (*Targaxan*).



Based on these costs, and a cost for ciprofloxacin of £1.10 for 10×500 mg tablets (excluding VAT; cost taken from [Drug Tariff](#), March 2014)

- A course of rifaximin 400 mg 3 times daily for 4 weeks costs £282.80
- A course of rifaximin 1 g twice daily plus ciprofloxacin 500 mg twice daily for 2 weeks costs £238.75
- Three months' prophylaxis with rifaximin 200–1800 mg daily costs £141.40 to £1272.60

### *Current drug usage*

[Prescription cost analysis for England](#) showed that in 2012 there were a total of 3975 prescription items for rifaximin 200 mg in primary care at a cost of £623,723, and 1 prescription item for rifaximin 550 mg at a cost of £128. No information is available on the proportion of these prescriptions that was prescribed for the treatment of pouchitis.

### **Evidence strengths and limitations**

There is limited published research examining rifaximin for the treatment of pouchitis. Four relevant studies were identified that have been published in full, which were of different study design, examined different indications for rifaximin and used different dosing regimens.

[Isaacs et al. \(2007\)](#) was the only identified randomised controlled trial (RCT) of rifaximin for the treatment of pouchitis. It was double-blind and had a suitable method of randomisation, but it is unclear if allocation was concealed. The trial was limited by its small size, with only 17 people in the intention-to-treat analysis, which meant that it lacked statistical power. The authors reported that they had planned to recruit 66 people, which would have resulted in a trial of sufficient statistical power to detect a true difference in clinical remission rates between the rifaximin and placebo groups. The trial included people with both active and chronic pouchitis but the small sample size makes subgroup analyses unreliable.

The single published RCT provides limited evidence about the effectiveness and safety of rifaximin for the treatment of acute or chronic active pouchitis.

The majority of people in the studies by [Gionchetti et al. \(1999\)](#) and [Abdelrazeq et al. \(2005\)](#) obtained remission or improvement in their pouchitis. However, these 2 small, non-comparative observational studies (n=18 and n=8, respectively) provide limited evidence about the

effectiveness and safety of rifaximin in combination with ciprofloxacin for chronic refractory pouchitis.

The study by [Shen et al. \(2008\)](#) on the effects of open-label rifaximin maintenance treatment is limited because it was non-comparative, and because the authors reported outcomes using the modified Pouchitis Disease Activity Index (mPDAI) score, rather than the full PDAI as used by the other studies. The mPDAI includes symptomatic and endoscopic, but not histological, criteria. Moreover, the authors reported that endoscopy data were available for only 21 of the 51 participants.

Although rifaximin 200 mg daily was the dose used by majority of people, doses up to a maximum of 1800 mg daily were given. This makes it difficult to determine an optimal dose for maintenance of remission.

This relatively small, non-comparative study provides limited evidence about the effectiveness and safety of rifaximin for the maintenance of remission in people whose pouchitis responded to a 2-week course of antibiotics but relapsed without long-term treatment.

Large double-blind RCTs are needed to determine whether rifaximin is effective and safe for the treatment of acute or chronic pouchitis and pouchitis refractory to other antibiotics, or for maintenance of antibiotic-induced remission.

## Summary for patients

A [summary written for patients](#) is available on the NICE website.

## References

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## Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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### *Declarations of interest*

No relevant interests declared.

## **Appendix: Search strategy and evidence selection**

### *Search strategy*

#### **General background, guidelines and technology assessments**

- Broad internet search: Google:
  - allintitle: rifaximin pouchitis filetype:pdf
  - allintitle: pouchitis treatment filetype:pdf
- Trip Database: Rifaximin pouchitis

#### **MEDLINE (via Ovid)**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> (via Ovid)

Search Strategy:26/11/13

1 exp Rifamycins/ (17967)

2 rifaximin.ti,ab. (595)

3 1 or 2 (18166)

4 Colonic Pouches/ (1125)

5 Pouchitis/ (606)

6 pouchitis.ti,ab. (1114)

7 ileo?anal pouch.ti,ab. (301)

8 4 or 5 or 6 or 7 (2236)

9 3 and 8 (21)

10 limit 9 to english language (21)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed

Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:02/12/13

1 exp rifamycins/ (17995)

2 rifaximin.ti,ab. (596)

3 1 or 2 (18194)

4 ileal pouch\*.ti,ab. (1824)

5 pouch ileitis.ti,ab. (19)

6 4 or 5 (1833)

7 3 and 6 (7)

8 limit 7 to english language (7)

## **Embase (via Ovid)**

Embase <1988 to 2013 November 26>

Search Strategy:27/11/13

1 exp rifamycin/ (1614)

2 rifaximin.ti,ab. (912)

3 1 or 2 (2434)

4 exp proctocolectomy/ (3625)

5 ileitis/ (3271)

6 pouchitis.ti,ab. (1516)

7 ileo?anal pouch.ti,ab. (378)

8 4 or 5 or 6 or 7 (6636)

9 3 and 8 (32)

10 limit 9 to (english language and exclude medline journals) (4)

## **Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley interface)**

Search strategy: 27/11/13

#1 MeSH descriptor: [Rifamycins] explode all trees

#2 rifaximin:ti,ab

#3 #1 or #2

#4 MeSH descriptor: [Colonic Pouches] explode all trees

#5 MeSH descriptor: [Pouchitis] explode all trees

#6 pouchitis:ti,ab

#7 ileoanal pouch:ti,ab

#8 ileo-anal pouch:ti,ab

#9 ileo anal pouch:ti,ab

#10 #4 or #5 or #6 or #7 or #8 or #9

#11 #3 and #10

## CRD HTA, DARE and EED database (via CRD interface)

Search Strategy: 27/11/13

1 MeSH DESCRIPTOR rifamycins EXPLODE ALL TREES

2 (rifaximin)

3 #1 OR #2

4 MeSH DESCRIPTOR colonic pouches EXPLODE ALL TRE

5 MeSH DESCRIPTOR pouchitis EXPLODE ALL TREES

6 (pouchitis) OR (ileoanal pouch) OR (ileo anal pouch)

7 (ileo-anal pouch)

8 #4 OR #5 OR #6 OR #7

9 #3 AND #8

## Grey literature and ongoing trials

- [NICE Evidence Services](#)

- [Health Canada – Clinical Trials Search](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

## Manufacturer's website

[Norgine](#)

## *Evidence selection*

The evidence was reviewed with no restriction on patient population studied (including underlying medical indication for ileal pouch-anal anastomosis); indication for rifaximin (including treatment of acute or chronic pouchitis and refractory pouchitis, or as maintenance therapy after remission); dose or duration of rifaximin; use of rifaximin as monotherapy or in combination with other treatments; or comparators. Because of the limited published evidence available, all identified randomised controlled trials and observational studies of rifaximin for the treatment of pouchitis were included. Systematic reviews that did not provide evidence for rifaximin beyond the already identified primary studies were excluded. Conference abstracts were also excluded.

## About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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