# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Premeeting briefing

## Prucalopride for the treatment of chronic constipation in women

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

**The manufacturer was asked to provide:**

- further information on the use of laxatives in the clinical trials
- details of the patient data used to inform the clinical effectiveness of prucalopride
- data on adverse events from the trials
- details of data used in the economic model
- details of any comparators used in the economic model
- details of any probabilistic sensitivity analyses
- details of the assumptions used in the economic model, including the stopping rules applied.

### Licensed indication

Prucalopride (Resolor, Movetis) is indicated for the 'symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief'.

# Key issues for consideration

## *Clinical effectiveness*

- Many patients responded to the use of bisacodyl treatment during the trials and may not have been laxative-refractory. Up to 1.56 bowel movements per week were induced by bisacodyl and up to 17.5% of patients considered treatment with placebo effective. Does the Committee consider the population from the trials reflects the population (laxative-refractory) under consideration in this appraisal? Are there sufficient clinical data to form conclusions on the clinical effectiveness of prucalopride?
- Placebo was used as the comparator during the trials, supplemented by only one form of laxative (rescue therapy). Does the Committee consider the comparator used in the submission to be appropriate?
- There was high attrition of patients from the long-term observational studies (>50% at 12 months) and patients continuing treatment were likely to have been those satisfied with their treatment compared to those who discontinued treatment. Does the Committee consider these data accurately reflect the long-term clinical effectiveness of prucalopride?
- Results for (rarer) adverse events (those in <5% participants) were not reported in the manufacturer's submission. Does the Committee have any concerns regarding this missing information?

## *Cost effectiveness*

- Patient Assessment of Constipation quality-of-life (PAC-QOL), a disease-specific quality-of-life measure was used, which was then converted to EQ-5D using a two stage mapping equation. Does the Committee consider the mapping process to be robust? Does the Committee have any concerns about the utility values used in the economic analysis and the assumptions made around them?

- No adverse events or their associated costs were included in the model. Does the Committee consider this appropriate?
- In the economic model, it is assumed that the last measured QALY gain (at 4 or 12 weeks) is sustained for the rest of the year. This is based on data from the single arm long-term observational studies. Does the Committee consider this assumption plausible?
- Only the cost of prucalopride was included in the economic model. No comparator costs were included. Does the Committee consider this appropriate?

# 1 Decision problem

## *1.1 Decision problem approach in the manufacturer's submission*

| | |
|---|---|
| Population | Women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief |
| Intervention | For women aged 65 years or younger, the dosage of prucalopride is 2 mg once daily. For women older than 65 years, the dosage is 1 mg once daily, which can be increased to 2 mg once daily if needed. If once daily prucalopride is not effective after 4 weeks of treatment, the treatment should be stopped. |
| Comparators | Standard therapy without prucalopride. In the manufacturer's submission, this refers to rescue therapy with laxatives. |
| Outcomes | • Proportion of patients with three or more spontaneous complete bowel movements per week<br>• Number of spontaneous complete bowel movements per week<br>• Improvement in symptoms of constipation<br>• Adverse effects of treatment<br>• Health-related quality of life |
| Economic evaluation | Quality-adjusted life years (QALYs) are used in the economic analysis and are derived through mapping PAC-QOL measurements to EQ-5D. The time horizon is 1 year. Costs are estimated from the perspective of the NHS. |

## *1.2 Evidence Review Group comments*

### 1.2.1 Population

The population defined in the scope for this appraisal was 'women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief and for whom more invasive procedures such as direct rectal intervention are being considered'. The trials underpinning the manufacturer's submission were conducted in adults (10% men and 90% women), of whom many had responded to treatment with bisacodyl. The Evidence Review Group (ERG) noted that the patient data analysed by the manufacturer was not consistent with the population defined in the decision problem. Consequently, the scope's emphasis on those who have received numerous laxative treatments and are considering more invasive measures was reduced.

### 1.2.2 Intervention

Prucalopride belongs to a subgroup of drugs that act on serotonin receptors (serotonin (5-HT4) receptor agonist) that stimulate motility in the colon. It is not considered to fall into one of the five classes of laxative treatments. Prucalopride currently has a marketing authorisation only for the symptomatic treatment of chronic constipation in women and is not licensed in men.

### 1.2.3 Comparators

The comparator in the manufacturer's submission was standard therapy without prucalopride. Other comparators outlined in the scope of this appraisal, that is, invasive procedures (such as rectal interventions, including enemas, suppositories and manual evacuation) and bowel surgery, were not considered by the manufacturer. The ERG thought the exclusion of these comparators was unjustified because invasive treatments are likely to be used after failure with all laxative treatments. The ERG also considered that the comparator used in the trials (placebo plus rescue therapy), which underpins the

manufacturer's submission, was not appropriate because it did not represent standard clinical practice for chronic constipation. The ERG proposed that a variety of laxative treatments at the discretion of the treating clinician would have been a more appropriate comparator for this patient group.

### 1.2.4 Outcomes

The ERG noted that the outcomes included in the manufacturer's submission were in accordance with the NICE scope for this guidance. The primary outcome measure was three or more spontaneous complete bowel movements per week. The ERG noted that quality of life was specified as an outcome in the scope but a more specific measure of quality of life (PAC-QOL) was used in the submission.

Complete results for adverse events were not presented in the manufacturer's submission. Of note, the incidences of rarer adverse events (that is, those that occurred in less than 5% of patients) were not provided.

### 1.2.5 Time frame

The time frame used in the economic model was 52 weeks. The ERG explained that data from 12-week single-arm trials (4-week trials in some cases) were extrapolated to 52 weeks. The ERG noted that these studies had a high attrition rate (average greater than 50% at 12 months), which may have biased the data because patients who were more satisfied with their treatment were more likely to remain in the studies. In addition, no information was available about patients receiving placebo treatment, so assumptions about long-term comparative effectiveness could not be made.

## *1.3 Statements from professional/patient groups and nominated experts*

The clinical specialists stated that dietary and lifestyle modifications, followed by laxatives, should be used before prucalopride is considered. They noted

that about half of the patients had a bowel movement only once in 2 weeks before treatment with prucalopride and therefore the modest proportion (25%) of patients who met the primary end point in the clinical trials (normalisation of bowel frequency, defined as three or more spontaneous complete bowel movements per week) was not fully representative of those who benefited from treatment. They considered that patients felt improvements in quality of life are more important in managing this chronic problem. They also noted that there was a high incidence of adverse events associated with prucalopride, including headache and diarrhoea.

The patient representatives noted that prucalopride would be beneficial to women who would otherwise undergo rectal administration of laxatives, which most women find unacceptable. They also noted that headache, nausea and diarrhoea were common but not serious side effects.

# 2 Clinical effectiveness evidence

## *2.1 Clinical effectiveness in the manufacturer's submission*

The manufacturer's submission describes nine trials that provide evidence on the clinical effectiveness of prucalopride. There are three pivotal trials in adults (18 years or older; PRU-INT-6 [Tack 2009], PRU-USA-11 [Camilleri 2008] and PRU-USA-13 [Quigley 2009]), one trial in older patients (65 years or older; PRU-INT-12), one trial in patients with opioid-induced constipation (PRU-INT-8), one re-treatment study (PRU-USA-28) and three extended, single-arm, observational studies (PRU-INT-10, PRU-USA-22 and PRU-INT17).

The key clinical evidence was derived from the three pivotal trials, which reported the efficacy prucalopride compared with best supportive care in adult women, and a trial that reported the efficacy prucalopride compared with best

supportive care in older women (see table 1). The manufacturer also presented other trials that reported additional safety considerations and response rates.

**Table 1 Summary of key studies of prucalopride**

| Trial name | Design and duration | Participants | Intervention and comparator | Primary outcome |
|---|---|---|---|---|
| PRU-INT-6 | 12 weeks<br>Phase III double-blind multicentre RCT including 11 sites in the UK<br>(n = 716) | Adults with a history of chronic constipation[†], and one or more of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements | Prucalopride:<br>2 mg o.d. (n = 238)<br>4 mg o.d. (n = 238)<br>Placebo o.d.<br>(n = 240) | Proportion of patients having ≥ 3 SCBM/week, averaged over 12 weeks |
| PRU-USA-11 | 12 weeks<br>Phase III double-blind multicentre RCT (USA only)<br>(n = 620) | Adults with a history of chronic constipation[†], and one or more of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements | Prucalopride:<br>2 mg o.d. (n = 207)<br>4 mg o.d. (n = 204)<br>Placebo o.d.<br>(n = 209) | Proportion of patients having ≥ 3 SCBM/week, averaged over 12 weeks |
| PRU-USA-13 | 12 weeks<br>Phase III double-blind multicentre RCT (USA only)<br>(n = 641) | Adults with chronic constipation[†], and one or more of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements | Prucalopride<br>2 mg o.d.: (n = 214)<br>4 mg o.d. (n = 215)<br>Placebo o.d.<br>(n = 212) | Proportion of patients having ≥ 3 SCBM/week, averaged over 12 weeks |
| PRU-INT-12 | 4 weeks<br>Phase III double-blind multicentre RCT including 13 sites in the UK<br>(n = 303) | Adults ≥ 65 years with chronic constipation[†], and one or more of the following[‡]: very hard or hard stools, a sensation of incomplete evacuation, or straining during defecation with at least 25% of bowel movements | Prucalopride:<br>1 mg o.d. ( n = 76)<br>2 mg o.d. (n = 75)<br>4 mg o.d. (n = 80)<br>Placebo o.d.<br>(n = 72) | Proportion of patients having ≥ 3 SCBM/week, averaged over 4 weeks |

SCBM, spontaneous complete bowel movements; o.d., once daily; RCT, randomised controlled trial.
[†] Defined as ≤ 2 SCBM/week; [‡] For a minimum of 6 months before the screening visit

There was a 2-week run-in period for each trial (PRU-INT-6, PRU-USA-11, PRU-USA-13 and PRU-INT-12) during which no laxative medication (except for rescue medication) was allowed. Patients were then randomised 1:1:1 to either prucalopride 2 mg, prucalopride 4 mg or placebo. For the women aged

65 years or older, a 1 mg dose was administered. If patients had not had a bowel movement for 3 days or more, they could receive a single dose of 15 mg bisacodyl as rescue medication. The dose of bisacodyl could be increased until the patient had a bowel movement otherwise an enema would be administered. Patients were followed up for 12 weeks (4 weeks for the trial in older women) and data was collected at 4- and 12-week time points. (For more information, see pages 32-48 of the manufacturer's submission.)

The manufacturer's submission (page 18) states that for the purpose of the trials, chronic constipation is defined according to the Rome III criteria. These criteria are the presence of two or more of the following symptoms for at least 3 months, with symptom onset at least 6 months before diagnosis:

- straining during at least 25% of defecations
- lumpy or hard stools in at least 25% of defecations
- sensation of incomplete evacuation for at least 25% of defecations
- sensation of anorectal obstruction/blockage for at least 25% of defecations
- manual manoeuvres to facilitate at least 25% of defecations (for example, digital evacuation, support of the pelvic floor)
- fewer than three defecations per week.

**Results**

A summary of the primary and secondary outcomes from the pivotal trials is shown in tables 2, 3 and 4. All trials showed significantly more patients achieved the primary outcome measure when treated with prucalopride compared with placebo. For more information see pages 59-77 of the manufacturer's submission and pages 24-26 of the ERG report.

**Table 2. Primary Outcome: proportion patients with a mean of three or more spontaneous complete bowel movements per week for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2 mg | Placebo | % Difference |
|---|---|---|---|---|
| PRU-INT-6 | Weeks 1 - 4 | 56/236 (23.7%)*** | 25/240 (10.4%) | 13.3% |
| | Weeks 1 - 12 | 46/236 (19.5%)** | 23/240 (9.6%) | 9.9% |
| PRU-USA-11 | Weeks 1 - 4 | 61/190 (32.1%)*** | 19/193 (9.8%) | 22.3% |
| | Weeks 1 - 12 | 55/190 (28.9%)*** | 25/193 (13.0%) | 15.9% |
| PRU-USA-13 | Weeks 1 - 4 | 61/209 (29.2%)*** | 24/208 (11.5%) | 17.7% |
| | Weeks 1 - 12 | 50/209 (23.9%)** | 25/207 (12.1%) | 11.8% |
| **$Pooled results** | | | | |
| | Weeks 1 - 4 | 28.0% | 10.6% | 17.4% |
| | Weeks 1 - 12 | 23.8% | 11.4% | 12.4% |
| ***p < 0.001 compared with placebo<br>**p < 0.01 compared with placebo<br>$As calculated by the ERG | | | | |

**Table 3. Secondary Outcome: proportion of patients with a mean increase of one or more spontaneous complete bowel movements per week for patients in pivotal trials**

| Trial | Time point | Prucalopride 2 mg | Placebo | % Difference |
|---|---|---|---|---|
| PRU-INT-6 | Weeks 1 - 4 | 93/227 (41.0%)*** | 49/235 (20.9%) | 20.1% |
| | Weeks 1 - 12 | 86/226 (38.1%)*** | 49/234 (20.9%) | 17.2% |
| PRU-USA-11 | Weeks 1 - 4 | 100/177 (56.5%)*** | 46/189 (24.3%) | 32.2% |
| | Weeks 1 - 12 | 89/177 (50.3%)*** | 49/189 (25.9%) | 24.4% |
| PRU-USA-13 | Weeks 1 - 4 | 102/209 (48.8%)*** | 53/208 (25.5%) | 23.3% |
| | Weeks 1 - 12 | 89/209 (42.6%)*** | 57/207 (27.5%) | 15.1% |
| **$Pooled results** | | | | |
| | Weeks 1 - 4 | 48.2% | 23.4% | 24.8% |
| | Weeks 1 - 12 | 43.2% | 24.6% | 18.6% |
| ***p < 0.001 compared with placebo<br>$As calculated by the ERG | | | | |

**Table 4. Mean number of spontaneous complete bowel movements per week for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2 mg (mean change from baseline) | Placebo (mean change from baseline) |
|---|---|---|---|
| PRU-INT-6 | Weeks 1 - 4 | 1.7 (1.4)*** n = 236 | 0.9 (0.5) n = 240 |
| | Weeks 1 - 12 | 1.6 (1.2)*** n = 236 | 1.0 (0.5) n = 240 |
| PRU-USA-11 | Weeks 1 - 4 | 2.5 (2.1)*** n = 190 | 1.1 (0.7) n = 193 |
| | Weeks 1 - 12 | 2.3 (1.9)*** n = 190 | 1.3 (0.8) n = 193 |
| PRU-USA-13 | Weeks 1 - 4 | 2.1 (1.6)*** n = 209 | 1.0 (0.6) n = 208 |
| | Weeks 1 - 12 | 1.9 (1.5)*** n = 209 | 1.2 (0.8) n = 207 |
| **$Pooled results (weighted by study size)** | | | |
| | Weeks 1 - 4 | 2.1 (1.7) | 1.0 (0.6) |
| | Weeks 1 - 12 | 1.9 (1.5) | 1.2 (0.7) |

***p < 0.001 compared with placebo
**p < 0.01 compared with placebo
$As calculated by the ERG

The manufacturer reported quality-of-life data from the pivotal trials, which were derived from the Patient Assessment of Constipation – Symptoms (PAC-SYM) score and the PAC-QOL score. All trials showed a significantly greater improvement in PAC-QOL scores for patients treated with prucalopride compared with placebo. Surveys of the short form 36 (SF-36) mental component summary (MCS) were taken during the run-in period and at weeks 4 and 12. These were not used to inform the inputs in the manufacturer's model. No trials showed a significantly greater improvement in SF-36 MCS scores for patients treated with prucalopride compared with placebo. A summary of the quality of life outcomes from the pivotal trials is shown in tables 5, 6, 7 and 8. For further information, see the manufacturer's submission pages 64 - 66.

**Table 5. Mean PAC-SYM score (mean change from baseline) for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2mg | Placebo | % Difference |
|---|---|---|---|---|
| PRU-INT-6 | Week 4 | 1.46 (-0.67)*** | 1.73 (-0.34) | -0.33 |
| | Week 12 | 1.44 (-0.66) | 1.69 (-0.37) | -0.29 |
| PRU-USA-11 | Week 4 | 1.26 (-0.65)*** | 1.57 (-0.38) | -0.27 |
| | Week 12 | 1.26 (-0.63)* | 1.49 (-0.46) | -0.17 |
| PRU-USA-13 | Week 4 | 1.40 (-0.65)*** | 1.59 (-0.38) | -0.27 |
| | Week 12 | 1.26 (-0.78)*** | 1.52 (-0.45) | -0.33 |
| $Pooled results (weighted by study size) | | | | |
| | Weeks 1-4 | 1.38 (-0.66) | 1.64 (-0.37) | -0.29 |
| | Weeks 1-12 | 1.33 (-0.69) | 1.57 (-0.42) | -0.27 |

*** p≤0.001 compared to placebo * p≤0.05 compared to placebo
$ As calculated by the ERG

**Table 6. Mean PAC-QOL score (mean change from baseline) for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2mg | Placebo | % Difference |
|---|---|---|---|---|
| PRU-INT-6 | Week 4 | 1.37 (-0.65)*** | 1.72 (-0.31) | -0.34 |
| | Week 12 | 1.36 (-0.65)*** | 1.66 (-0.38) | -0.27 |
| PRU-USA-11 | Week 4 | 1.28 (-0.87)*** | 1.83 (-0.38) | -0.49 |
| | Week 12 | 1.29 (-0.84)*** | 1.73 (-0.47) | -0.37 |
| PRU-USA-13 | Week 4 | 1.43 (-0.77)*** | 1.67 (-0.43) | -0.34 |
| | Week 12 | 1.34 (-0.85)*** | 1.65 (-0.47) | -0.38 |
| $Pooled results (weighted by study size) | | | | |
| | Weeks 1-4 | 1.36 (-0.76) | 1.74 (-0.37) | -0.39 |
| | Weeks 1-12 | 1.33 (-0.77) | 1.68 (-0.44) | -0.33 |

*** p<0.001 compared to placebo
$ As calculated by the ERG

**Table 7. Mean SF-36 MCS score (mean change from baseline) for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2mg | Placebo |
|---|---|---|---|
| PRU-INT-6 | Week 4 | 46.4 (2.2) | 45.9 (0.7) |
| | Week 12 | 47.6 (3.2) | 46.1 (1.5) |
| PRU-USA-11 | Week 4 | 48.8 (3.5) | 46.7 (1.3) |
| | Week 12 | 48.0 (2.1) | 47.3 (2.0) |
| PRU-USA-13 | Week 4 | 47.6 (2.7) | 47.4 (1.3) |
| | Week 12 | 48.6 (3.4) | 47.3 (1.4) |
| [$] Pooled results (weighted by study size) | | | |
| | Weeks 1-4 | 47.5 (2.8) | 46.6 (1.1) |
| | Weeks 1-12 | 48.1 (2.9) | 46.9 (1.6) |
| [*] p≤0.05 compared to placebo [$] As calculated by the ERG | | | |

**Table 8. Mean SF-36 PCS score (mean change from baseline) for all patients in pivotal trials**

| Trial | Time point | Prucalopride 2mg | Placebo |
|---|---|---|---|
| PRU-INT-6 | Week 4 | 46.7 (2.6)[*] | 44.9 (1.1) |
| | Week 12 | 46.3 (2.1) | 45.6 (1.8) |
| PRU-USA-11 | Week 4 | 48.5 (2.3) | 47.1 (0.9) |
| | Week 12 | 49.4 (2.7) | 47.9 (1.4) |
| PRU-USA-13 | Week 4 | 48.9 (2.5) | 48.7 (1.6) |
| | Week 12 | 49.1 (2.7) | 49.4 (2.5) |
| [$] Pooled results (weighted by study size) | | | |
| | Weeks 1-4 | 48.0 (2.5) | 46.8 (1.2) |
| | Weeks 1-12 | 48.2 (2.5) | 47.5 (1.9) |
| [*] p≤0.05 compared to placebo<br>[$] As calculated by the ERG | | | |

PRU-INT-12 reported the efficacy of prucalopride compared with best supportive care in older women (65 years or older) with chronic constipation. The methodology for this trial was identical to that of the three pivotal trials except that patients were randomised to placebo or doses of 1 mg prucalopride (with an increase in dose to 2 mg also permitted) and that the duration of the study was only 4 weeks. The proportion of women treated with prucalopride

1 mg and 2 mg who had a mean of three or more spontaneous complete bowel movements per week during weeks 1-4 was 39.5% and 32.0% respectively compared with 20.0% for placebo (see table 9). In addition, the proportion of patients treated with prucalopride 1 mg and 2 mg who had an average increase of one or more spontaneous complete bowel movements per week during weeks 1-4 was 61.1% and 56.9% respectively compared with 33.8% for placebo ($p \leq 0.05$). For more information please see pages 67-68 of the manufacturer's submission.

**Table 9: Results for spontaneous complete bowel movements, symptoms and quality of life for older patients (>65yrs) in the PRU- INT-12 trial (page 29 of the ERG report)**

| | Prucalopride 1 mg (n = 76) | Prucalopride 2 mg (n = 75) | Placebo (n = 70) |
|---|---|---|---|
| a) Mean of ≥ 3 SCBMs/week, n (%) | | | |
| Run-in | 0/76 | 0/75 | 2/70 (2.9) |
| Week 1-4 | 30/76 (39.5) | 24/75 (32.0) | 14/70 (20.0) |
| b) Average increase of ≥ 1 SCBM/week, n (%) | | | |
| Week 1-4 | 44/72 (61.1)* | 41/72 (56.9)* | 22/65 (33.8) |
| c) Average number of SCBM/week, mean (mean change from baseline) | | | |
| Week 1-4 | 2.7 (1.9)* | 2.4 (1.7)* | 1.7 (0.6) |
| d) Overall PAC-SYM score, mean (mean change from baseline) | | | |
| Week 4 | 0.88 (-0.53)* | 1.10 (-0.37) | 1.22 (-0.23) |
| e) Overall PAC-QOL score, mean (mean change from baseline) | | | |
| Week 4 | 0.95 (-0.53)* | 1.12 (-0.30) | 1.26 (-0.20) |

*p ≤ 0.05 compared with placebo

PAC-QOL, Patient Assessment of Constipation – quality of life; PAC-SYM, Patient Assessment of Constipation – Symptoms; SCBM, spontaneous complete bowel movement.

The PRU-INT-12 trial also reported quality-of-life data derived from the PAC-SYM and PAC-QOL scores. The overall mean PAC-SYM scores for

prucalopride 1 mg and 2 mg was 0.88 and 1.10 respectively compared with 1.22 for placebo (see table 9). The overall mean PAC-QOL scores for prucalopride 1 mg and 2 mg at 4 weeks was 0.95 and 1.12 respectively compared with 1.26 for placebo ($p \leq 0.05$).

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

- PRU-INT-10 – includes patients from PRU-INT-6 (pivotal trial) and PRU-INT-12 (older patient trial) studies.
- PRU-USA-22 – includes patients from PRU-USA-3 (a phase II, dose-response trial), PRU-USA-11 and PRU-USA-13 (pivotal trials), PRU-USA-21 (a phase II 'other' dose-response trial), PRU-USA-25 (a phase III, 'other' dose-titration trial), PRU-USA-27 (an opioid-induced chronic constipation trial) and PRU-USA-28 (a phase III retreatment trial) studies.
- PRU-INT-17 – includes patients from PRU-INT-8 and PRU-INT-14 (both opioid-induced chronic constipation trials) studies.

Studies PRU-INT-10, PRU-USA-22 and PRU-INT-17 had a duration of 24, 36 and 12 months respectively. All patients received prucalopride doses ranging from 0 to 4 mg. A summary of the patient demographics, and reasons for treatment discontinuation in these trials is shown in table 10. At 12 months, on average, less than 50% of patients remained in these trials. These studies were continued until patients had dropped out. Reasons for treatment discontinuation included insufficient treatment response (17%), withdrawal of consent (15%) and adverse events (8%), however the majority of discontinuations were due to the decision of the previous trial sponsor to stop the prucalopride developmental program worldwide. For more details, see pages 30 - 33 of the ERG report.

**Table 10: Summary of patient demographic data and reasons for discontinuation (extended observational studies)**

| | PRU-INT-10 | PRU-USA-22 | PRU-INT-17 |
|---|---|---|---|
| Number of patients enrolled (M/F) | 693 (100/593) | 1775 (199/1576) | 96 (33/63) |
| Mean age years (range) | 50.8 (18-92) | 47.2 (18-89) | 52.4 (24-83) |
| Mean duration of treatment days (range) | 342.2 (1-733) | 231.17 (1-721) | 127.32 (2-286) |
| Discontinuations (n[%]) | 658 (95) | 1775 (100) | 96 (100) |
| Insufficient response | 119 (17) | 316 (17.8) | 12 (12.5) |
| Adverse event | 70 (10) | 140 (7.9)[†] | 6 (6.3) |
| Withdrew consent | 53 (8) | 326 (18.4) | 7 (7.3) |
| Lost to follow-up | 29 (4) | 209 (11.8) | 1 (1.0) |
| Non-compliant | 11 (2) | 59 (3.3) | 1 (1.0) |
| Ineligible to continue | 4 (1) | 17 (1.0) | - |
| Asymptomatic/cured | 3 (<1) | 13 (<1) | - |
| Death | 1 (<1) | - | 4 (4.2) |
| Other | 368 (53)[‡] | 695 (39.2)[‡] | 65 (67.7)[‡] |

[†]Three deaths included; [‡]Mostly discontinuations due to the decision of previous sponsor to stop the prucalopride developmental program

The manufacturer reported that prucalopride was generally well tolerated and that the majority of adverse events were mild or moderate. In PRU-INT-6, 80.8% of patients 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 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 first day of treatment and the duration was short. The manufacturer reported that when day one was excluded from the analysis, the incidence of adverse events was comparable between the treatment groups. A summary of the types of adverse events reported in the pivotal trails are shown in table 11. For more details see pages 85-87 of the manufacturer's submission and pages 34-35 of the ERG report.

**Table 11: Number (percentage) of adverse events (page 35 of ERG report)**

| | **Older women (>65yrs)** | | **Adults (≥18yrs)** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **PRU-INT-12** | | **PRU-INT-6** | | **PRU-USA-11** | | **PRU-USA-13** | |
| | Placebo | PRU | Placebo | PRU | Placebo | PRU | Placebo | PRU |
| Patients with adverse event | 32 (44.4) | 104 (45.0) | 161 (67.1) | 348 (73.1) | 149 (71.3) | 326 (79.3) | 140 (66.0) | 336 (78.3) |
| Gastrointestinal disorders | 6 (8.3) | 38 (16.5) | 96 (40.0) | 225 (47.3) | 80 (38.3) | 211 (51.3) | 53 (25.0) | 189 (44.1) |
| Cardiac disorders | 3 (4.2) | 7 (3.0) | 6 (2.5) | 20 (4.2) | 2 (1.0) | 9 (2.2) | 4 (1.9) | 7 (1.6) |
| Nervous system disorders | 6 (8.3) | 19 (8.2) | 49 (20.4) | 160 (33.6) | 35 (16.7) | 148 (36.0) | 41 (19.3) | 126 (29.4) |
| Renal and urinary disorders | 1 (1.4) | 4 (1.7) | 4 (1.7) | 22 (4.6) | 9 (4.3) | 22 (5.4) | 0 (0.0) | 16 (3.7) |

PRU: prucalopride

## *2.2 Evidence Review Group comments*

The ERG noted that the manufacturer had provided results from several trials to support the clinical effectiveness of prucalopride. However, the following issues were identified:

- The ERG noted that three trials were identified by the manufacturer as being pivotal (PRU-INT-6, PRU-USA-11, PRU-USA-13) and formed the basis for most of the assessment of clinical effectiveness. However, the rationale for the particular focus on these three trials was not given.

- The ERG noted that there is a considerable quantity of clinical effectiveness evidence in adults that suggests an improvement in constipation from prucalopride compared to placebo
- The ERG felt that it was unclear how participants from the original trials were selected for follow-up studies as no baseline data for these patients were provided in the manufacturer's submission. The ERG also noted that the patients in these studies included a mixture of older patients and those with opioid-induced chronic constipation and that the results were not separated for these different groups. The ERG was concerned that the high rate of attrition of patients from these studies (more than 50% at 12 months) was likely to have resulted in a patient group continuing with treatment who were relatively more satisfied with their treatment compared with those dropping out.
- The ERG considered that the criteria used to recruit patients into the trials did not fit the patient population in the licensed indication because patients with severe chronic constipation are likely to have been having treatment for far longer than the 6 months that was enforced in the trials. It also considered that the patients would have had numerous treatments and not necessarily just one type of laxative.
- The ERG considered that patients having one or two bowel movements per week while on laxative treatment were likely to be having beneficial effects from laxatives, and therefore were not laxative refractory. The ERG also noted that just any two of the criteria used by the manufacturer to describe chronic constipation alone would be unlikely to be sufficient evidence of treatment failure with laxatives.
- The ERG noted that satisfaction scores at 12 months from three extension trials were used to justify the assumption of the sustained effectiveness of prucalopride from 12 to 52 weeks for the economic model. The ERG noted that many patients dropped out due to insufficient response (17%), withdrawal of consent (15%) and adverse events (8%). The ERG also noted

that at 12 months, on average less than half of the patients remained in these trials. The ERG therefore considered this assumption to be unjustified. The ERG also stated that without a placebo arm in the trials, the true effectiveness of prucalopride is uncertain.

- The ERG considered the comparator used in the pivotal trials to be inappropriate. It considered that an appropriate comparator may have been a variety of laxative treatments, at the discretion of the treating clinician and that the use of a single laxative treatment as rescue therapy does not represent clinical practice. The ERG also considered that discounting any bowel movements that occurred due to laxatives was biased against the placebo group that received more laxative therapy than the prucalopride group.

# 3 Cost effectiveness

## *3.1 Cost effectiveness in the manufacturer's submission*

The manufacturer developed a decision analytic model based on patient-level data for women only. The model compared prucalopride with placebo. In both arms, rescue therapy with bisacodyl was allowed. In the base case, results were presented for women aged younger than 65 years (adults) who receive prucalopride 2 mg daily and women aged 65 years and above (elderly) who receive prucalopride 1 mg daily. Treatment duration was 4 weeks after which patients could only continue treatment if they had three or more spontaneous complete bowel movement per week). Two additional analyses were presented, one that incorporated data for adult women only and one that incorporated data for older women only. For the first 12 weeks, the model for adult women includes randomised controlled trial data for all women treated with prucalopride 2 mg. Additional observational trial data were incorporated up to a further 40 weeks beyond the initial trial period. The model in older women incorporated randomised controlled trial data for patients treated with

prucalopride 1 mg in the first 4 weeks followed by observational data up to 1 year. No discounting was applied in the model because both costs and utilities were modelled for 1 year. Costs and utilities of best supportive care were not included in the model. The manufacturer stated that the costs of best supportive care are negligible and would not affect the outcome of the analysis. Adverse events were not included in the model. The manufacturer acknowledged that the rates of adverse events were comparable between the prucalopride and the placebo arms and therefore it was considered that including these events would not affect the outcome of the analysis. For more information, please refer to pages 115 - 124 of the manufacturer's submission.

**Health-related quality of life (HRQoL)**

Clinical data incorporated into the model were derived from the three pivotal trials, the trial for older women, the continuation studies and other trials not fully described in the manufacturer's submission. Three additional dose-response trials (PRU-INT-1, PRU-INT-2 and PRU-USA-3), one trial in older patients (PRU-USA-26) and two phase II trials (FRA-1, GBR-4) were used to inform the model but no methods or results for these trials were detailed in the submission. PAC-SYM and PAC-QOL data from the clinical trials were mapped into EQ-5D using the generalised least squares regression method. Non-responders were assumed to have no QALY gain. The relationship between PAC-QOL and EQ-5D is shown in figure 1 below. PAC-QOL is an inverse measure from 1 (mild symptoms) to 4 (severe symptoms), and a patient who suffers from severe chronic constipation (PAC-QOL 4) would map onto an EQ-5D score of 0.585 (on the 0 to 1 EQ-5D scale). The assumed trend of health related quality of life for patients who either responded or did not respond to treatment compared to placebo are shown in figure 2. For more information, please refer to pages 125-134 of the manufacturer's submission and pages 54-56 of the ERG report.

**Figure 1. Relationship between PAC-QOL and EQ-5D scores (page 55 of ERG report)**

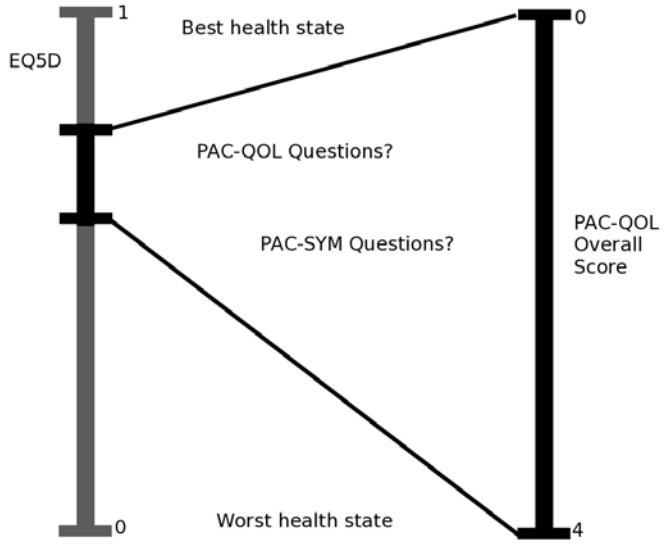
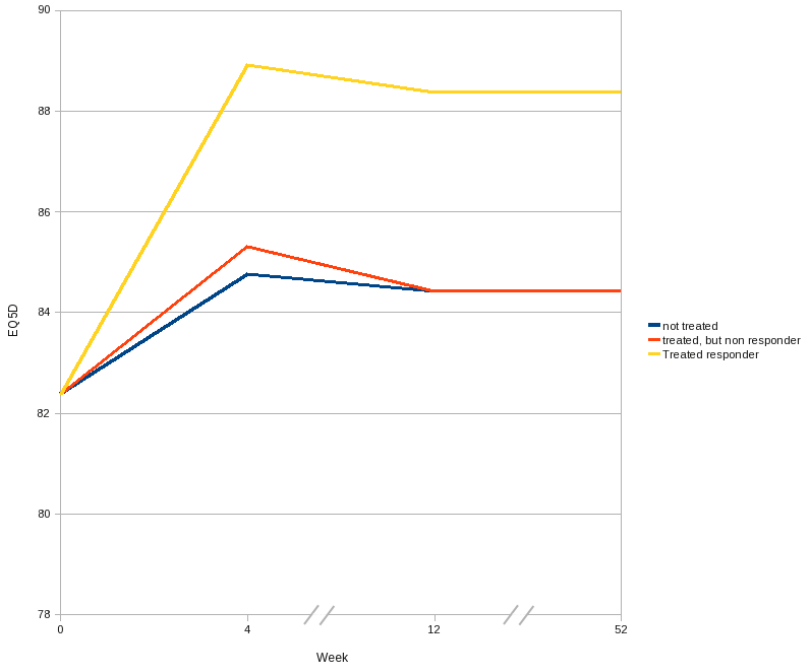



**Figure 2. Assumed health related quality of life over 12 months**




## Costs

The only costs incorporated into the economic model were the list prices of prucalopride 2 mg (£2.13 per tablet) and prucalopride 1 mg (£1.38 per tablet).

No cost was assumed for the comparator arm. The manufacturer assumed that patients would take their medication for only part of the year. Treatment compliance was included in the economic model. For more information, please refer to pages 60-63 of the ERG report. A summary of the costs used in the economic model is provided in table 12.

**Table 12 Costs**

| Cost | Dose | Cost/ tablet | Annual price (365 days) |
|---|---|---|---|
| Acquisition cost of prucalopride | 1 mg<br>2 mg | £1.38<br>£2.13 | £503<br>£777 |
| **Assuming 80% treatment compliance** | | | |
| Mean acquisition cost of prucalopride | 1 mg (older patients) annual cost | | £402 |
| | 2 mg (adult) annual cost | | £622 |
| | All women annual cost | | £498 |

## Results

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. Table 13 details the results for the groups analysed by the manufacturer.

**Table 13. Cost and QALY results for patients who had 3 or more SCBM (primary outcome; page 65 of the ERG report)**

| ≥ 3 SCBM responders | Average incremental cost/year | Average QALY gained per year (SD) | Average cost/QALY (SD) |
|---|---|---|---|
| **All women** | £498 | 0.0316 (0.1124) | £15,700 (961) |
| **Adult women** | £622 | 0.0369 (0.0450) | £16,800 (-) |
| **Older women (≥65yrs)** | £403 | 0.0342 (0.1495) | £11,700 (-) |
| QALY, quality-adjusted life year; SCBM, spontaneous complete bowel movement; SD, standard deviation. | | | |

The manufacturer also presented an analysis that included all patients who had an additional bowel movement per week (defined as partial responders). The results are presented in table 14 below.

**Table 14: Cost and QALY data for partial responders (those who had at least one SCBM; page 65 of the ERG report)**

| ≥1 SCBM responders | Average incremental cost/year (SD) | Average QALY gained per year (SD) | Average cost/QALY (SD) |
|---|---|---|---|
| **All women** | £498 (108) | 0.0277 (0.1133) | £18,000 (934) |
| **Adult women** | £622 (0) | 0.0342 (0.0430) | £18,000 ((-) |
| **Older women (≥65yrs)** | £403 (0) | 0.0255 (0.1466) | £15,815 (-) |
| QALY, quality-adjusted life year; SCBM, spontaneous complete bowel movement; SD, standard deviation. | | | |

The manufacturer presented probabilistic sensitivity analyses for the following groups: all women; adults (18–64 years) and older patients (65 years or older) with and without adjusting for baseline severity of constipation. The results are presented in table 15.

The key drivers of cost effectiveness were the effect of constipation severity at baseline on treatment effectiveness (that is, if treatment effect is assumed to be the same regardless of baseline severity, ICER is lowered), the ability to

identify non-responders at a very early stage of treatment, assumptions around response rates over 12 months, assumptions around stopping and continuation rules at 4 and 12 weeks, the acquisition cost of prucalopride and the utility values derived from the  mapping process (page 151 of the manufacturer's submission).

**Table 15 Probabilistic sensitivity analysis results (page 151 of the manufacturer's submission)**

| | All women | Adults (18 - 64 years) | Older women (> 65 years) |
|---|---|---|---|
| **Probability of cost effectiveness at £20,000/QALY** | | | |
| Adjusted for baseline constipation | 44.9% | 44.0% | 47.4% |
| Unadjusted for baseline constipation | 24.8% | 10.5% | 36.0% |
| **Probability of cost effectiveness at £30,000/QALY** | | | |
| Adjusted for baseline constipation | 40.0% | 35.5% | 45.3% |
| Unadjusted for baseline constipation | 14.7% | 0.3% | 25.4% |
| QALY, quality-adjusted life year. | | | |

## *3.2 Evidence Review Group comments*

The ERG considered that the approach used by the manufacturer in its cost-effectiveness analysis was acceptable. It also agreed that excluding the cost of the comparator was a conservative assumption but acceptable. However, the ERG had the following concerns:

- The ERG was concerned that precise details of patients that were used to inform the model (which patients and from which trials) were not given in the submission. The ERG noted that trials and studies used to inform the economic model did not fully correspond to those described in the submission. It noted that five trials used to populate the economic model

were not fully described in the submission (PRU-INT-1, PRU-INT-2 and PRU-USA-3, FRA-1 and GBR-4). Overall results from the trials were not considered to be transparently incorporated into the economic model.

- The ERG was concerned that many of the patients whose data informed the economic model did not have laxative-refractory chronic constipation because they were still responsive to laxative treatment. The ERG noted that at baseline, some patients were satisfied with their current treatments and, in many patients, bisacodyl was effective as a rescue therapy. The ERG also noted the wide range of baseline scores from the histograms supplied by the manufacturer and considered that it was not a homogenous patient group. It also noted that the distributions were skewed towards the higher end of the baseline, suggesting that many patients whose data was used to inform the economic model did not have severe chronic constipation and may not have fallen in the category of those who may be eligible for treatment with prucalopride according to the marketing authorisation.
- The ERG noted that data from PAC-QOL and PAC-SYM scores were extrapolated to EQ-5D to generate data for the economic model. This was done by first establishing the relationship between PAC and SF-36 data for each patient. The known relationship between SF-36 and EQ-5D was then used to extrapolate PAC data directly to EQ-5D. The ERG was concerned that 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 done to test the impact of SF-36 results.
- The ERG noted that the model only allowed variation in the response rate and mean treatment rates to be addressed through the compliance calculations included. The ERG noted that no explicit allowance was made for withdrawal from treatment at any time after 4 weeks. It also noted that the assumption that the last measured QALY gain is sustained for the rest of the year was not tested in the model.

- The ERG stated that presenting results that combined adult women and older women was not appropriate because the dose of prucalopride was different for the two. It considered that the results separated by age groups were more appropriate.
- The ERG noted there were more adverse events in the prucalopride arms than the placebo arms of the trials. They were concerned that adverse events, including rare events (that is, those occurring in less than 5% of patients in the trials) were not included in the model. The ERG considered that adverse event costs could be higher with prucalopride treatment, but noted that these were also not included in the model.
- The ERG was unable to verify the regression equations used to determine the treatment effects in the model. This included both the clinical effectiveness and the mapping of patient outcomes to EQ-5D.

The ERG ran the model using different alternative scenarios and assumptions including:

- Assuming that responders would receive treatment for a mean of 220 days or 365 days and using response rates taken from pooled estimates at week 4 at the appropriate dose calculated in the effectiveness review.

- Allowing for the possibility that adverse events may be higher in the treatment arm than the comparator by increasing costs by 5% and reducing QALY gains by 5% in the treatment 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 noted that the results were not significantly different from those provided by the manufacturer, as shown in tables 16 and17.

**Table 16. Deterministic analysis on adults (18-64yrs)**

| | Primary End Point (≥3 SCBM per week) | | | |
|---|---|---|---|---|
| | All patients | | Only patients answered yes to laxative question | |
| | ICERs (£/QALY) | | | |
| | WITH SRTE* | WITHOUT SRTE* | WITH SRTE* | WITHOUT SRTE* |
| Manufacturer's modelling assumptions | 16800 | 15400 | 15400 | 14200 |
| Use of pooled response rates | 16800 | 15400 | 15400 | 14200 |
| Responders treated for 365 days | 25000 | 23000 | 23100 | 21200 |
| Allowance for adverse events | 18500 | 16900 | 17000 | 15600 |
| QALY gain reduced by 25% | 22400 | 20500 | 20600 | 18900 |
| QALY gain reduced by 50% | 33600 | 30700 | 30800 | 28300 |
| QALY gain reduced by 75% | 67200 | 61400 | 61700 | 56600 |

* SRTE: Baseline Constipation Severity Related Treatment Effect

**Table 17. Deterministic analysis on older women (≥65yrs)**

| | Primary End Point (≥3 SCBM per week) | | | |
|---|---|---|---|---|
| | All patients | | Only patients answered yes to laxative question | |
| | ICER (£/QALY) | | | |
| | WITH SRTE* | WITHOUT SRTE* | WITH SRTE* | WITHOUT SRTE* |
| Manufacturer's modelling assumptions | 13800 | 14800 | 11800 | 12600 |
| Use of pooled response rates | 12400 | 13300 | 10600 | 11400 |
| Responders treated for 365 days | 19200 | 20700 | 16500 | 17700 |
| Allowance for adverse events | 13600 | 14700 | 11700 | 12500 |
| QALY gain reduced by 25% | 16500 | 17800 | 14200 | 15200 |
| QALY gain reduced by 50% | 24800 | 26700 | 21300 | 22800 |
| QALY gain reduced by 75% | 49500 | 53300 | 42600 | 45500 |

* SRTE: Baseline Constipation Severity Related Treatment Effect

### *3.3 Further considerations following premeeting briefing teleconference*

## 4 Equalities issues

No equalities issues were raised. It was noted that the marketing authorisation restricts the use of prucalopride to women only. This may appear to discriminate against men however the burden of this condition is far greater in women. From the clinical trials, approximately 85% of patients with chronic constipation were female.

## 5 Authors

Raphael Yugi and Fiona Rinaldi, with input from the Lead Team (David Black, Daniele Bryden and David Chandler).

# Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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

- Pennant M, Orlando R, Barton P et al. Prucalopride for the treatment of chronic constipation in women: A Single Technology Appraisal. WMHTAC, University of Birmingham, June 2010

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Movetis

II Professional/specialist, patient/carer and other groups:

- British Society of Gastroenterology
- NHS Greenwich
- PromoCon