NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Prucalopride for the treatment of chronic constipation in women

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Prucalopride is recommended as an option for the treatment of chronic constipation only 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.

1.2 If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.

1.3 Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has supervised the woman's previous courses of laxative treatments specified in 1.1.

2 The technology

2.1 Prucalopride (Resolor, Movetis) is a selective serotonin (5-HT4) receptor agonist that predominantly stimulates colonic motility. Prucalopride has a UK marketing authorisation for the 'symptomatic

treatment of chronic constipation in women in whom laxatives fail to provide adequate relief'.

2.2 Prucalopride is administered orally. The summary of product characteristics (SPC) states that the recommended dose of prucalopride is 2 mg once daily for adult women (up to 65 years old) and 1 mg once daily for older women (over 65 years). The dose for older women can be increased to 2 mg once daily if needed. If once-daily prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.

2.3 The SPC reports that the most common adverse effects that may be associated with prucalopride treatment include headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhoea). Most adverse effects occur at the start of treatment and usually subside within a few days of continued treatment. For full details of side effects and contraindications, see the SPC.

2.4 Prucalopride is available in 1-mg and 2-mg tablets. The acquisition cost of prucalopride 1 mg is £38.69 for a pack of 28 tablets. The acquisition cost of prucalopride 2 mg is £59.52 for a pack of 28 tablets (excluding VAT; 'British National Formulary' [BNF], 60th edition). The manufacturer estimated that the annual cost of treatment with prucalopride is £622 for adult women and £403 for older women (excluding any monitoring costs), assuming that each woman receives treatment for an average of 220 days each year. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of prucalopride and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer described nine trials that provided evidence on the clinical effectiveness of prucalopride in people with chronic constipation. There were three pivotal phase III randomised, double-blind, placebo-controlled trials in adults (aged 18–65 years) with chronic constipation (PRU-INT-6, PRU-USA-11 and PRU-USA-13), one phase III, randomised, double-blind, placebo-controlled trial in older people (65 years or older, PRU-INT-12), one trial in adults (18 years or older) with opioid-induced constipation (PRU-INT-8), one retreatment study (PRU-USA-28) and three extended, open-label, single-arm, observational studies (PRU-INT-10, PRU-USA-22 and PRU-INT-17). The key clinical evidence presented by the manufacturer was derived from the three pivotal trials, which reported the efficacy of prucalopride compared with placebo in adults, and PRU-INT-12, which reported the efficacy of prucalopride compared with placebo in older people. The number of people randomised to PRU-INT-6, PRU-USA-11, PRU-USA-13 and PRU-INT-12 was 720, 628, 651 and 305 respectively. Approximately 90% of people in the pivotal trials were women. The manufacturer also presented other trials, which reported additional safety considerations and response rates (see section 3.8). The manufacturer's submission stated that people were enrolled in the pivotal trials and PRU-INT-12 if they had a history of chronic constipation (defined as no more than two spontaneous complete bowel movements per week) and one or more of the following for at least 6 months before the screening visit:

- straining during at least 25% of bowel movements

- very hard or hard stools in at least 25% of bowel movements
- sensation of incomplete evacuation for at least 25% of bowel movements.

3.2 There was a 2-week run-in period for each pivotal trial and for PRU-INT-12, in which no laxative medication (except for rescue medication) was allowed. People in the pivotal trials were then randomised 1:1:1 to prucalopride 2 mg, prucalopride 4 mg or placebo. People in PRU-INT-12 were also randomised to prucalopride 1 mg. If people had not had a bowel movement for 3 days or more, they could receive a single dose of 15 mg bisacodyl as rescue medication (medications used for quick relief of symptoms). If a bowel movement did not occur, the dose of bisacodyl could be increased; if there was still no bowel movement after this, an enema could be administered. In the pivotal trials people were treated for 12 weeks and in PRU-INT-12 people were treated for 4 weeks. Data were collected at 4- and 12-week time points in the pivotal trials and at 4 weeks in PRU-INT-12.

3.3 The primary outcome measure in the pivotal trials was three or more spontaneous complete bowel movements per week which was evaluated over the first 4 weeks of treatment and averaged over the full 12 weeks of the trial. The proportion of people with an average increase of one or more spontaneous complete bowel movements per week compared with baseline was measured as a secondary outcome in the trials. The proportion of people treated with prucalopride 2 mg in the pivotal trials who had three or more spontaneous complete bowel movements per week during weeks 1–4 ranged from 23.7% to 32.1%, compared with 9.8% to 11.5% for placebo (all $p \leq 0.001$). During weeks 1–12, the proportion of people treated with prucalopride 2 mg who had three or more spontaneous complete bowel movements per week ranged from

19.5% to 28.9% compared with 9.6% to 13.0% for placebo (all $p \leq 0.01$).

3.4 The proportion of people treated with prucalopride 2 mg in the pivotal trials who had an average increase of one or more spontaneous complete bowel movements per week (the secondary outcome measure) during weeks 1–4 ranged from 41.0% to 56.5% compared with 20.9% to 25.5% for placebo (all $p \leq 0.001$). During weeks 1–12 of treatment, the proportion of people who had an average increase of one or more spontaneous complete bowel movements per week ranged from 38.1% to 50.3% for prucalopride 2 mg compared with 20.9% to 27.5% for placebo (all $p \leq 0.001$).

3.5 In PRU-INT-12 the proportion of people treated with prucalopride who had an average of three or more spontaneous complete bowel movements per week during weeks 1–4 was 39.5% for prucalopride 1 mg and 32.0% for prucalopride 2 mg, compared with 20.0% for placebo ($p \leq 0.05$). In addition, the proportion of people treated with prucalopride who had an average increase of one or more spontaneous complete bowel movements per week during weeks 1–4 was 61.1% for prucalopride 1 mg and 56.9% for prucalopride 2 mg compared with 33.8% for placebo ($p \leq 0.05$).

3.6 The manufacturer's submission reported quality-of-life data from the pivotal trials, which were derived from Patient Assessment of Constipation – Symptoms (PAC-SYM) and Patient Assessment of Constipation – Quality of Life (PAC-QOL) scores. All pivotal trials showed a significantly greater improvement in PAC-QOL scores for people treated with prucalopride compared with placebo at weeks 1–4 and weeks 1–12 (both $p < 0.001$ compared with placebo). Statistically significant improvements in PAC-SYM scores were also seen in all three trials at weeks 1–4 ($p \leq 0.001$ compared with placebo) and in all trials except PRU-INT-6 at weeks 1–12

($p \leq 0.05$). PRU-INT-12 also reported quality-of-life data for older women derived from PAC-SYM and PAC-QOL scores. Statistically significant improvements in PAC-SYM and PAC-QOL scores were shown for prucalopride 1 mg compared with placebo at week 4 (both $p \leq 0.05$). Improvements in PAC-SYM and PAC-QOL scores for prucalopride 2 mg compared with placebo were seen at week 4 but they did not reach statistical significance.

3.7 Surveys of the SF-36 mental component summary and the SF-36 physical component summary were taken during the run-in period and at weeks 4 and 12 of the pivotal trials. No trials showed statistically significantly greater improvements in SF-36 scores for prucalopride 2 mg compared with placebo at week 12. A statistically significant improvement in the SF-36 physical component summary at week 4 was only seen in the PRU-INT-6 study for prucalopride 2 mg compared with placebo ($p \leq 0.05$). Additional evidence provided by the manufacturer in response to the appraisal consultation document suggested however that when only the cohort of patients who responded to treatment is compared with placebo, a statistically significant difference between the effect of prucalopride and placebo is shown. The SF-36 data were not used further in subsequent sections of the manufacturer's submission.

3.8 The following three single-arm extension studies were designed to assess the long-term tolerability and safety of prucalopride:

- PRU-INT-10: included people from PRU-INT-6 (pivotal trial) and PRU-INT-12 (trial in older people).
- PRU-USA-22: included people from PRU-USA-3 (phase II dose–response trial), PRU-USA-11 and PRU-USA-13 (pivotal trials), PRU-USA-21 (phase II dose–response trial), PRU-USA-25 (phase III dose–titration trial), PRU-USA-27 (opioid-induced

chronic constipation trial) and PRU-USA-28 (phase III retreatment trial).

- PRU-INT-17: included people from PRU-INT-8 and PRU-INT-14 (both opioid-induced chronic constipation trials).

Studies PRU-INT-10, PRU-USA-22 and PRU-INT-17 had durations of 24, 36 and 12 months respectively. People received prucalopride doses ranging from 0 to 4 mg. Results from these studies reported that prucalopride treatment was associated with an improvement in constipation from baseline at all time points (this was statistically significant in PRU-INT-10 and PRU-USA-22) and a decrease in the use of laxatives. At 12 months, on average, less than 50% of people remained in these trials. The reasons for stopping treatment included insufficient treatment response (18%), withdrawal of consent (15%) and adverse events (9%). However for the three trials, most people (approximately 45%) discontinued treatment because the previous trial sponsor decided to stop the prucalopride development programme worldwide.

3.9 The manufacturer reported that prucalopride was generally well tolerated and that the majority of adverse events in the clinical trials were mild or moderate. In PRU-INT-6, 80.8% of people in the prucalopride 2 mg arm reported at least one adverse event, compared with 66.0% in the placebo arm. The incidence of serious adverse events was 2.1% in both the prucalopride and placebo arms. The most frequently reported adverse events included headache, nausea and abdominal pain. The incidence of diarrhoea in the prucalopride 2 mg arm (13.0%) was more than twice that of the placebo arm (5.4%). The adverse event profiles in the PRU-USA-11 and PRU-USA-13 trials were similar to those in the PRU-INT-6 trial. The onset of these adverse events was most frequently reported on the day after the start of treatment (‘day one’) and the

duration was short. The manufacturer reported that when day one was excluded from the analysis, the incidence of adverse events was comparable among the treatment groups.

3.10 The manufacturer developed a decision analytic model based on patient-level data from the clinical trials. All data from the included trials, for men and women, were used in the model, however all analyses presented by the manufacturer were derived using data from women only. The model compared prucalopride 1 mg daily (for older women) and prucalopride 2 mg daily (for adult women) with placebo for up to 52 weeks. In both arms, bisacodyl as rescue medication was allowed, and if it was used, any bowel movements in the following 48 hours were not included in the analysis. In the base case, results were presented for all women (that is, adult women and older women). Treatment duration was 4 weeks, after which women could only continue treatment if they had three or more spontaneous complete bowel movements per week.

3.11 Two additional analyses were presented. One incorporated data for adult women only and one incorporated data for older women only. For the first 12 weeks, the model for adult women included randomised controlled trial data for all women treated with prucalopride 2 mg. Additional observational trial data were incorporated up to a further 40 weeks after the initial trial period. The model in older women incorporated randomised controlled trial data for women treated with prucalopride 1 mg in the first 4 weeks followed by observational data for up to 1 year.

3.12 No discounting was applied in the model because both costs and utility values were modelled for 52 weeks. The only costs incorporated in the economic model were the list prices of prucalopride 2 mg (£2.13 per tablet) and prucalopride 1 mg (£1.38 per tablet). Costs and utility values for placebo plus rescue therapy

were not included in the model. The manufacturer assumed that women would take their treatment for only part of the year (220 days). Adverse events and their associated costs were not included in the model. The manufacturer acknowledged that the rates of adverse events were comparable between prucalopride and placebo and therefore they considered that including these events would not affect the outcome of the analysis.

3.13 Clinical data incorporated in the model were derived from the three pivotal trials, two trials in older people (PRU-INT-12 and PRU-USA-26) and the extension studies. Patient characteristics from these studies were used to inform the disease states in the model. Further patient characteristics were obtained from other trials not fully described in the manufacturer's submission, including three additional dose–response trials (PRU-INT-1, PRU-INT-2 and PRU-USA-3) and two phase II trials (PRU-FRA-1 and PRU-GBR-4). No methods or results for these trials were included in the submission. PAC-SYM and PAC-QOL data from the clinical trials were mapped to EQ-5D through SF-36 scores using the generalised least squares regression method. People who had chronic constipation who did not respond to prucalopride were assumed to have no quality-adjusted life year (QALY) gain.

3.14 The manufacturer's base case presented an average cost-effectiveness ratio because no cost for the comparator was included in the model. The average cost of prucalopride for all women was £498 with an average QALY gain of 0.0316, resulting in an average incremental cost-effectiveness ratio (ICER) of £15,700 per QALY gained. The average cost of prucalopride for adult women (18–64 years) was £622 with an average QALY gain of 0.0369, resulting in an ICER of £16,800 per QALY gained. The average cost of prucalopride for older women (65 years or older)

was £403 with an average QALY gain of 0.0342, resulting in an ICER of £11,700 per QALY gained.

3.15 The manufacturer also presented an analysis that included all women who had an additional bowel movement per week (the secondary outcome measure in the pivotal trials). The manufacturer estimated that, for all women, the annual cost per person to reach this secondary outcome would be £498 with an average QALY gain of 0.0277, resulting in an ICER of £18,000 per QALY gained. For adult women, the cost would be £622 with an average QALY gain of 0.0342, resulting in an ICER of £18,000 per QALY gained. The cost for older women was £403 with a QALY gain of 0.0255, resulting in an ICER of £15,800 per QALY gained.

3.16 The manufacturer presented probabilistic sensitivity analyses for all women, adult women and older women, with and without an adjustment for baseline severity of constipation. The probabilistic sensitivity analysis results showed that the probabilities of the ICERs for prucalopride exceeding £20,000 per QALY gained were approximately 45%, 44% and 47% for all women, adult women and older women respectively. The probabilities of the ICERs for prucalopride exceeding £30,000 per QALY gained were approximately 40%, 36% and 45% for all women, adult women and older women respectively. The manufacturer reported that the main factors affecting cost effectiveness were:

- the effect of constipation severity at baseline on treatment effectiveness (that is, if the treatment effect is assumed to be the same regardless of baseline severity, the probability of prucalopride being cost effective at £20,000 per QALY gained is increased)
- the ability to identify women whose constipation did not respond to prucalopride at a very early stage of treatment

- the acquisition cost of prucalopride
- the utility values derived from mapping PAC outcome measures (PAC-SYM and PAC-QOL) to EQ-5D scores.

3.17 The ERG reviewed the evidence submitted by the manufacturer on the clinical and cost effectiveness of prucalopride. It noted that the three pivotal trials (PRU-INT-6, PRU-USA-11 and PRU-USA-13) formed the basis of the manufacturer's assessment of clinical effectiveness. The ERG was unclear how people from the original trials were selected for the extension studies because no baseline data were provided in the manufacturer's submission. The ERG considered it possible that the people in the extension studies had constipation that was not necessarily refractory to laxative treatment. The ERG further noted that the extension studies included both older people and people with opioid-induced chronic constipation and that the results were not separated. The ERG was also concerned that the high rate of withdrawal from the extension studies (more than 50% of people at 12 months) was likely to have resulted in people who were relatively more satisfied with their treatment continuing with treatment compared with those dropping out.

3.18 Overall, the ERG noted that there was a considerable quantity of clinical-effectiveness evidence in adults that suggested an improvement in chronic constipation for people treated with prucalopride compared with placebo. The ERG calculated the weighted average of the effect of prucalopride across the pivotal trials and estimated that 28% of people reached the primary outcome of three or more spontaneous complete bowel movements per week after treatment with prucalopride 2 mg compared with 10.6% of people treated with placebo after 1–4 weeks. After 1–12 weeks, 23.8% of people treated with prucalopride 2 mg reached the

primary outcome compared with 11.4% of people treated with placebo.

3.19 The ERG was uncertain whether the population in the trials reflected the population covered by the marketing authorisation or decision problem for prucalopride. It noted that in the three pivotal trials, 17% of people at baseline answered that they had found their previous laxative treatment adequate and may not have been eligible for the trials (that is, not laxative refractory). The ERG further considered that people who have one or two bowel movements per week while on laxative treatment were likely to be having beneficial effects from laxatives and therefore their constipation may not have been refractory to laxatives. It also considered that any two of the criteria used alone by the manufacturer to describe chronic constipation (section 3.1 above) would be unlikely to be sufficient evidence of treatment failure with laxatives.

3.20 The ERG considered that the comparator used in the pivotal trials (placebo plus rescue medication with bisacodyl) did not represent standard clinical practice for chronic constipation. It suggested that a more appropriate comparator would have been a variety of oral laxative treatments, at the discretion of the treating clinician. It further commented that the manufacturer's submission did not consider some of the comparators outlined in the decision problem, including invasive procedures (such as rectal interventions) and bowel surgery.

3.21 The ERG assessed the manufacturer's cost-effectiveness analysis and considered its methodological approach acceptable. It noted that the manufacturer's decision to exclude the cost of the comparator from the analysis was conservative. However, the ERG was concerned that precise details of the trials used to inform the

inputs in the economic model were not given or did not fully correspond with those described in the manufacturer's submission. It noted that five trials used for the economic model (PRU-INT-1, PRU-INT-2, PRU-USA-3, PRU-FRA-1 and PRU-GBR-4) were not fully described in the submission.

3.22 The ERG noted that quality of life data from PAC-QOL and PAC-SYM scores were mapped to the EQ-5D using SF-36 scores obtained from the trials. The ERG was concerned that the SF-36 data did not directly contribute to EQ-5D scores, even though these results were available from the trials, and no sensitivity analysis was undertaken by the manufacturer to test the impact of using SF-36 results.

3.23 The ERG noted that the manufacturer's model only allowed for variation in the response rate and mean treatment rates to be analysed. It also noted that no explicit allowance was made for withdrawal from treatment at any time after 4 weeks and that the assumption that the last measured QALY gain was sustained for the rest of the year was not tested in the model.

3.24 The ERG noted there were more adverse events in the prucalopride arms than in the placebo arms of the trials. It was concerned that adverse events, including rare events, and their associated costs were not included in the model.

3.25 The ERG ran the manufacturer's model using alternative scenarios and assumptions including the following:

- Assuming that people who responded to treatment with prucalopride would receive treatment for a mean of 220 days or 365 days.
- Using response rates taken from pooled trial estimates at week 4 calculated in the effectiveness review.

- Allowing for the possibility that adverse events may be higher in the prucalopride arm than the placebo arm by increasing costs by 5% and reducing QALY gain by 5% in the prucalopride arm.
- Reducing the effectiveness (QALY) of prucalopride and placebo uniformly by 25%, 50% and 75% to allow for possible variation in the regression method used to calculate the QALYs.

The ERG concluded that the results from its sensitivity analysis were not significantly different from those provided by the manufacturer.

3.26 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of prucalopride, having considered evidence on the nature of chronic constipation and the value placed on the benefits of prucalopride by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee discussed the nature of chronic constipation and current clinical practice for the treatment of people with laxative-refractory chronic constipation. The clinical specialists stated that chronic constipation has a wide spectrum of severity and that for a minority of people with intractable constipation there can be very low quality of life and feelings of hopelessness. The Committee understood that current practice is a stepped approach to management starting with lifestyle and dietary changes. If these changes provide inadequate relief, different classes of oral

laxatives are available. For some people chronic constipation can become intractable, and relatively invasive procedures (such as suppositories, enemas, rectal irrigation and manual disimpaction) may be tried. The Committee heard from the manufacturer that the intended position of prucalopride in the treatment pathway for chronic constipation is after failure of oral laxatives due to inadequate efficacy or intolerance. The Committee noted the clinical specialists' advice that people who have had an inadequate response to an oral laxative often try many different types before considering invasive options. The Committee was aware that the scope for this appraisal was to consider the use of prucalopride in women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief, and for whom invasive procedures are being considered.

4.3 The Committee discussed patient selection and the conduct of the clinical trials. The Committee noted that the inclusion criteria in the trials were people with chronic constipation in whom laxatives failed to provide adequate relief. The Committee also noted that it was unclear how inadequate relief had been defined in the trials. In addition, the Committee heard from the ERG that up to 30% of the people in the trials responded to laxatives, so their constipation may not have fitted these inclusion criteria. The Committee was also aware of concerns raised during consultation that because adequate relief had not been properly defined by the manufacturer, this could contribute to widespread use of prucalopride in people in whom laxatives had not necessarily failed. However, the Committee heard from the clinical specialists that it is often difficult to differentiate between people for whom laxatives do not provide adequate relief and those who no longer want to use laxatives because of the side effects, despite any treatment benefit they may achieve. Based on advice from the clinical specialists, the

Committee concluded that inadequate relief from previous laxative treatments could be defined by duration of follow-up and by the number of laxatives previously used.

4.4 The Committee considered the comparator, placebo plus rescue medication with bisacodyl, used in the clinical trials. The Committee noted the concerns of the NHS representatives that the use of placebo as a comparator did not reflect current clinical practice for chronic constipation and that prucalopride had not been compared with some of the less expensive oral laxatives commonly used in the NHS. It was aware that similar concerns had been raised during consultation. The Committee also noted that bisacodyl was used as rescue medication in the clinical trials and it could have been a comparator. However it heard from the manufacturer that in clinical practice, people for whom laxatives fail to provide adequate relief sometimes adopt a 'do nothing' approach and later present with faecal impaction. At this stage, invasive procedures (such as rectal irrigation and faecal disimpaction) and occasionally surgery are used to resolve the constipation. The Committee also heard from the clinical specialists that people whose constipation has not responded adequately to laxatives would usually be encouraged to stop all current treatments and then restart their laxative regimen in a stepwise manner. The clinical specialists further stated that in clinical trials for studies of chronic constipation, placebo is often the comparator. The clinical specialists noted that invasive procedures have risks and provide only temporary relief, and are therefore not appropriate comparators to prucalopride. In view of the different classes of laxatives used in clinical practice and the fact that many of these are often used in rotation to avoid tolerance, the Committee agreed that it would be difficult to define a standard laxative regimen as a comparator for people with laxative-refractory chronic constipation.

4.5 The Committee discussed the clinical effectiveness of prucalopride. It was aware of the data presented by the manufacturer that showed prucalopride to be more effective than placebo in women with chronic constipation during the trial periods of 4 weeks for older women (65 years and older) and 12 weeks for adult women (18–64 years). The Committee was aware of concerns from consultees that the short duration of the clinical trials may not adequately reflect the efficacy of a drug that treats a long-term condition. It was also aware of the open-label extension studies that showed that prucalopride was efficacious in the long term. The Committee questioned how well the extension studies proved that the clinical effectiveness of prucalopride is sustained, given the high drop-out rate. However, it heard from the manufacturer that 90% of the people whose constipation did not respond to treatment in the extension studies also had no response in the randomised trial period (that is, were already non-responders), which suggests that people who do not respond early with prucalopride will not respond with continued treatment. The Committee heard from the manufacturer that people whose constipation responds to treatment with prucalopride are likely to have a response within 28 days of treatment, and that people whose constipation does not respond in that period are unlikely to have a response with treatment longer than 28 days. The Committee also heard from the clinical specialists that prucalopride's mechanism of action is on the gut muscle rather than the mucosa and that this mechanism of action means that efficacy could be sustained in the long term. Although some consultees argued that the mechanism of action of prucalopride is not unique and that it did not prove that tolerance to prucalopride (and subsequent dose increases) did not occur, the Committee was persuaded that some people may benefit from continued use of prucalopride. The Committee was persuaded that the stopping rule in the SPC for prucalopride, which restricts

treatment after 4 weeks to women who gained normal bowel movements while on treatment, would be followed by prescribing clinicians and limit use in people who do not respond early to treatment with prucalopride.

4.6 The Committee noted from the ERG's analysis that a substantial proportion of people with chronic constipation in the pivotal trials responded to placebo (see section 3.18). The clinical specialists stated that it was not unusual for people with gastrointestinal conditions to respond to placebo, and that they were not surprised by the high response to placebo in the trials. The Committee was assured that in clinical practice, any treatment that provides at least a 10% improvement in response over placebo is considered to be clinically meaningful. The Committee considered that the available data demonstrated that prucalopride was clinically effective in providing relief to women with laxative-refractory chronic constipation.

4.7 The Committee considered the adverse effects of prucalopride. It noted that diarrhoea and headaches were common in the clinical trials but that most side effects were mild to moderate in severity. The Committee heard from the clinical specialists that these side effects are often symptoms of chronic constipation and may not always be caused by prucalopride. It also heard that people regularly have their medication reviewed by their clinicians to make sure that their constipation is not a side effect of any treatments they are receiving (prescription and non-prescription). The Committee was aware that prucalopride belongs to the same class of drugs as cisapride, which is associated with serious cardiovascular side effects. The Committee heard from clinical specialists that prucalopride has a selective mechanism of action and may not have the same cardiovascular side effects as

cisapride. However, the Committee was concerned that some side effects of prucalopride, such as possible cardiovascular effects, may only be apparent after long-term treatment and were not observed in the clinical trials conducted.

Cost effectiveness

4.8 The Committee considered the quality-of-life data presented in the manufacturer's submission. The Committee noted that disease specific quality-of-life measures (PAC-QOL and PAC-SYM) were mapped to EQ-5D using SF-36 scores obtained from the trials. The Committee heard from the clinical specialists that people with a PAC-QOL score of 4 (equating to an EQ-5D of 0.585), as observed in the clinical trials, have substantially limited quality of life. Although PAC-QOL and therefore EQ-5D improved with prucalopride treatment, the Committee noted that this was not reflected in the SF-36 data directly measured in the trials. The Committee was aware of the concerns raised by the ERG that the assumptions used in the mapping equation could not be tested and may therefore not be robust. It questioned if SF-36 data from the trials would give similar EQ-5D improvement had they been used in the model; and why this had not been tested in a sensitivity analysis. The manufacturer stated that further SF-36 data (not in the submission) for people whose constipation responded to treatment showed statistically significant improvement for prucalopride compared with placebo. Sensitivity analyses of these outcomes were conducted by the manufacturer and were considered to be consistent with results from the ERG's analyses when assumptions regarding the acquisition cost of prucalopride and the number of days on treatment were varied. The Committee concluded that changing the mapping equation to include SF-36 instead of PAC-QOL would unlikely alter the results of the model substantially.

4.9 The Committee discussed the manufacturer's ICER calculations and the ERG's exploratory analysis, in which the ERG ran the manufacturer's model using different alternative scenarios and assumptions. The Committee noted that in the base case presented by the manufacturer, the average cost of prucalopride for all women was £498 with a QALY gain of 0.0316, resulting in an ICER of £15,700 per QALY gained. The average cost of prucalopride for adult women was £622 with a QALY gain of 0.0369, resulting in an ICER of £16,800 per QALY gained. The average cost of prucalopride for older women was £403 with a QALY gain of 0.0342, resulting in an ICER of £11,700 per QALY gained. Although the Committee had concerns about the generalisability of the populations selected for the clinical trials to the decision problem and about the extrapolation of benefits beyond the trials, the Committee concluded that the ERG had shown the manufacturer's cost-effectiveness estimates to be reasonably stable under varied assumptions.

4.10 The Committee 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. It agreed that these costs could be reduced by using prucalopride. Based on these considerations, the Committee agreed that the costs of chronic constipation presented by the manufacturer in its economic model were probably conservative and if the true resource costs were included, it was likely that the ICERs presented by the manufacturer would be reduced.

4.11 The Committee was persuaded that the most plausible ICER for prucalopride compared with placebo plus rescue medication was likely to be below £20,000 per QALY gained. Therefore, the Committee agreed that prucalopride would be an appropriate use

of NHS resources and recommended that prucalopride should be considered as an option for the treatment of chronic constipation in women only when they have used the highest tolerated recommended doses of at least two laxatives from different classes for at least 6 months, without having adequate relief of their constipation, and invasive treatment is being considered. The Committee acknowledged that if treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered, in line with current advice in the marketing authorisation. The Committee agreed with the clinical specialists that women suitable for treatment with prucalopride should be treated by a clinician with experience in managing chronic constipation, who has supervised the use of previous courses of laxatives in the same women.

Summary of Appraisal Committee's key conclusions

TAXXX (STA)	**Appraisal title:** Prucalopride for the treatment of chronic constipation in women	**FAD section(s)**
Key conclusion		
Prucalopride is recommended as an option for the treatment of chronic constipation only 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 patient should be re-examined and the benefit of continuing treatment reconsidered. Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has supervised the woman's previous courses of laxative treatments specified above.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee noted that for some people chronic constipation can become intractable and relatively invasive procedures (such as suppositories, enemas, rectal irrigation or manual disimpaction) may be tried when oral laxatives fail to provide adequate relief. However these measures are associated with risks and only provide temporary relief. The clinical specialists stated that chronic constipation has a wide spectrum of severity and that for a minority of people with intractable constipation there can be very low quality of life and feelings of hopelessness.	4.2, 4.4
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee was aware that the scope for this appraisal was to consider the use of prucalopride in women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief, and for whom invasive procedures are being considered. The Committee heard from the clinical specialists that in clinical practice, any treatment that provides at least a 10% improvement in response over placebo is considered to be clinically meaningful. The Committee considered that the available data demonstrated that prucalopride was clinically effective in providing relief to women with laxative-refractory chronic constipation.	4.2. 4.6
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the manufacturer that the intended position of prucalopride in the treatment pathway for chronic constipation	4.2

	is after failure of oral laxatives because of inadequate efficacy or intolerance. The Committee recommended that prucalopride should only be offered to women who have used the highest tolerated recommended doses of at least two laxatives from different classes for at least 6 months, without having adequate relief, and for whom invasive treatment is being considered for their constipation.	4.11
Adverse effects	The Committee noted that diarrhoea and headaches were common in people who were treated with prucalopride, but that most side effects were mild to moderate in severity. The Committee was concerned that some side effects of prucalopride, such as possible cardiovascular effects, may only be apparent after long-term treatment and were not observed in the clinical trials conducted.	4.7
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered that the available data demonstrated that prucalopride was clinically effective in providing relief to women with laxative-refractory chronic constipation. The Committee was aware of concerns from consultees that the short duration of the clinical trials may not adequately reflect the efficacy of a drug that treats a long-term condition.	4.6 4.5
Relevance to general clinical practice in the NHS	The Committee was aware that the scope for this appraisal was to consider the use of prucalopride in women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief, and for whom invasive procedures are being considered. The Committee noted that the comparator used in clinical trials was placebo plus rescue medication with bisacodyl, which did not reflect current practice for chronic constipation in the NHS. The Committee heard that more invasive procedures such as rectal irrigation and occasionally surgery are used to treat people with laxative-refractory constipation. It heard from the clinical specialists that generally people whose constipation has not responded adequately to laxatives would usually be encouraged to stop all current treatments, and	4.2, 4.4

	then restart their laxative regimen in a stepwise manner. The Committee agreed that it would be difficult to define a standard laxative regimen as a comparator for people with laxative-refractory chronic constipation. The Committee agreed that the resource costs of treating chronic constipation such as referrals to secondary care and invasive procedures could be reduced by using prucalopride.	4.10
Uncertainties generated by the evidence	The Committee noted the concerns of the NHS representatives that the use of placebo as a comparator did not reflect current clinical practice for chronic constipation. The Committee noted that it was unclear how inadequate relief had been defined in the trials. The Committee also noted that up to 30% of the people in the trials responded to laxatives, so their constipation may not have been laxative refractory. The Committee questioned how well the extension studies proved that the clinical effectiveness of prucalopride is sustained, given the high drop-out rate.	4.4 4.3 4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The manufacturer provided separate analyses of adult women (18–64 years), older women (65 years or older) and all women combined. The marketing authorisation states that the recommended dose of prucalopride is 2 mg once daily for adult women (up to 65 years old) and 1 mg once daily for older women (over 65 years). The dose for older women can be increased to 2 mg once daily if needed.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee considered that the available data demonstrated that prucalopride was clinically effective in providing relief to women with chronic constipation.	4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered evidence on the cost effectiveness of prucalopride compared with placebo, including quality-of-life estimates, costs and ICERs presented by the manufacturer.	4.8 - 4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that disease specific quality-of life measures (PAC-QOL and PAC-SYM) were mapped to EQ-5D using SF-36 scores obtained from the trials. The	4.8

	Committee was aware of the concerns raised by the ERG about the mapping process. The Committee had concerns about the generalisability of the populations who were selected for the clinical trials to the decision problem, and about the extrapolation of benefits beyond the trials. The Committee noted the sensitivity analysis conducted by the ERG showed the model results to be stable under various assumptions.	4.9 4.8
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that disease specific quality-of-life measures (PAC-QOL and PAC-SYM) were mapped to EQ-5D using SF-36 scores obtained from the trials. Although PAC-QOL and therefore EQ-5D improved with prucalopride treatment, the Committee noted that this was not reflected in the SF-36 data directly measured in the trials. The Committee was aware that the SF-36 data presented in the manufacturer's submission were not used in the model and were not tested in a sensitivity analysis. The Committee heard from the manufacturer that further SF-36 data that were not in their submission for people whose constipation responded to treatment showed statistically significant improvement in chronic constipation for those treated with prucalopride compared with placebo. Sensitivity analyses of these outcomes were conducted by the manufacturer and were considered to be consistent with results from the ERG's analyses when assumptions regarding the acquisition cost of prucalopride and the number of days on treatment were varied.	4.8
Are there specific groups of people for whom the technology is particularly cost effective?	For adult women the ICER was £16,800 per QALY gained. For older women, the ICER was £11,700 per QALY gained.	4.9
What are the key drivers of cost effectiveness?	The Committee 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. It agreed that the costs of chronic	4.10

	constipation presented by the manufacturer in its economic model were probably conservative and if the true resource costs were included, it was likely that the ICERs presented by the manufacturer would be reduced.	
Most likely cost-effectiveness estimate (given as an ICER)	The Committee was persuaded that the most plausible ICER for prucalopride compared with placebo plus rescue medication was likely to be below £20,000 per QALY gained.	4.11
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	-
End-of-life considerations	Not applicable to this appraisal.	-
Equalities considerations	No equality issues were raised during the scoping exercise or through the course of this appraisal.	-

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline 61(2008). Available from www.nice.org.uk/guidance/CG61
- Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. NICE clinical guideline 99 (2010). Available from www.nice.org.uk/guidance/CG99

7 Review of guidance

7.1 The guidance on this technology will be considered for review in October 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee C
September 2010

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Kathryn Abel

Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine/Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay Member

Dr Mary Cooke

Lecturer School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Physician, Bucknall Hospital

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance Research and Development Unit

Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager UK and Ireland, Medtronic

Dr Wasim Hanif MD FRCP

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Professor Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital

Professor Gary McVeigh

Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay Member

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman

Health Economics Research Group, Brunel University

Dr Judith Wardle

Lay Member

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Raphael Yugi
Technical Lead

Fiona Rinaldi
Technical Adviser

Lori Farrar
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration (WMHTAC):

- Pennant M, Orlando R, Barton P et al. Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief, June 2010

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Movetis

II Professional/specialist and patient/carer groups:

- PromoCon
- Association of Continence Advice
- British Society of Gastroenterology
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS Greenwich
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Napp Pharmaceuticals (dantron)
- Norgine Pharmaceuticals (sterculia/frangula, macrogol, docusate sodium enema)
- National Institute for Health Research Health Technology Assessment Programme
- West Midlands Health Technology Assessment Collaboration (WMHTAC)

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on prucalopride for the treatment of chronic constipation in women by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Anton Emmanuel, Senior Lecturer and Hon Consultant Gastroenterologist, nominated by British Society of Gastroenterology – clinical specialist
- Professor Peter Whorwell, Professor of Medicine and Gastroenterology, nominated by Movetis – clinical specialist
- June Rogers MBE, Team Director, nominated by PromoCon – patient expert

D The following individuals were nominated as NHS Commissioning experts by the selected NHS Trust allocated to this appraisal. They gave their NHS commissioning personal view on prucalopride for the treatment of chronic constipation in women by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Rena Amin, Joint Head of Medicines Management selected by NHS Greenwich – NHS Commissioning expert

E Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Movetis