London Medicines Evaluation Network Review

Prucalopride for chronic idiopathic constipation in men

November 2015

Summary

Background and licensed indication

Chronic constipation is common in men and women and prevalence increases with age. Prucalopride (Resolor®) is a selective, high affinity, 5-HT4 receptor agonist with potent enterokinetic activity on gastric, intestinal and colonic smooth muscle. It was approved in 2009 for the symptomatic treatment of chronic constipation in women for whom laxatives fail to provide adequate relief. This review presents the evidence which supported the license extension for using Resolor® in men as well as women.

Dosing

Oral dose of 2 mg once daily with a lower dose of 1mg once daily for use in older people (>65 years) and for patients with severe renal or liver impairment.

Alternatives

Lubiprostone is the other option for management of chronic idiopathic constipation in men or women in whom lifestyle changes and simple laxatives have failed. It enhances chloride rich intestinal fluid secretion.

NICE

Current NICE guidance recommends prucalopride as an option for the treatment of chronic constipation in women, for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief, and invasive treatment for constipation is being considered. If treatment with prucalopride is not effective after 4 weeks, the woman should be re-examined and continuation of treatment reconsidered.

Clinical studies

The SPD555-302 study was a multicentre, randomised, double-blind, placebo controlled, phase III trial evaluating the efficacy, quality of life, safety and tolerability of prucalopride vs. placebo in 374 men with chronic constipation. After a 2-4 week run-in phase, men were randomised to receive prucalopride 1-2mg (n=184) or placebo (n=186). After 12 weeks, more men in the prucalopride group reported a mean of ≥3 Spontaneous Complete Bowel Movements (SCBM’s) per week (37.9%) vs. placebo (17.7%; p<0.0001). The proportion achieving ≥3 SCBM’s was greater in the prucalopride group vs. placebo at 1-4 weeks (29.9% vs. 14.9%, p<0.005), 5-8 weeks (41.2% vs. 23.2%, p≤0.0001) and 9-12 weeks (39% vs. 23.8%, p<0.005).

Safety

In the SPD555-302 study, adverse effects were reported by 42.4% of men taking prucalopride group vs. 34.4% of men taking placebo. Adverse effects were mild to moderate in severity and the most common were headache, diarrhoea, nausea and abdominal pain. Transient prolongation of the QT interval occurred in one man taking prucalopride. For lubiprostone, the most common adverse effects are mild to moderate nausea (very common), mild to moderate diarrhoea (common), headache (common) and dyspnoea. Long term safety data in men (beyond 24 weeks) are currently lacking for prucalopride.

Convenience

Prucalopride and lubiprostone (24mcg) are both given orally; prucalopride with or without food once daily and lubiprostone twice daily after food (to prevent nausea). Efficacy and need for continued use should be re-assessed after 4 weeks with prucalopride use and after 2 weeks with lubiprostone use.

Risk assessment

Patients taking prucalopride should seek medical attention if palpitations occur and caution is advised in those with history of arrhythmias. Lubiprostone is cautioned for patients with dyspnoea or chest discomfort/pain. Both must be used with caution in patients with severe liver disease.

Budget impact

(See main text for further details)

<table>
<thead>
<tr>
<th>Basic NHS Costs</th>
<th>Per pack</th>
<th>Daily</th>
<th>2 weeks</th>
<th>12 weeks</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prucalopride (Resolor®) Tablets</td>
<td>1mg (28) - £38.69</td>
<td>£1.38</td>
<td>£19.32</td>
<td>£115.92</td>
<td>£503.70</td>
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<tr>
<td></td>
<td>2mg (28) - £59.52</td>
<td>£2.13</td>
<td>£29.82</td>
<td>£178.92**</td>
<td>£777.45</td>
</tr>
<tr>
<td>Lubiprostone (Amitiza®) Capsules</td>
<td>24 mcg (28) - £29.68</td>
<td>£1.91</td>
<td>£26.74</td>
<td>£160.44***</td>
<td>£697.15</td>
</tr>
<tr>
<td></td>
<td>24 mcg (56) - £53.48</td>
<td></td>
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</table>

Funding

The likely commissioning pathway will be through CCGs.

Suggested place in therapy

Prucalopride is an option for treating chronic constipation in men (as well as women) for whom treatment with at least two laxatives from different classes, at optimal doses for >6 months, has failed and for whom invasive treatment is being considered. If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered. The relative place in therapy for prucalopride and lubiprostone will be based on their differing tolerability and safety profiles given that their efficacy and cost-effectiveness were judged to be similar by NICE. Neither prucalopride, nor lubiprostone, are approved for use in opioid induced constipation.
1. Background and introduction

Constipation can broadly be defined as a real or perceived significant change in normal bowel habit that is unsatisfactory because of infrequent stools, difficult passage of hard stools, or seemingly incomplete defecation. Stools are often dry and hard, and may be abnormally large or small. [1] This definition of constipation is subjective and attempts continue to be made to develop and agree more objective criteria for the definition of functional constipation, most notably by the Rome criteria. [2] The ROME III criteria for Function Bowel Disorders define chronic constipation as two or more of the following symptoms of >3 months with symptom onset >6 months prior to diagnosis.[2,3]

- Straining during >25% of defecations
- Lumpy/hard stools in at >25% of defecations
- Sensation of incomplete evacuation for >25% of defecations
- Sensation of anorectal obstruction/blockage for >25% of defecations
- Manual manoeuvres to facilitate >25% of defecations
- Fewer than 3 defecations/week
- Loose stools rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndromes (IBS).

Chronic constipation is common and is thought to occur in around 16% (reported prevalence rates vary between 4-20%) of the population overall. It is more commonly reported by women than men and prevalence increases with age. Constipation can affect quality of life and productivity and complications include urinary retention, abdominal distension, nausea, vomiting, anorexia, haemorrhoids, anal fissures, perianal abscesses and intestinal obstruction which can be life threatening. [3] Management of chronic constipation involves dietary and lifestyle changes (ensuring adequate fluids and fibrous foods in the diet and taking exercise) as first line. If this fails, medication such as bulk forming laxatives, osmotic and stimulant laxatives or faecal softeners should be considered. If these are ineffective, use of suppositories, enemas and use of newer agents such as lubiprostone or prucalopride may be used. Last line options include rectal irrigation or manual disimpaction which may require assessment and management in hospital. [3] Prescribing choice mainly depends on the presenting symptoms, patient preference and cost. Prolonged treatment in adults is seldom necessary, except occasionally in the elderly and in palliative care. [1,4]

Prucalopride (Resolor®) is a selective, high affinity, 5-HT4 receptor agonist with potent enterokinetic activity on gastric, intestinal and colonic smooth muscle via non-cholinergic, cholinergic and non-adrenergic neurotransmission pathways. [3,5] It is available as an oral tablet usually dosed once a day (up to 2mg), for up to 4 weeks before it is reviewed. [5,6]

Resolor® was approved in the EU in October 2009 for the symptomatic treatment of chronic constipation in women for whom laxatives fail to provide adequate relief. At the time of first marketing authorisation in 2009, the efficacy of prucalopride was demonstrated in three large phase III studies. The proportion of men in these studies was relatively low (only 12.2%) which reflects the smaller proportion of men who seek treatment for chronic constipation. In a subgroup analysis of the male participants, the effect of prucalopride 2mg on the primary efficacy endpoint (≥ 3 spontaneous complete bowel movements (SCBM) per week over a 12 week treatment period) was no different to placebo. This lack of difference in treatment effect was largely due to the presence of more severe constipation at baseline in the male participants randomised to the treatment group. Therefore, at the time of first approval in 2009, data to support the efficacy for using prucalopride in men was not considered sufficient and it was approved for use in women only. This approval was made on the condition that follow up controlled study data were to be provided for use of prucalopride in men in the future. These data are now available in the form of study SPD555-302 which supports the evidence for efficacy of prucalopride in men as well as women. As a result prucalopride is now approved for use in men since May 2015. [5]

2. Proposed place in therapy

Prucalopride is approved for symptomatic treatment of chronic idiopathic constipation in adults in whom second line laxatives fail to provide adequate relief. [5] Prucalopride is intended as a third/last line therapy for treatment of chronic constipation in men, offering another treatment option for those who do not respond to treatment with at least two previous laxatives from different classes and in whom invasive treatment is being considered. Lubiprostone is also a relatively new orally administered option for adults with chronic idiopathic constipation in whom treatment with at least two laxatives from different classes have been tried at the highest recommended dose for >6 months and have failed to provide adequate relief. Lubiprostone acts by enhancing chloride rich intestinal fluid secretion. Lubiprostone is also suitable for those in whom invasive measures such as rectal irrigation and manual disimpaction are being considered. [3,4]

3. Evidence selected for inclusion

Study SPD555-302 was published in 2015 following the EU approval of prucalopride in women in 2009, which was on the condition that follow up controlled study data be provided for use of prucalopride in men in the future. Study SPD555-302 (NCT01147926) [7] was a 12 week, multicentre, randomised, double-blind, placebo controlled phase III trials which involved 374 men with a history of constipation. The study manuscript does not detail what previous laxatives these men had used prior to enrolment. The objective of the trial was to evaluate the efficacy, quality of life, safety and tolerability of prucalopride compared with placebo in men with chronic constipation. After a 2-4
week run in phase, patients were randomised in a 1:1 ratio to one of two groups to receive either prucalopride (n=184) or matched placebo (n=186). Of the 374 men, 12 were excluded due to protocol violation at one centre. Randomisation was stratified according to the number of weekly complete bowel movements (CBM) at baseline. The men took their assigned tablet each morning before breakfast. Men aged 65 years or over took 1mg of prucalopride or matched placebo which was increased to 2mg/day if response was insufficient and those younger than 65 years took 2mg of prucalopride or matched placebo. If required, bisacodyl was allowed as a rescue medication if patients had not had a bowel movement for 3 days. After the baseline visit at week 0, the men returned for visits at weeks 2, 4, 6, 8 and 12 and completed a global assessment of the severity of their constipation using a five point scale from 0-4 (absent to very severe). Patients completed an assessment of constipation symptoms questionnaire (PAC-SYM) at weeks 4 and 12 – this validated tool comprised 12 items assessing the severity of constipation on three subscales of stool, abdominal and rectal symptoms each measured on another 5 point Likert-type scale; 0-4 absent to very severe with the overall score a mean of all measures. A total score for the PAC-SYM can range from 0 to 48. Quality of life was assessed using a questionnaire (PAC-QOL) measuring physical discomfort, psychosocial discomfort, worries and concerns and satisfaction again using a 5 point Likert-type scale; 0-4 absent to very severe with the overall score a mean of all measures. Patients also completed diaries to record bowel frequency and details of bowel movements date, time, consistency using the Bristol Stool Chart, degree of straining, feeling of complete evacuation and use of rescue medication. The primary efficacy endpoint was the proportion of patients with an average weekly frequency of three or more spontaneous complete bowel movements (SCBM’s) per week (responders) over 12 weeks of treatment. [7,8]

Primary outcome measure: After 12 weeks, more men in the prucalopride group reported a mean of three or more SCBM’s per week (37.9%) than in the placebo group (17.7%; p=0.0001). Hence the number needed to treat (NNT) is 5, which means that 5 men need to be treated with prucalopride for 12 weeks to achieve an average weekly frequency of three or more SCBM’s in one man. The proportion of men achieving ≥3 SCBM’s was greater in the prucalopride group than in the placebo group at 1-4 weeks (29.9% vs. 14.9%, p<0.005), 5-8 weeks (41.2% vs. 23.2%, p=0.0001) and 9-12 weeks (39% vs. 23.8%, p=0.005). In a subgroup analyses by country, the proportion of responders was greater in prucalopride groups vs. placebo groups (20-66% vs. 0-55%). In another subgroup analysis by baseline severity, men with zero CBM at baseline reported greater improvement on prucalopride over placebo (31.8% vs. 10%, p=0.0003). Results were similar in men who had more than zero CBM’s at baseline; they also reported greater improvement on prucalopride over placebo (43.5% vs. 23.8%, p=0.0081). [7]

Secondary efficacy variables were derived from patient diary entries and data are presented below:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Prucalopride group</th>
<th>Placebo group</th>
<th>Statistical Comparison (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with ≥3 SCBMs/week and an increase of ≥1 SCBM per week for ≥75% of 12-week treatment period and ≥75% of last third of treatment period.</td>
<td>27.7%</td>
<td>12.2%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Percentage of patients with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 spontaneous bowel movements (SBMs)/week</td>
<td>77.4%</td>
<td>60.8%</td>
<td>0.0011</td>
</tr>
<tr>
<td>≥3 CBMs/week</td>
<td>39.5%</td>
<td>21.5%</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥3 BMs/week</td>
<td>80.8%</td>
<td>68.0%</td>
<td>0.0064</td>
</tr>
<tr>
<td>an increase of ≥1 SCBM/week</td>
<td>53.7%</td>
<td>45.3%</td>
<td>0.0743 (ns)</td>
</tr>
<tr>
<td>Number of SBMs/week (mean change from baseline to week 12)</td>
<td>2.17</td>
<td>1.25</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percentage of SBMs with hard/very hard consistency (mean change from baseline to week 12)</td>
<td>-28.9%</td>
<td>-19.2%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Median time from day 1 to first SCBM (In hours from taking prucalopride or placebo on day 1 (95% CI))</td>
<td>110.3 (70.8 to 172.8)</td>
<td>218.9 (143.9 to 291.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Number of SBMs with severe/very severe straining, mean change from baseline to week 12</td>
<td>-24.8%</td>
<td>-16.0%</td>
<td>Not performed</td>
</tr>
<tr>
<td>Number of bisacodyl tablets taken/week (mean change from run-in to week 12)</td>
<td>-1.0</td>
<td>-0.7</td>
<td>Not performed</td>
</tr>
<tr>
<td>PAC-SYM overall score (mean change from baseline to final on-treatment assessment)</td>
<td>-0.76</td>
<td>-0.59</td>
<td>0.0623 (ns)</td>
</tr>
<tr>
<td>PAC-QOL overall score (mean change from baseline to final on-treatment assessment)</td>
<td>-0.79</td>
<td>-0.59</td>
<td>0.0158</td>
</tr>
</tbody>
</table>

In addition the distribution of constipation severity was rated by patients across five possible responses (absent, mild, moderate, severe, very severe). The difference was statistically significantly (p<0.05) between treatment groups at all time points, with more patients in the prucalopride group showing improvement across the possible responses over 12 weeks. The proportion of patients rating their treatment as ‘fairly or extremely effective’ at 12 weeks was 30.4% and 46.7% in the placebo and prucalopride groups respectively, p<0.0001. [7]
4. Critical evaluation

4.1. Clinical application

The SPD555-302 study fulfils the European Medicines Agency (EMA) approval criteria for its use in men. The design of the pivotal PIII SPD555-302 study in men was broadly similar to the previous four pivotal PII studies which enrolled predominantly female patients. A key difference was that in the original studies which included mostly women, the doses used were 2-4mg whereas the present study uses licensed doses of up to 2mg in men. However this should not impact efficacy because doses of more than 2mg are not considered effective. The percentage of those using the lower 1mg dose was greater in the present study of men compared to previous studies of predominantly women. [9] Like the men in study SPD555-302, the women in previous licensing studies had a history of chronic constipation (≤2 SCBM per week over the last 6 months with straining or a sensation of incomplete evacuation of the bowels or hard stools with at least 25% of bowel movements). The previous studies also included a 2 week run-in period followed by double blind treatment with either prucalopride or placebo for 12 weeks. As in this study, rescue with bisacodyl was allowed. The same primary efficacy endpoint was used; the proportion of patients with a mean of >3 SCBM’s per week. Findings from this study were consistent with the overall results from the previous studies which reported that between 9.9-20% of patients achieved the primary endpoint over placebo (compared to 20.2% in the present study). [7] However with respect to one of the secondary outcomes, the change in PAC-SYM score for symptoms of constipation, this study found no significant difference between prucalopride and placebo whereas the previous studies carried out predominantly in women found a significant difference in PAC-SYM scores between prucalopride and placebo. Investigators suggest that this lack of significance is due to the relatively small size of the present study. Overall, this suggests that the response rate, in terms of the number of bowel movements, is similar in men and women. There is currently no evidence that prucalopride makes a difference to men in terms of their symptoms of constipation but a difference might be noticeable if larger studies were carried out. [7,9,10]

The SPD555-302 study had a few limitations which may affect the internal or external validity of its findings:

- Patients with <14 days of data in their diary were assumed to be non-responders and patients with ≥7 days data at the start but <84 days in total had their results from the last 7 days repeatedly copied in for all missing days. The number of patient diaries with missing data from each group is not reported in the manuscript and was requested from the manufacturer. The figures for patients who did not complete e-diaries on ≥75% of days were 3.8% in the placebo group and 5.4% in the prucalopride group. [7,11]
- Although men on prucalopride had the same duration of constipation as men on placebo, they reported fewer SCBM’s at baseline. Also at baseline, 30% of men in the prucalopride group reported a feeling of not completely emptying the bowels at baseline vs. 18% on placebo (p=0.009). This meant that there was a chance that the prucalopride group had more troublesome constipation compared with the placebo group, possibly underestimating efficacy later. However, complete bowel motions (CBM) were similar between the groups at baseline (p=0.2869). [7]
- The SPD555-302 study was carried out only at European sites and in a predominantly caucasian population so it is not clear how effective prucalopride may be in men of other ethnicities/geographies/lifestyles. [7]
- The SPD555-302 study was of a relatively short duration of 12 weeks and since constipation is a chronic condition, it would be helpful to know whether it remains safe and effective in the longer term. [7]
- It is not known what prior laxative medicines the men included in this study had used prior to enrolment. [7]

Prucalopride has not been compared with an active comparator. Given its proposed place in therapy as third line after lifestyle modification and conventional laxatives, its natural comparator would be lubiprostone which is intended to have a similar place in therapy. The NICE committee assessing lubiprostone carried out an indirect analysis comparing it with prucalopride because of the absence of any head-to-head randomised controlled trials comparing them. The Committee concluded that, on balance, lubiprostone and prucalopride were similarly effective. [12] Choice would therefore be based upon their respective tolerability and on cost-effectiveness.

4.2. Safety

4.2.1. Key adverse events

The safety of prucalopride is reasonably well established from the studies of predominantly women which were carried out before its first approval in 2009. In the SPD555-302 study, at least one treatment emergent adverse event (TEAE) was reported by 42.4% of patients in the prucalopride group and 34.4% of patients in the placebo group, the majority of these were mild to moderate in severity. The relative risk of experiencing a TEAE in the prucalopride group compared with the placebo group was 1.23 (95% CI, 0.95 to 1.60). The most common TEAE associated with the use of prucalopride were gastrointestinal disorders (nausea, diarrhoea and abdominal pain) and headache. Gastrointestinal disorders were experienced by 20.1% of patients in the prucalopride group compared with 14.0% in the placebo group. Headache was experienced by 9.2% of patients who received prucalopride compared with 3.8% of those taking placebo. Only one patient taking prucalopride experienced a serious TEAE (atrial fibrillation in a patient with previous medical history of this) compared with the placebo group in which there were four TEAE’s (myocardial ischaemia, lower limb fracture, glottis carcinoma and atelectasis). The most common TEAE’s which led to discontinuation of treatment in the prucalopride group were diarrhoea (n=8), nausea (n=2), headache (n=3) and dizziness (n=2). The discontinuation rates were similar between the prucalopride and placebo groups (15.5% and 14.4% respectively). One patient in the prucalopride group was found to have QT interval prolongation on an ECG carried out at 4 weeks. Prucalopride was continued and this resolved by week 12. The safety of prucalopride has been confirmed by several large-scale studies, including a thorough QT study and a trial specifically in elderly patients who are at higher risk of cardiac arrhythmias. [7]

For comparison, the safety of lubiprostone was investigated in 301 patients in pivotal trials and from post-marketing data. The most common adverse effect for lubiprostone was mild to moderate nausea (very common) and mild to moderate diarrhoea (common) and
headache (common). Dyspnoea was reported by a few patients in post-marketing studies. [12,13]

4.2.2. Risk assessment.
The EPAR 2015 and its summary of safety concerns for prucalopride outlines that there is risk of palpitations and potentially increased risk of cardiovascular and cerebrovascular ischaemic events, QT prolongation, related ventricular events and syncope. The SPC states that patients should seek medical attention if palpitations occur whilst using prucalopride. Prucalopride should be used with caution in patients with severe and clinically unstable concomitant cardiovascular disease or a history of arrhythmias or ischaemic cardiovascular disease. [5] Lubiprostone is cautioned for patients with dyspnoea or chest discomfort/pain. Both prucalopride and lubiprostone must be used with caution in patients with underlying severe liver disease due to limited data in these patients. [13]

4.3. Potential advantages and disadvantages over existing technologies

4.3.1. Convenience
Prucalopride offers another treatment for management of laxative refractory chronic constipation in men (and women) whose treatment options may be limited and who might otherwise be considered for invasive therapy such as manual evacuation. It is taken orally once daily with or without food at any time of day. If it is effective after 4 weeks of use, there is no maximum duration for its use though trials are limited to 12 weeks duration. [10] Lubiprostone is also a relatively new option for the management of chronic idiopathic constipation in men and women. It is dosed twice each day with food (to prevent nausea) and can be used for up to 2-4 weeks before review. [13]

4.3.2. Healthcare resource utilisation
As a further option for the management of chronic constipation, prucalopride (like lubiprostone) may help to reduce the referral rate of patients for specialist advice or management and potentially avoid use of invasive procedures.

4.3.3. Suitability for shared care
Prucalopride is likely to be suitable for use in primary or secondary care. There are no specific patient selection, monitoring or dose titration requirements.

4.3.4. Drug cost and likely budgetary impact
There are two potential options for the management of chronic idiopathic constipation in men or women in whom lifestyle changes and simple laxatives have failed; prucalopride and lubiprostone. Prucalopride is indicated for treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief. It is recommended that if there is no effect after 4 weeks of use, it should be stopped. If prucalopride is effective, it can continue in the relative long term; the longest follow period for its safe use was over 24 weeks though the manufacturer notes that efficacy is not proven for longer than 12 weeks and suggests re-assessment of benefit at regular intervals. [10,12,13]

<table>
<thead>
<tr>
<th>Table 2: Relative drug costs for prucalopride and lubiprostone</th>
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<tbody>
<tr>
<td>(Adapted from the NICE costing statement for lubiprostone and MIMS November 2015) [12,14]</td>
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<td></td>
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<tr>
<td><strong>Basic NHS Costs</strong></td>
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<tr>
<td></td>
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<td>Per pack</td>
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<td>Prucalopride (Resolor®) Tablets</td>
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<td>Lubiprostone (Amitiza®) Capsules</td>
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*Most patients would be using the 2mg/day dose of prucalopride (78%). The 1mg/day dose is intended for elderly patients or those with renal or hepatic impairment. ** Prucalopride is not recommended for use for longer than 12 weeks without assessment due to lack of evidence for efficacy beyond this time. ***Lubiprostone is not recommended for use for longer than 2 weeks without assessment.

However, after an initial 2 week treatment course and assessment, it may be decided to continue treatment with lubiprostone for longer. There is a 56 capsule pack available at cost of £53.48 for this situation. [14]

The manufacturer of prucalopride has confirmed that to estimate budgetary impact of adopting the use of prucalopride in men across England and Wales, the same cost effectiveness model developed by NICE for prucalopride in women can be used. [11] This is available at [http://www.nice.org.uk/guidance/ta211/resources](http://www.nice.org.uk/guidance/ta211/resources) and can be used to assess local impact.

<table>
<thead>
<tr>
<th>Table 3 From NICE Costing Statement for Lubiprostone based on prucalopride usage [12]</th>
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<tbody>
<tr>
<td>Per curency (%) of patients</td>
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<td>--------------------------------</td>
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<tr>
<td>Prevalence of GP diagnosed constipation in England and Wales</td>
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<tr>
<td>Proportion of England only</td>
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<tr>
<td>Proportion treated with laxatives for chronic constipation</td>
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<tr>
<td>Proportion considered partial or complete non-responders to 2 cycles of laxatives</td>
</tr>
<tr>
<td>Estimated number of partial or complete non-responders to 2 cycles of laxatives currently receiving prucalopride</td>
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</tbody>
</table>

§ Note that these estimated figures are derived from a study involving GP diagnosed constipation and a significant proportion of these patients were known to have opioid induced constipation. Given that neither prucalopride nor lubiprostone are licensed for opioid induced constipation, the actual numbers of eligible patients for these treatments may be smaller.
5. **Health Economics**

The manufacturer of prucalopride confirmed that the same cost effectiveness modelling that was used in women can be applied to men. [11] For adult women, the Incremental Cost Effectiveness Ratio (ICER) was £16,800 per QALY gained and for older women the ICER was £11,700 per QALY gained. The NICE committee assessing this considered the true resource costs of treating chronic constipation when laxatives fail to provide adequate relief, such as referrals to secondary care, rectal irrigation and surgery. They concluded that the economic model provided by the manufacturer were probably conservative. The committee were persuaded that the most plausible ICER for prucalopride compared with placebo plus rescue medication was likely to be £20,000 per QALY gained. The NICE committee reviewing lubiprostone considered that the ICER of lubiprostone compared with prucalopride, noting the small absolute difference between lubiprostone and prucalopride in terms of the total cost (£22) and QALYs (0.0007) in the probabilistic base case. The Committee concluded that, in a fully incremental analysis, it was sufficiently satisfied that the incremental costs and benefits of lubiprostone compared with placebo were comparable to those for prucalopride compared with placebo. [12,15]

6. **Likely commissioning and funding pathway**

The likely commissioning pathway will be through CCGs.

7. **Suggested place in therapy**

The evidence supports similar efficacy over placebo of prucalopride in men as well as women. [7,9] Therefore it will have a similar place in therapy. Therefore, the following recommendation is adapted from NICE technology appraisal guidance on prucalopride for the treatment of chronic constipation in women. [15] Prucalopride is recommended as an option for the treatment of chronic constipation in adults for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered. [12,15] The relative place in therapy for prucalopride and lubiprostone are likely to be based on their differing tolerability and safety profiles given that their efficacy and cost-effectiveness were judged to be similar by NICE. Note that neither prucalopride, nor lubiprostone, are approved for use in opioid induced constipation. [10,13]

References


6. UK Pharmascan Technology Summary (492513): Prucalopride for chronic constipation in adults in whom laxatives fail to provide adequate relief. Published 6/8/15 <Accessed 20/08/15>.


Search Strategy

*Medline via PubMed 1950-present: PRUCALOPRIDE/ AND MALE/ AND CLINICAL TRIAL/"

*Embase via NHS Evidence 1980-present: (PRUCALOPRIDE/ct [tc=Clinical Trial] AND MALE/) OR (PRUCALOPRIDE/ AND MALE/ AND CLINICAL TRIAL/"

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