BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE

New Medicine Review

Prucalopride (Resolor®)

Medicine	Prucalopride (Resolor ®)
Document status	Final
Date of last revision	June 2020
Proposed Sector of prescribing	Primary and Secondary Care
Introduction **Summary Key points** **Evidence level**	Prucalopride was previously licensed for use only in women, due to a lack of supportive data for use in men from clinical trials. The National Institute for Health and Care Excellence (NICE) Technology Appraisal 211 recommends prucalopride as a treatment option in women with chronic constipation who have tried at least two different types of laxatives at the highest possible recommended doses, for at least six months, in whom invasive treatment for constipation is being considered. The license extension for use in men was supported by a phase III, randomised, double-blind, placebo-controlled trial conducted in men only. This had a similar design and inclusion criteria as the earlier trials that supported the use of prucalopride in women, and enrolled patients with ≤ two spontaneous complete bowel motions (SCBM) per week for at least six months. There are no alternatives available to prucalopride at this stage of treatment as lubiprostone has been withdrawn from the market. In the last financial year, 239 patients were prescribed prucalopride in Bedfordshire CCG (total cost £99,900) and 207 patients in Luton CCG (total cost £71,694). A small increase in patient numbers of up to 12% is anticipated if usage is extended to men, although uptake would be gradual and offset by some existing prescribing in male patients. All Wales Medicines Strategic Group (AWMSG) recommend prucalopride as an option for use within NHS Wales for the treatment of chronic constipation in men in whom laxatives fail to provide adequate relief. A SPS review conducted in 2015 supports similar efficacy over placebo of prucalopride in men as well as women. The review therefore concludes that prucalopride is a suitable treatment option for men, in the same circumstances as women (as outlined in NICE TA 211). Other CCGs such as Somerset CCG, Midlands and Lancashire have since extended the use of prucalopride in men. Subsequent studies have confirmed efficacy and safety of prucalopride.
The intervention **Mechanism of action**	Prucalopride is a selective, high affinity, 5-HT4 receptor agonist with potent enterokinetic activity on gastric, intestinal and colonic smooth muscle.

Licensed indication	Chronic constipation when other laxatives fail to provide an adequate response.
Formulation/Available Products	1mg & 2mg film coated tablets
Usual dosage	*For Adult* 2 mg once daily, review treatment if no response after 4 weeks. *For Elderly and patients with severe renal or liver impairment* Initially 1 mg once daily, increased if necessary to 2 mg once daily, review treatment if no response after 4 weeks.
Treatment alternatives/ place in therapy	There are no treatment alternatives as Lubiprostone was discontinued in January 2019 due to commercial reasons. Prucalopride should be used when other laxatives fail to provide an adequate response as per criteria in NICE TA211.
Future alternatives	None identified.
National guidance	NICE TA211 indicated for use in women only.
Local Guidance	Females only, with authorisation from a Gastroenterologist, in line with NICE TA211. Patient must have tried at least two different types of laxatives at the highest possible recommended doses, for at least 6 months, and are considering invasive treatment for constipation. Treatment must be reviewed after 4 weeks. N.B. Only to prescribe in women as NICE have not approved for use in men yet.
Evidence for use	Prucalopride was previously licensed for use only in women, due to a lack of supportive data for use in men from clinical trials. The National Institute for Health and Care Excellence (NICE) Technology Appraisal 211 recommends prucalopride as a treatment option in women with chronic constipation who have tried at least two different types of laxatives at the highest possible recommended doses, for at least six months, in whom invasive treatment for constipation is being considered. The license extension for use in men was supported by a phase III, randomised, double-blind, placebo-controlled trial conducted in men only. This had a similar design and inclusion criteria as the earlier trials that supported the use of prucalopride in women, and enrolled patients with ≤ two spontaneous complete bowel motions (SCBM) per week for at least six months. Prucalopride significantly increased the primary endpoint of the proportion of men achieving a mean of ≥ three SCBMs per week over a 12-week treatment period compared with placebo (37.9% vs. 17.7%, p<0.0001; Number Needed Treat (NNT) = 5). The European Public Assessment Report includes a pooled analysis across six phase III or IV trials, including the above trial in men, which suggests comparable efficacy in men and women.

<table>
<tr><td></td><td>The Summary of Product Characteristics notes that, if prucalopride is not effective after four weeks of treatment, the benefit of continuing treatment should be reconsidered. It also notes that efficacy has not been demonstrated beyond three months in placebo-controlled studies, and in case of prolonged treatment, the benefit should be reassessed at regular intervals.</td></tr>
<tr><td>Safety*</td><td>The Committee for Medicinal Products for Human Use (CHMP) concluded that prucalopride was generally well tolerated; common adverse events were consistent with previous clinical trials and no new safety concerns were identified in men.

In an integrated analysis of 17 double-blind placebo-controlled studies, prucalopride was given orally to approximately 3,300 patients with chronic constipation. Of these, over 1,500 patients received prucalopride at the recommended dose of 2 mg per day, while approximately 1,360 patients were treated with 4 mg prucalopride daily. The most frequently reported adverse reactions associated with prucalopride 2 mg therapy are headache (17.8%) and gastrointestinal symptoms (abdominal pain (13.7%), nausea (13.7%) and diarrhoea (12.0%)). The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse events were mild to moderate in intensity.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Costs
Tariff status
Activity costs</td><td>
<table>
<tr><th>Drug & Dosage</th><th>30 day cost/per patient</th><th>Annual Cost per patient</th></tr>
<tr><td>Prucalopride 2mg tablets, Adult dose, 2 mg once daily, review treatment if no response after 4 weeks.</td><td>£63.77</td><td>£765.24</td></tr>
<tr><td>Prucalopride 1mg tablets, Elderly dose, Initially 1 mg once daily, increased if necessary to 2 mg once daily, review treatment if no response after 4 weeks.</td><td>£41.45 for 1mg daily dose.

If dose increased to 2mg, then cost of 2mg for 30 days is £63.77.</td><td>£497.40 (1mg dose)</td></tr>
<tr><td>Senna 7.5mg tablets, two daily</td><td>£2.33</td><td>£27.96</td></tr>
<tr><td>Docusate 100mg capsules, 200mg daily</td><td>£4.18</td><td>£50.16</td></tr>
<tr><td>Macrogol compound oral powder sachets NPF sugar free, 1-2 daily</td><td>£4.14-£8.28</td><td>£49.68 - £99.36</td></tr>
</table>
N.B. Doses are for general comparison and do not imply therapeutic equivalence.
</td></tr>
<tr><td>Cost effectiveness (if available)</td><td>N/A</td></tr>
<tr><td>Potential number of patients in Bedfordshire and Luton</td><td>From the AWMSG assessment of prucalopride use in men:
Based on incidence figures from the NICE costing template for TA211, the company estimates there are 574 women eligible for prucalopride in NHS Wales in the first year. In earlier prucalopride trials, approximately 12% of</td></tr>
</table>

Impact per 100,000 population **Affordability considerations**	enrolled patients were male, which the company assumes reflects the proportion of male patients in practice. The company therefore estimates the number of men eligible for prucalopride treatment to be 78, of which it anticipates uptake will be 10% in the first year, rising to 50% by year five. The company assumes population growth of 1% per annum, and also assumes that a third of patients discontinue prucalopride each year. This analysis is based on prucalopride displacing use of lubiprostone, on the basis that their respective NICE recommendations (NICE TA211 and NICE TA318) position them similarly in the care pathway. In the last financial year, 239 patients were prescribed prucalopride in Bedfordshire CCG (total cost £99,900) and 207 patients in Luton CCG (total cost £71,694) – in both cases, the sex of the patients who were prescribed prucalopride is unknown. Based on the assumption from the above trial, quoted by AWMSG, that 12% reflects the proportion of male patients in practice eligible for prucalopride, we would expect 29 male patients in Bedfordshire CCG and 25 male patients in Luton CCG to be prescribed prucalopride. However, we anticipate that these numbers will be smaller as we are already aware of a small number of male patients who have been prescribed prucalopride, and that uptake would be gradual. There may also be a cost saving associated with not prescribing other laxatives e.g. senna, macrogol. Both hospitals may also see a reduction in the number of hospital admissions for men with chronic constipation who were previously not eligible for prucalopride due to the formulary status. However, it is difficult to quantify the cost saving but worth taking into consideration. Overall, we anticipate that there will only be a small number of male patients who will be prescribed prucalopride.
Decisions from other bodies **Comments sought from –**	NHS Midlands and Lancashire Commissioning Supporting Unit https://www.lancsmmg.nhs.uk/medicines-library/prucalopride/ NHS Somerset Clinical Commissioning Group http://formulary.somersetccg.nhs.uk/?page_id=484 All Wales Medicines Strategy Group http://www.awmsg.org/awmsgonline/app/appraisalinfo/918
Evidence strengths and limitations	None

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1- Search Strategy

Appendix 2 – References

1. LMEN: Prucalopride for chronic idiopathic constipation in men Specialist Pharmacy Services (SPS) review. Accessed May 2020. https://www.sps.nhs.uk/articles/prucalopride-for-chronic-idiopathic-constipation-in-men/

2. Efficacy and Safety of Prucalopride in Chronic Constipation: An Integrated Analysis of Six Randomized, Controlled Clinical Trials. Accessed May 2020. https://link.springer.com/article/10.1007/s10620-016-4147-9

3. Use of Prucalopride for Chronic Constipation: A Systematic Review and Meta-analysis of Published Randomized, Controlled Trials. Accessed May 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930296/ .

4. An overview of the efficacy and safety of prucalopride for the treatment of chronic idiopathic constipation. Accessed May 2020. https://www.tandfonline.com/doi/abs/10.1080/14656566.2019.1668927

5. Prucalopride for the treatment of constipation: a view from 2015 and beyond. Accessed May 2020. https://www.tandfonline.com/doi/abs/10.1080/17474124.2019.1568238

6. eBNF, accessed May 2020, https://bnf.nice.org.uk/.

7. Summary of Product Characteristics for Prucalopride (Resolor) 2mg film-coated tablets. Accessed May 2020. https://www.medicines.org.uk/emc/product/586/smpc

8. Prucalopride. NHS Midlands and Lancashire Commissioning Supporting Unit. Accessed May 2020. https://www.lancsmmg.nhs.uk/medicines-library/prucalopride/

9. Prescribing Formulary. NHS Somerset Clinical Commissioning Group. Accessed May 2020. http://formulary.somersetccg.nhs.uk/?page_id=484

10. Prucalopride (Resolor). All Wales Medicines Strategy Group. Accessed May 2020. http://www.awmsg.org/awmsgonline/app/appraisalinfo/918

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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