

# Lubiprostone for treating chronic idiopathic constipation

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**NICE technology appraisal guidance 318**

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## 1 Guidance

- 1.1 Lubiprostone is recommended as an option for treating chronic idiopathic constipation, that is, for adults in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered.
- 1.2 If treatment with lubiprostone is not effective after 2 weeks, the person should be re-examined and the benefit of continuing treatment reconsidered.
- 1.3 Lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments specified in 1.1.

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## 2 The technology

- 2.1 Lubiprostone (Amitiza, Sucampo Pharma Europe) has a UK marketing authorisation for the 'treatment of chronic idiopathic constipation and associated symptoms in adults when response to diet and non-pharmacological measures (for example, educational measures, physical activity) are inappropriate'. It is given orally at a dose of 24 micrograms twice daily. The summary of product characteristics states that a course of treatment for constipation with lubiprostone is 2 weeks.
- 2.2 The summary of product characteristics lists the following adverse reactions for lubiprostone: nausea, palpitations, diarrhoea, abdominal distension, flatulence, abdominal discomfort, abdominal pain, indigestion, oedema (including peripheral), chest discomfort, headache, dizziness, dyspnoea, hyperhidrosis and hot flushes. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The price of lubiprostone 24 microgram capsules is £53.48 for a 56-capsule pack and £29.68 for a 28-capsule pack (prices excluding VAT; eMC Dictionary of Medicines and Devices Browser). The cost of an initial 2-week course of treatment is £29.68, after which response is assessed, and those people continuing treatment receive the 56-capsule packs. Costs may vary in different settings because of negotiated procurement discounts.

## 3 The manufacturer's submission

- 3.1 The Appraisal Committee ([section 7](#)) considered evidence submitted by the manufacturer of lubiprostone and a review of this submission by the Evidence Review Group (ERG; [section 8](#)).

### *Clinical effectiveness*

- 3.2 Evidence on the clinical effectiveness was taken from 3 phase III randomised controlled trials, 2 phase II dosing studies and 4 open-label studies. The 3 phase III randomised controlled trials were parallel-group, double-blind, placebo-controlled, multicentre studies conducted in the US (SC0131, n=242 and SC0232, n=237) and Japan (CC0831, n=124).
- 3.3 Participants of the 3 phase III trials were randomised to 4 weeks of lubiprostone (24 micrograms twice daily) or placebo. The primary outcome of the US phase III trials was frequency of spontaneous bowel movements (defined as any bowel movement occurring 24 hours or more after rescue medication) at week 1. The primary outcome of the Japanese phase III trial was the change from baseline in spontaneous bowel movements at week 1. Key secondary efficacy outcomes for all phase III trials were frequency of spontaneous bowel movements during weeks 2, 3 and 4 of treatment, and treatment response (defined as a patient with a spontaneous bowel movement frequency rate of 3 or more for a given week) at 2 weeks, for which meta-analyses were conducted. The trials also assessed the effect of lubiprostone on the symptoms of chronic constipation (number of spontaneous bowel movements within 24 hours, stool consistency, the degree of straining, constipation severity, abdominal bloating, abdominal discomfort and a global assessment of treatment effectiveness). Rescue medication (10 mg bisacodyl suppository or a saline laxative) was allowed in the trials if a patient did not have a spontaneous bowel movement for more than 3 days. Studies SC0131 and SC0232 permitted no rescue medication 48 hours before randomisation or in the first week after randomisation, and study CC0831 permitted no rescue medication 24 hours before and 48 hours after the start of treatment.

- 3.4 A modified version of the Rome II criteria for chronic idiopathic constipation was used across all phase III trials. Patients needed to have 1 or more of the following symptoms associated with at least 25% of bowel movements for at least 6 months before the baseline visit: very hard (little balls) and/or hard stools, a sensation of incomplete evacuation or straining at defecation. Patients in studies SC0131 and SC0232 also had a baseline constipation severity of fewer than 3 spontaneous bowel movements per week during the 2-week wash-out period, and patients in study CC0831 had an average of fewer than 3 spontaneous bowel movements per week for at least 6 months.
- 3.5 Overall baseline characteristics were similar across all phase III studies and treatment groups. The percentage of women ranged between 86 and 90%, mean age between 42 and 49 years, and the mean baseline spontaneous bowel movement frequency between 1.3 and 1.7 per week. Of the 479 people enrolled in studies SC0131 and SC0232, around 250 were reported as taking a medication for their constipation during the 90 days prior to enrolment. The manufacturer considered this 'previously treated' post-hoc subgroup represented a population for whom 2 lines of prior laxatives treatment had an inadequate response. This is in line with the manufacturer's proposed positioning for lubiprostone in clinical practice.
- 3.6 Lubiprostone was associated with statistically significantly higher mean spontaneous bowel movement frequencies compared with placebo at week 1 across all phase III trials (5.69 compared with 3.46,  $p < 0.0001$  [US study SC0131]; 5.89 compared with 3.99,  $p < 0.0001$  [US study SC0232]; 5.37 with lubiprostone compared with 2.93,  $p < 0.0001$  [Japanese study CC0831]). The difference in mean spontaneous bowel movement frequency at week 1 between the lubiprostone and placebo arms ranged from 1.99 to 2.44 across the phase III trials. A secondary outcome was the frequency of spontaneous bowel movements at weeks 2 to 4. During the 4 weeks of studies SC0131 and SC0232, there was a statistically significant ( $p < 0.0001$ ) difference in mean spontaneous bowel movement frequency per week between the lubiprostone and placebo arms, ranging from 1.46 to 2.41. In study CC0831, the difference was also statistically significant over the 4 weeks ( $p \leq 0.003$  at any week), although the effect plateaued at week 4. Another secondary outcome was response to treatment, which was initially classified according to the following

responder statuses: 'non-responder' (<3 spontaneous bowel movements per week), 'moderate responder' (≥3 but <4 spontaneous bowel movements per week), and 'full responder' (≥4 spontaneous bowel movements per week). In studies SC0131 and SC0232, there were statistically significant differences in responder status in favour of lubiprostone across all 4 weeks between the lubiprostone and placebo arms ( $p \leq 0.0171$ ). In study CC0831, the difference in responder status for lubiprostone compared with placebo was statistically significant at week 1 but not at weeks 2 to 4. The manufacturer attributed this to the less severe baseline constipation in the Japanese patients and the comparably small patient numbers ( $n=62$  in each arm).

- 3.7 The manufacturer conducted a post-hoc analysis for the response to treatment, in which a person initially classified as a 'moderate' or 'full responder' was reclassified as a 'responder'. The manufacturer's submission noted that over 60% of people treated with lubiprostone responded to treatment during each study week. The manufacturer assessed the response to treatment at week 2, showing a response rate of between 64.5% and 69.4% in the lubiprostone arm compared with 30.6% to 35.5% in the placebo arm, and supporting the 2-week course of treatment stated in the marketing authorisation. The manufacturer also conducted meta-analyses on the response rate for 2 different populations: the intention-to-treat population (based on all 3 phase trials) and the 'previously treated' population (based on studies, SC0131 and SC0232). The meta-analysis for the intention-to-treat population reported a relative risk of response at 2 weeks of 1.30 (95% confidence interval [CI]: 1.15 to 1.48) in favour of lubiprostone. The meta-analysis for the 'previously treated' population reported a relative risk of response at 2 weeks of 1.90 (95% CI: 1.13 to 3.17).
- 3.8 The manufacturer presented a number of other secondary outcomes for the phase III trials, including spontaneous bowel movement within 24 hours after first drug dose, time to first spontaneous bowel movement, stool consistency, degree of straining, abdominal bloating, abdominal discomfort, severity of constipation and treatment effectiveness. The results showed that lubiprostone statistically significantly improved all outcomes compared with placebo except for abdominal bloating, in which statistical significance was reached in study SC0131 but not in studies SC0232 and CC0831.

- 3.9 Health-related quality of life was assessed as a secondary endpoint in 1 of the 3 phase III trials (Japanese study CC0831), which involved self-evaluation using the SF-36 standard edition questionnaire and irritable bowel syndrome-quality of life measure questionnaire during follow-up visits 2 and 5. There was no statistically significant difference between the lubiprostone and placebo groups in any of the domains of the SF-36 questionnaire. The manufacturer also collected baseline SF-36 data in the US open-label studies.
- 3.10 In the absence of head-to-head randomised controlled trials, the manufacturer presented an indirect analysis using Bucher methodology to explore the clinical effectiveness of lubiprostone and prucalopride. Data on the effectiveness of lubiprostone were taken from the pivotal phase III trials and 2 abstracts (Rao 2012a and Rao 2012b) comparing the effectiveness of lubiprostone (25 patients) with placebo (12 patients). Data from the principal prucalopride studies were taken from the Canadian product monograph.
- 3.11 The manufacturer considered the participants of the lubiprostone trial to be more severely constipated than those in the prucalopride trials, and that the baseline spontaneous bowel movement frequency in the lubiprostone trials was around 1.5 compared with 3.5 in the prucalopride trials. It also considered the different primary outcome measure used in the prucalopride trials (complete spontaneous bowel movements). The manufacturer stated that the clinical relevance of this outcome was different to that of the spontaneous bowel movement outcome used in the lubiprostone trials, and therefore incomparable. As a result, the manufacturer conducted an indirect comparison to assess the relative clinical effectiveness of lubiprostone with prucalopride for all common outcomes, including change in spontaneous bowel movement from baseline, percentage of patients achieving an average increase in spontaneous bowel movement of 1 or more over weeks 1 to 4, spontaneous bowel movements rated as normal, hard or very hard, with no straining, with severe/very severe straining, and mean change in complete spontaneous bowel movements from baseline over weeks 1 to 4. The results of the indirect comparison showed that there was only a statistically significant difference in treatment effect in 2 of the 7 outcomes: spontaneous bowel movements rated as normal, which favoured prucalopride, and spontaneous bowel movements with severe/very severe straining, which favoured lubiprostone. For the other

outcomes lubiprostone was slightly more effective but the values did not reach statistical significance. The manufacturer concluded that lubiprostone is likely to be at least as effective as prucalopride.

- 3.12 The manufacturer's submission presented data from a pooled analysis on the number of adverse events from 7 phase II and III studies conducted in the US for lubiprostone (n=1113) and compared with placebo (n=316). The manufacturer noted that although there were more adverse events associated with lubiprostone than with placebo (the most common being nausea and diarrhoea), lubiprostone was well tolerated with most adverse events found to be mild to moderate in intensity, identified early and self-limiting. Lubiprostone resulted in no serious adverse events in the phase III trials, with no deaths reported in any of the studies. The overall discontinuation rate as a result of adverse events was 19.8% for lubiprostone compared with 1.6% for placebo.

## **Cost effectiveness**

- 3.13 The manufacturer developed a de novo Markov cohort model which compared the cost effectiveness of lubiprostone with prucalopride in adults with chronic idiopathic constipation and associated symptoms whose condition had not adequately responded to 2 lines of previous laxatives and who were being considered for additional investigations and invasive procedures. A comparison with laxative treatment was not provided because the population was assumed to be refractory to laxative treatment. The model included 5 health states that were differentiated by whether a patient was on or off treatment. All patients entered the model in the 'treatment' state, and the response to treatment was assessed at the end of a 2-week cycle for lubiprostone and at the end of a 4-week cycle for prucalopride in accordance with the UK marketing authorisations. Patients were considered to respond to treatment if they had 3 or more spontaneous bowel movements in a week and if they had not used rescue medication in the previous week. Patients in each treatment arm who were 'responders' after the first assessment remained in the 'treatment' state and a discontinuation curve (based on US prescription data) was used to model the movement of patients to an 'investigative/invasive procedures' state in subsequent cycles. Patients whose condition did not achieve a treatment response (either initially or when they are maintained on

treatment) moved either to the 'investigations/invasive procedures' state, or directly to an 'unresolved' state. In the 'investigations/invasive procedures' state, the majority of patients (95%) had a colonoscopy, after which some patients (61.2%) had invasive procedures and transitioned either to the 'resolved' state if the treatment cured constipation or the 'unresolved' state. Patients were assumed to remain in the 'unresolved' state for the remainder of the model time horizon. At the end of each cycle patients could also move from any of the states to death. The model considered the costs and health benefits from the perspective of the NHS and personal social services which were discounted by 3.5% per year over a time horizon of 1 year.

- 3.14 The manufacturer's base-case model used a 2-week response rate for patients on lubiprostone of 69.3%, which was estimated indirectly by multiplying the probability of responding after a 2 week course of treatment for placebo by the relative risk for lubiprostone compared with placebo. The manufacturer estimated the relative effect for lubiprostone compared with prucalopride based on the results of the indirect treatment comparisons, which therefore provided 7 potential outcomes from which to choose. The manufacturer's base-case model used a 4-week response rate for patients on prucalopride of 61.5% which was estimated indirectly from the lubiprostone response rate and the relative risk of prucalopride compared with lubiprostone (using the outcome from the indirect analysis of 'mean change in spontaneous bowel movements from baseline at weeks 1–4').
- 3.15 The utility values used in the manufacturer's base-case were taken from a randomised controlled trial of linaclotide compared with placebo in people with irritable bowel syndrome with constipation by Huang et al. (2012). The manufacturer chose this source because of the large sample size (1200 people), the use of the EQ-5D, and the separate utility of 'responders' (defined as 4 or more spontaneous bowel movements per week) and 'non-responders'. The model does not include separate disutility values for adverse events because the manufacturer considered that the impact of adverse events on health-related quality of life was minimal and likely already captured in the literature utility values from the Huang et al. study.

- 3.16 The manufacturer reported a cost of £53.48 for the 56-capsule pack of lubiprostone and a cost of £29.68 for the 28-capsule pack. The unit cost of prucalopride was based on British national formulary (BNF) prices. The manufacturer's model distinguished between adults and older people in the costing of prucalopride: 11% of those in the lubiprostone trials were aged over 65 years, and this proportion was assigned the cost of taking 1 mg prucalopride (£38.69 per 28-tablet pack). The remaining 89% were assigned the cost of taking 2 mg prucalopride (£59.52 per 28-tablet pack).
- 3.17 Healthcare resource use estimates were based on a study by Guest et al. (2008) of macrogol 4000 compared with lactulose for the treatment of chronic functional constipation, from the perspective of the NHS in the UK. Each state in the manufacturer's model was associated with drug acquisition cost, GP appointment cost, resource use and rescue medication cost. In the initial 2-week treatment period the costs of initial consultation and assessment of response at week 2 were also added. The 'investigation/invasive procedures' state incorporated the costs of relevant diagnostic and invasive procedures (outpatient appointment, colonoscopy, stoma surgery, sacral neuromodulation and biofeedback). 'Resolved' and 'unresolved' health states were assigned additional resource use costs (for example, the slow transit constipation test); although no rescue medication costs were assigned to the 'unresolved' state.
- 3.18 In the manufacturer's base-case model (in which lubiprostone was compared with prucalopride) lubiprostone dominated prucalopride (that is, was more effective and less costly), resulting in a cost saving of £20 to £22 compared with prucalopride and a quality-adjusted life year (QALY) gain of 0.0007 to 0.0008 for the deterministic and probabilistic analyses respectively. For the deterministic base-case analysis, the manufacturer reported net benefits for lubiprostone of £37 and £46 compared to prucalopride if the maximum acceptable incremental cost-effectiveness ratios (ICERs) were £20,000 and £30,000 per QALY gained, respectively.
- 3.19 The manufacturer carried out a series of one-way deterministic sensitivity analyses on the effect of assessing response at week 2 or 4, the utility of 'responders', the ingestion rate of lubiprostone, the age of patients and the cost of a GP visit. The incremental net benefit remained positive in all cases. The

model was most sensitive to changes in the relative effect of lubiprostone compared with prucalopride on spontaneous bowel movement frequency from baseline at weeks 1–4, causing the net benefit to vary between approximately £23 and £47.

- 3.20 The manufacturer presented an analysis which explored the impact of different end points in the indirect analysis on the ICERs. In all analyses, lubiprostone was associated with a positive net benefit compared with prucalopride, ranging from £21 to £53 if the maximum acceptable ICER was £20,000 or £30,000 per QALY gained respectively. Lubiprostone dominated prucalopride in the end points of change in spontaneous bowel movement from baseline, spontaneous bowel movements rated as hard or very hard, and spontaneous bowel movements with no straining. Lubiprostone was associated with relatively small ICERs compared with prucalopride for the end points spontaneous bowel movements with severe/very severe straining (£2,895 per QALY gained) and mean change in complete spontaneous bowel movement from baseline over weeks 1–4 (£9660 per QALY gained). When the outcomes spontaneous bowel movements rated as normal and percentage of patients having an average increase in spontaneous bowel movement of 1 or more over weeks 1–4 were considered, lubiprostone was less costly but also less effective than prucalopride (ICERs of £27,228 and £116,150 per QALY gained for prucalopride compared with lubiprostone respectively). The manufacturer acknowledged that the uncertainty in the ICER related to very small QALY differences between lubiprostone and prucalopride (0.008 in the base case).
- 3.21 After a clarification request from the ERG about a discrepancy between discontinuation rates adopted in the model and the discontinuation evidence suggested in the manufacturer's submission, the manufacturer presented a revised model which also included a placebo arm (that is, the placebo arm of the trials which included rescue medication but no laxative treatment). The response to treatment in the placebo arm was assessed at the end of a 4-week cycle. The response rates used in the model for placebo were 53.3% and 50% at weeks 2 and 4, respectively. In an incremental analysis, lubiprostone dominated prucalopride and prucalopride was associated with an ICER of £87,085 per QALY gained compared with placebo. Lubiprostone was

associated with an ICER of £64,464 per QALY gained compared with placebo at an incremental cost of £165, and an incremental QALY gain of 0.0026.

## ***ERG's critique and exploratory analyses***

- 3.22 The ERG reviewed the decision problem presented by the manufacturer and noted that the population and comparators differ to those defined in the NICE scope. The ERG considered that the 'refractory' population is where lubiprostone is likely to be used in clinical practice. For this reason, the ERG thought it reasonable that the decision problem deviated from the NICE scope by excluding laxative therapies as comparators and by focusing on a population whose condition has failed to respond to laxative therapies.
- 3.23 The ERG queried whether the trial patients (adults who have been diagnosed with chronic idiopathic constipation for at least 6 months with an average spontaneous bowel movement frequency of fewer than 3 per week) matched the scope of the appraisal (adults with chronic idiopathic constipation and associated symptoms when response to diet and other non-pharmacological measures are inappropriate). The ERG noted that no information was presented on whether or not patients had failed dietary and exercise interventions for the intention-to-treat trial population of the trial. The ERG also noted that, although 85 to 94% of patients across the trial arms were white, and most were women under 50 years of age, the trial participants were reasonably representative of patients in clinical practice in the UK. The ERG noted that although it is plausible that the 'previously treated' subgroup of people who had used anti-constipation therapy within 90 days of enrolment reflect a population refractory to 2 lines of laxative, it was not certain that this criterion meaningfully distinguished the 2 groups. The ERG also noted the similarity between the baseline characteristics of the intention-to-treat population and the previously treated subgroup, including the mean baseline frequency of spontaneous bowel movements (1.30 to 1.50 in the intention-to-treat population compared with 1.33 to 1.71 per week in the 'previously treated' subgroup).
- 3.24 The ERG explored the impact that the definition of response has on the estimate of cost-effectiveness. In an exploratory analysis, the ERG calculated

relative risks of response at 2 weeks for the intention-to-treat and the 'previously treated' population using 2 different measures of a patient being a 'responder' for the individual phase III trials: 3 or more spontaneous bowel movements in a week, and 3 or more spontaneous bowel movements in a week plus at least an increase of 1 spontaneous bowel movement per week (which ensured that every 'responder' had a meaningful improvement in spontaneous bowel movement). The ERG conducted a meta-analysis using data from the 2 US phase III trials, the results of which showed that the relative risk of response at 2 weeks decreased from 1.31 to 1.14 in the intention-to-treat population, and increased from 1.34 to 1.44 in the 'previously treated' population when a more stringent criteria of response was used (3 or more spontaneous bowel movements in a week plus at least an increase of 1 spontaneous bowel movement per week). Following the clarification stage the manufacturer provided data on a further subpopulation of patients who had received 2 previous laxative treatments, which enabled the ERG to assess the impact of different criteria of response on this subpopulation. The meta-analysis results for this subgroup who had received 2 previous laxatives showed an increase in the relative risk of response at 2 weeks from 1.49 using the response definition of 3 or more spontaneous bowel movements in a week, to 1.62 using the more stringent definition of response. The ERG concluded from the meta-analysis of the relative risk of being a 'responder' by trial, by population and different responder definitions that the different populations had little discernible impact on the results.

- 3.25 The ERG considered that the manufacturer's economic submission met the requirements of the NICE reference case, although it noted a number of uncertainties related to the ingestion rate of lubiprostone, the use of different response criteria, the relevance of the model population, the exclusion of placebo from the manufacturer's base-case model, the effectiveness inputs and the source of utility data. The ERG conducted exploratory analyses to explore the impact of these uncertainties using a model which assumed continuous dosing of lubiprostone (see section 3.26) and included a placebo arm comparator as it considered this to more closely reflect the use of lubiprostone in clinical practice.

- 3.26 The ERG considered the assumption related to the 83% ingestion rate of lubiprostone based on 'as needed' dosing from an open-label trial. Clinical advisers to the ERG considered continuous treatment with lubiprostone to be more plausible; therefore, the ERG re-ran the model with the assumption of continuous dosing of lubiprostone which resulted in an increase in the ICER of lubiprostone compared with placebo from £64,464 in the manufacturer's revised base-case analysis to £75,808 per QALY gained.
- 3.27 The ERG considered the impact of a more stringent definition of response rate (3 or more spontaneous bowel movements per week plus 1 or more change in spontaneous bowel movements from baseline per week) on the ICER. The ERG noted that the reduced treatment effect (response rate from 1.31 to 1.14) reduced the cost effectiveness of lubiprostone from dominating prucalopride (using a response defined as 3 or more spontaneous bowel movements per week) to being extendedly dominated (when 3 or more spontaneous bowel movements weekly plus 1 or more change in spontaneous bowel movements). A treatment option is extendedly dominated when its ICER is higher than that of the next, more effective, option when compared to a common baseline. The ICER also increased for the pairwise comparison of lubiprostone with placebo, from £74,071 to £150,821 per QALY gained. The more stringent response criteria also had an impact on the ICER of prucalopride compared with placebo, which increased from £85,069 (when using a response defined as 3 or more spontaneous bowel movements per week) to £149,965 per QALY gained.
- 3.28 The ERG noted that although the manufacturer presented the results for the clinical effectiveness of the 'previously treated' subgroup, it did not carry out further cost-effectiveness analyses in this subgroup. The ERG was unclear whether the intention-to-treat or previously treated populations would be most relevant to clinical practice in the UK. Using the meta-analysis of the relative risk of response for lubiprostone compared with placebo for the previously treated population, the ERG assessed the impact of this subgroup on the ICER. The results showed that the different populations had little effect on the ICER, which decreased for the pairwise comparison of lubiprostone with placebo from £74,071 per QALY gained (when using the intention-to-treat population) to £72,746 (when using the previously treated population). The

different populations also had an impact on the ICER of lubiprostone compared with prucalopride, whereby lubiprostone dominated prucalopride in the intention-to-treat population but was slightly more costly and marginally more effective than lubiprostone in the previously treated population, with an ICER of £75,418 per QALY gained.

3.29 The ERG noted that in the indirect analysis the direction of the treatment effect altered, favouring either lubiprostone or prucalopride according to the selected outcome. The ERG commented that the manufacturer's scenario analyses on the impact of the outcome on the ICER demonstrated that the ICER was subject to a significant degree of uncertainty, from lubiprostone dominating prucalopride to prucalopride extendedly dominating lubiprostone. The ERG noted that the 'proportion of patients achieving an increase of 1 or more spontaneous bowel movements at weeks 1–4', in which lubiprostone was extendedly dominated by prucalopride, was potentially the most appropriate outcome measure because it was derived from meta-analysed data as opposed to the remaining outcomes which were based on an aggregation of data across all relevant trials.

3.30 The ERG noted that the utility values from the Huang et al. (2012) study were based on a different treatment (linaclotide), and used a different definition of response to that used in the lubiprostone clinical trials (4 spontaneous bowel movements per week rather than at least 3 spontaneous bowel movements per week in the lubiprostone trials). In a sensitivity analysis, the manufacturer mapped the SF-36 values from the long-term US lubiprostone studies to the EQ-5D literature values. In this analysis, separate utility values were assigned to each of the health states in the model: 0.90, 0.86 and 0.83 for the 'resolved/responder', 'non-responder' and 'unresolved' states, respectively. The ERG noted that the difference in utilities between people whose condition responded and people whose condition did not, based on the Huang et al. study (0.04), was greater than that using the utilities data from the long-term US trials (0.027) which favoured lubiprostone. The ERG also noted that the 0.07 difference between a person in the 'responder' state (0.90) and a person in the 'unresolved' state (0.83) in the economic model differs considerably from the 0.027 difference in the long-term US trials. The ERG investigated the impact of using the trial data and literature values from Guest et al. (2008; the study from

which the resource use was based) on the ICER. The study by Guest et al. provided utility values of 0.90 and 0.74 for people in the 'resolved' and 'unresolved' states respectively (difference of 0.26). The ICERs for lubiprostone compared with prucalopride were £181,887 when utilities from long term lubiprostone trial data were used and £30,693 when data from Guest et al. were used, compared with the base-case ICER of £75,808 per QALY gained. The ERG noted that regardless of the source of utility values, lubiprostone continued to dominate prucalopride.

- 3.31 The ERG did not consider it appropriate to attach equal health-related quality of life values (0.90) to the 'responder' state and to the 'resolved' state, with the assumption that the quality of life of people whose disease was cured following surgery was equal to that of people whose disease responded to daily treatment but was not cured. The ERG also noted the lack of evidence to support the lower utility assigned to the 'unresolved' health state (0.83) compared with the 'non-responders' to treatment (0.86). The ERG explored alternative ways of quantifying health-related quality of life for patients whose condition did not resolve.
- 3.32 The ERG noted that 8% of people remain on lubiprostone at the end of the first year. For this reason, it felt that a 1-year horizon was not long enough. The ERG explored the sensitivity of the model results to the choice of time horizon, noting that a 20-year time horizon had little impact on the incremental ICERs (in which lubiprostone continued to dominate prucalopride) or the pairwise ICER of lubiprostone compared with placebo (which increased from £75,808 to £76,951 per QALY gained).
- 3.33 The manufacturer included a placebo comparison in the model as part of its response to clarifications, but argued that it did not represent an appropriate comparator as placebo is not a valid treatment option in clinical practice. The manufacturer noted that at the point lubiprostone would be used, if prucalopride was also not used, the comparator would be immediate referral to secondary care for further investigations and/or surgical intervention. The ERG considered that including placebo in the model was important for external validation (because it was a comparator in the prucalopride appraisal),

although it recognised the potential issues of how to interpret and use the placebo data within the context of the decision-making.

- 3.34 The ERG-modelled scenarios assumed that patients in the placebo arm would receive treatment with standard laxatives, and therefore included the costs of laxative treatment in addition to the same monitoring costs as those treated with lubiprostone. Although patients would not see any additional health benefit from the laxative treatment, the ERG explored the impact of varying the magnitude and duration of placebo benefits. In all of the analyses, patients in the treatment arm received continuous dosing with lubiprostone and lubiprostone dominated prucalopride in all of the incremental analyses. Assuming patients would accrue placebo benefits for the entire duration that they respond to treatment increased the pairwise ICER for lubiprostone compared with placebo from £64,464 per QALY gained in the base case (£75,808 per QALY gained) to £69,610 per QALY gained. A scenario was explored in which it was assumed that patients accrued no placebo benefits beyond 2 weeks; this was compared with the sustained health benefits gained by patients on lubiprostone after 2 weeks, which resulted in a decrease in the pairwise ICER for lubiprostone compared with placebo from £64,464 per QALY gained (£75,808 per QALY gained) to £16,061 per QALY gained. In this scenario, lubiprostone dominated prucalopride. A further scenario which included higher utility gains in the 'unresolved' health state to approximate switching between laxative treatment decreased the pairwise ICER for lubiprostone compared with placebo from £64,464 per QALY gained (£75,808 per QALY gained) to £30,953 per QALY gained. A scenario in which the placebo response rate at week 2 was reduced by 50% (reflecting how the subsequent chance of responding to further re-challenge and/or switching between treatments may be lower in later parts of the pathway) decreased the pairwise ICER for lubiprostone compared with placebo from £64,464 per QALY gained (£75,808 per QALY gained) to £20,256 per QALY gained.
- 3.35 The ERG queried the generalisability and transferability of US prescription data (used to estimate the discontinuation curves) to the UK healthcare setting. The ERG suggested, for example, that a proportion of the discontinuation seen in the US prescription data may reflect patients who stop receiving treatment due to affordability issues which may not be relevant to the UK healthcare system.

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The ERG assessed the discontinuation data from the open-label studies and noted that the definition of response to treatment differed from that applied in the phase III trials. However, the ERG found that the mean time on treatment estimated using the open-label data was similar to the time on treatment estimated by the US prescription data. In addition, it found that the proportion of patients the model estimated to remain on lubiprostone at the end of year 1 (8%) was similar to the proportion presented by the analysis of the open-label data (12%). Overall, the ERG considered the approaches used to synthesise the US prescription data and the trial data – and to produce the discontinuation curve – to be correct, and it concluded that the manufacturer's approach to discontinuation was acceptable.

3.36 Full details of all the evidence are [available](#).

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## 4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lubiprostone, having considered evidence on the nature of chronic idiopathic constipation and the value placed on the benefits of lubiprostone 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*

- 4.1 The Committee considered the treatment pathway for people with chronic idiopathic constipation. It noted that there was 1 NICE clinical guideline ('CG99: Diagnosis and management of idiopathic childhood constipation in primary and secondary care') listed in the scope, but that this guideline was not applicable to the population defined in the marketing authorisation and the scope, that is, 'for the treatment of chronic idiopathic constipation and associated symptoms in adults when response to diet and non-pharmacological measures (for example, educational measures, physical activity) are inappropriate'. The Committee discussed the population described in the manufacturer's submission. It understood the manufacturer had positioned lubiprostone in the treatment pathway after failure of 2 standard laxatives. The Committee heard from clinical specialists who advised that the vast majority of people who are referred to secondary care have already tried dietary and exercise interventions, and have tried at least 2 lines of laxatives that have proven inadequate. The Committee concluded that the population assessed in the manufacturer's submission was appropriate for its decision-making.
- 4.2 The Committee considered the comparators presented in the manufacturer's decision problem, which did not match the appraisal scope. In the scope the comparators were standard laxatives (such as bulk-forming laxatives, osmotic laxatives, stimulant laxatives) and prucalopride. The Committee also noted the manufacturer's claim that a comparison with laxative treatments was impossible because of the lack of controlled clinical trial data for laxative treatments in people with severe chronic idiopathic constipation. The Committee heard from clinical specialists that although prucalopride is only recommended in women, it is widely used in men, outside of its licensed

indication. The Committee therefore considered prucalopride to be a clinically relevant comparator in both women and men who have chronic idiopathic constipation. The Committee concluded that the exclusion of laxative treatment as a comparator was acceptable.

- 4.3 The Committee considered the characteristics of chronic idiopathic constipation, noting that it cannot be explained by any anatomical, physiological, radiological or histological abnormalities, and is defined as 2 or more of the following symptoms at least a quarter of the time for at least 6 months: straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction or blockage, and/or less than 3 spontaneous bowel movements per week. The Committee heard from clinical specialists and a patient expert that chronic idiopathic 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.
- 4.4 The Committee considered the management of chronic idiopathic constipation in clinical practice in England. It understood that current practice is a stepped approach, starting with lifestyle and dietary changes. However, if these changes provide inadequate relief, different classes of oral laxatives are available. The Committee heard that the condition is often poorly managed by people taking over-the-counter medication or more than 1 laxative of the same class in an attempt to restore bowel function; often leading to faecal incontinence. The Committee was aware that [Prucalopride for the treatment of chronic constipation in women](#) (NICE technology appraisal guidance 211) recommends prucalopride as a treatment option in women when at least 2 laxatives of different classes at the highest tolerated dose for at least 6 months fail to provide adequate relief of symptoms, and when invasive treatment for constipation is being considered in line with the UK marketing authorisation. If prucalopride fails to provide adequate relief of symptoms, diagnostic investigations (colonoscopy) and interventions such as biofeedback, less invasive colonic lavage and stoma surgery are considered. The Committee noted that the manufacturer's intended position for lubiprostone in the care pathway was the same as prucalopride, that is, after 2 different types of laxative have failed. It noted that lubiprostone has a different mechanism of action to prucalopride, as it activates chloride channels in gastrointestinal

epithelial cells, relieving symptoms of chronic constipation by improving intestinal secretion. The Committee heard from clinical specialists that surgical interventions would only be offered as a last resort. The Committee concluded that additional treatment options would be of value to people with chronic idiopathic constipation whose condition has not responded to laxative therapy, and considered that lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments.

- 4.5 The Committee considered the overall clinical effectiveness of lubiprostone in laxative-refractory chronic idiopathic constipation in the pivotal phase III randomised controlled trials. The Committee heard from the clinical specialists that the baseline characteristics of the trial population in the phase III randomised controlled trials were generalisable to people who present in secondary care in the UK. The Committee considered that the evidence demonstrated a statistically significantly higher frequency of mean spontaneous bowel movements in the lubiprostone arm compared with the placebo arm both at week 1 (the primary clinical outcome) and weeks 2 to 4 (a secondary outcome). The Committee further noted the clinically significant increase in the frequency of spontaneous bowel movements in the placebo arm at week 1, which was maintained up to week 4. The Committee considered the other secondary outcomes, including spontaneous bowel movement within 24 hours after first drug dose, time to first spontaneous bowel movement, stool consistency, degree of straining, abdominal bloating, abdominal discomfort, severity of constipation and treatment effectiveness. The Committee heard from clinical specialists that the severity of chronic idiopathic constipation depends on the individual's specific combination of symptoms, and noted that the effect of lubiprostone on the frequency of spontaneous bowel movements and all other secondary outcomes was potentially clinically important. The Committee noted that lubiprostone is associated with a statistically significant improvement in treating chronic idiopathic constipation compared with placebo for the primary and secondary outcomes (with the exception of abdominal bloating, see [section 3.8](#)). It concluded that lubiprostone is clinically effective compared with placebo.

- 4.6 The Committee considered evidence on the manufacturer's indirect comparison of lubiprostone with prucalopride. It noted that an indirect analysis was carried out because of the absence of any head-to-head randomised controlled trials comparing lubiprostone with prucalopride. The Committee was aware of the underlying uncertainty as to whether the baseline severity of constipation was comparable in the lubiprostone and prucalopride trials, but noted that this was the best available evidence. The Committee observed that the relative clinical effectiveness of lubiprostone compared with prucalopride depended on the specific outcome used in the indirect analysis, noting that 7 different outcomes were used, but that there was no statistically significant difference in 5 of these outcomes. It further noted that in the 2 outcomes where statistical significance was reached, lubiprostone was associated with an improvement in the symptoms associated with severe and very severe straining, whereas prucalopride was associated with improvements in the frequency of 'normal' bowel movements. The Committee concluded that, on balance, lubiprostone and prucalopride were similarly effective.
- 4.7 The Committee considered the clinical evidence presented by the manufacturer for a 'previously treated' subgroup of people who had received previous treatment within 90 days of trial enrolment. It understood that the manufacturer had explored this subgroup because it more closely matched a population that had failed 2 lines of laxative. The Committee noted that the baseline characteristics between the intention-to-treat and previously treated populations appeared very similar, and that the Evidence Review Group (ERG) meta-analysis outcomes were similar (see [section 3.25](#)). The Committee concluded there was no evidence to show the 2 populations were clinically different.
- 4.8 The Committee considered the adverse reactions experienced by people receiving lubiprostone treatment. The Committee heard from clinical specialists that there were differences in the adverse-event profiles of lubiprostone and prucalopride and that lubiprostone may be more tolerable for some people. The Committee concluded that the adverse-event profile of lubiprostone was manageable.

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## **Cost effectiveness**

- 4.9 The Committee considered the structure of the manufacturer's Markov model. It heard from clinical specialists that the structure of the economic model was relevant to the typical treatment pathway in clinical practice, in particular that treatment with lubiprostone would be continued in people whose condition adequately responds to treatment, but that all patients would eventually stop treatment over time as a result of decreasing efficacy or intolerable adverse reactions. It also heard that in clinical practice, people whose condition fails to respond to treatment would be referred to secondary care for further investigations, although some people who have already had diagnostic investigations earlier in their treatment would decline referral for further investigations and remain in the 'unresolved' health state, managing their condition with laxative treatment. The Committee concluded that the model structure was appropriate to capture the main aspects of chronic idiopathic constipation.
- 4.10 The Committee considered the assumptions made in the manufacturer's model and the critique presented by the ERG. In particular, the Committee considered assumptions about the proportion of patients who have colonoscopy as an investigation, discontinuation of treatment, utility values used in the model, and the inclusion of a placebo as a comparator. The Committee then reviewed the effect of these assumptions on the cost-effectiveness estimates for lubiprostone.
- 4.11 The Committee heard from clinical specialists that the assumption of 95% of patients having a colonoscopy in the 'investigations/invasive procedures' state may be unrealistically high. However, the Committee noted evidence from the ERG that when it increased the proportion of patients having colonoscopy to 100% this had little effect on the overall incremental cost effectiveness ratio (ICER). The Committee considered the model assumptions that stoma surgery and sacral neuromodulation account for 0.1% and 1% of invasive procedures respectively. It heard from clinical specialists who agreed with the model assumptions stating that these procedures are very rarely used in clinical practice in England as alternative treatments are used to avoid surgery where

possible. The Committee concluded that the clinical assumptions made in the economic model were appropriate.

- 4.12 The Committee discussed the appropriateness of discontinuation data curves based on US prescription data used in the manufacturer's model. The Committee noted that the high rate of discontinuation (92% at 1 year) may reflect people who stop receiving treatment because of affordability issues which may not be relevant to the UK healthcare system. The Committee heard from the manufacturer that based on open-label studies, the proportion of patients remaining on treatment after 1 year was 35%; and after 5 years, this fell to 19%. Clinical specialists were in agreement that the discontinuation rates seen in the model may be higher than those seen in clinical practice in the UK. The Committee concluded there was uncertainty as to the number of people who could be maintained on long-term treatment.
- 4.13 The Committee was aware that the scope for this appraisal included 3 types of laxative therapies (bulk-forming, osmotic and stimulant) as well as prucalopride. However, the Committee agreed with the clinical specialists and the manufacturer that people considered for lubiprostone would have already had an inadequate response to laxative therapies, and that therefore prucalopride was the most relevant comparator for most patients. The Committee noted that the ERG had explored the impact of including the costs and varying placebo benefits of laxative treatment in the placebo arm on the ICER for lubiprostone. The Committee also agreed that a comparison with placebo in the economic analysis provided an alternative basis for demonstrating the cost effectiveness of lubiprostone, one which is not subject to the uncertainties in the indirect analysis of lubiprostone and prucalopride (in terms of the degree of generalisability between the trial populations and the outcome measures). The Committee concluded that although prucalopride is perhaps the most relevant comparator, a placebo comparator was also appropriate for Committee decision making.
- 4.14 The Committee considered the different data sources for health-related quality of life in the economic model. The Committee understood that the study by Huang et al. (2012) assessed 1200 people with chronic constipation but noted that the study investigated a different treatment (linaclotide) to lubiprostone, as

well as using a different response definition (at least 4 spontaneous bowel movements per week) to that in the model (at least 3 spontaneous bowel movements per week). The Committee heard from the clinical specialists that people with severe chronic idiopathic constipation would not have the relatively high utility values observed by Huang et al. (ranging from 0.83 for people in the 'unresolved' state to 0.90 for people in the 'resolved' state). However, the Committee was aware that the experiences of people with severe symptoms as described by the clinical specialists may not be representative of the 'average' patient. The Committee considered the utilities derived from the study by Guest et al. (2008) and noted that it too investigated different treatments (laxatives) to lubiprostone, and that utility values were obtained by 308 members of the general public using standard gamble methodology. The Committee noted that in this study the difference in utilities between people whose condition responded and people whose condition did not was 0.16, compared with a difference of 0.04 in the Huang et al. study. As a result of the larger population size and the use of the EQ-5D, the Committee concluded that the utility values derived from Huang et al. were an appropriate and reasonable input into the economic model, although it considered the 'true' difference in utility was likely to be somewhere between those from the studies by Huang et al. and Guest et al.

- 4.15 The Committee noted the probabilistic base-case analysis presented by the manufacturer in which lubiprostone dominated prucalopride (that is, was more effective and less costly), with an incremental cost of £22 and an incremental quality-adjusted life year (QALY) gain of 0.0007. It understood that the very small differences in costs and QALYs makes the ICERs particularly unstable. It noted the results of the manufacturer's one-way sensitivity analysis, which showed that the ICER was most sensitive to the relative efficacy of lubiprostone and prucalopride based on the mean change in frequency of spontaneous bowel movement from baseline at weeks 1–4. The Committee further noted the effect of uncertainties in the indirect comparison used to measure the relative clinical effectiveness of lubiprostone and prucalopride on the incremental cost effectiveness analysis. In particular, that although lubiprostone was always less costly than prucalopride, in some cases (depending on the outcome chosen) it was less effective, so that lubiprostone was extendedly dominated by prucalopride (an option is 'extendedly

dominated' when its ICER is higher than that of the next, more effective, option when compared with a common baseline). In response to the ERG's request for further evidence, the manufacturer submitted a new version of the model which incorporated placebo as an additional comparator. Although lubiprostone continued to dominate (that is, more effective and less costly than) prucalopride in the revised base-case model, both drugs had high ICERs compared with placebo (£64,464 and £87,085 per QALY gained for lubiprostone and prucalopride respectively).

- 4.16 The Committee noted that although the manufacturer had presented results for the 'previously treated' subgroup (that is, people who had used anti-constipation therapy within 90 days of trial enrolment), it had not carried out further cost-effectiveness analyses in this subgroup. The Committee considered the ERG's exploratory analyses on the previously treated subgroup. The Committee noted that, when compared with the intention-to-treat population, the previously treated population had minimal effect on the absolute costs and QALYs. Prucalopride was no longer dominated by lubiprostone in the previously treated population but appeared slightly more costly and marginally more effective than lubiprostone, with an ICER of £75,418 per QALY gained. The ICER of lubiprostone compared with placebo was slightly reduced from £74,071 per QALY gained (in the intention-to-treat population) to £72,746 per QALY gained (in the previously treated population). The Committee concluded that there was very little difference between the previously treated subgroup and the intention-to-treat population. The Committee also considered the effect of different definitions of treatment response on the ICER. It noted that in the analysis which used a more stringent response definition, lubiprostone was extendedly dominated by prucalopride (compared with lubiprostone dominating prucalopride when the original definition of response were used). However, the Committee concluded that the different definitions of response had little overall impact on the absolute costs and QALYs
- 4.17 The Committee considered the results of the ERG's exploratory analyses on the manufacturer's probabilistic model with regard to assumptions about continuous dosing of lubiprostone, utility values, and the benefits and costs of a placebo comparator. The Committee heard from clinical specialists on the

subject of lubiprostone dosing and agreed with the ERG that continuous dosing was more plausible than the 'as-needed' dosing (according to an 83% ingestion rate) assumed by the manufacturer in the base case. It considered continuous dosing of lubiprostone to be more clinically relevant but noted that it resulted in an increased ICER for lubiprostone compared with placebo, from £64,464 to £75,808 per QALY gained. The Committee noted that although the assumption of continuous dosing increased the acquisition and total costs in the lubiprostone arm, in all of the analyses explored the total cost of lubiprostone was less than prucalopride. The Committee concluded that the assumption of continuous dosing was appropriate but its impact did not substantially affect the cost effectiveness of lubiprostone compared with prucalopride.

- 4.18 The Committee discussed the impact of the different sources of utility values on the cost-effectiveness results, noting that a more favourable outcome was seen for lubiprostone compared with prucalopride when utilities were derived from the study by Guest et al. rather than that by Huang et al. Utilities taken from the US open-label trial data resulted in the highest ICER, although the Committee was aware that the utilities were derived from small patient numbers and were not correlated to spontaneous bowel movement frequency. The Committee concluded that the most relevant source of utilities was the study by Huang et al. However, it considered the true ICER was likely to be somewhere between that from the study by Huang et al. (ICER for lubiprostone compared with placebo of £75,808 per QALY gained) and that from the study by Guest et al. (ICER for lubiprostone compared with placebo of £30,693 per QALY gained).
- 4.19 The Committee considered the exploratory ERG analyses that tested the impact of assumptions related to the placebo. The Committee noted that all of the scenarios relating to placebo included the addition of the cost of laxatives but included no additional health benefit from the laxatives. The scenarios then examined the impact of varied duration and size of the placebo response. The Committee noted that the inclusion of placebo benefits in the placebo arm represented the situation in standard care achieved when patients switched between laxative treatments. The Committee was also aware that people in the lubiprostone arm would benefit from a placebo effect as well as any effect from

lubiprostone. However, the Committee noted that in the scenarios relating to placebo, lubiprostone always dominated prucalopride. In one of these scenarios, a full magnitude and duration of placebo response was assumed, which resulted in an ICER of £69,610 per QALY gained for lubiprostone compared with placebo. The Committee considered this to be an excessive assumption not favouring lubiprostone. In another scenario, it was assumed that the full placebo benefit would only be maintained for 2 weeks, which resulted in a decreased ICER for lubiprostone compared with placebo of £16,061 per QALY gained. Scenarios that combined the benefits of a placebo response at 2 weeks and increased the utility of patients in the 'unresolved' state resulted in ICERs for lubiprostone compared with placebo of £30,953 (when assuming a full placebo response rate) and £20,256 (when assuming a placebo response rate of 50%) per QALY gained.

- 4.20 The Committee considered the incremental cost effectiveness of lubiprostone compared with prucalopride, noting the small absolute difference between lubiprostone and prucalopride in terms of the total cost (£22) and QALYs (0.0007) in the probabilistic base case. This resulted in pairwise ICERs compared with placebo that were particularly sensitive in many of the scenario analyses.
- 4.21 The Committee considered the cost effectiveness of lubiprostone compared with a placebo comparator (that is, 'do nothing'). The ICER for lubiprostone compared with a placebo comparator was high. However, the additional scenario analyses demonstrated that the ICER was particularly sensitive to assumptions about the long-term maintenance of health-related quality of life benefits attributed to the short-term placebo response rates seen in the phase III trials. In scenarios where these placebo benefits were considered to be transitory, the ICER for lubiprostone compared with placebo was shown to be lower than the range that would normally be considered cost effective. However, the Committee felt the assumption of a transitory placebo effect for 2 weeks was likely to underestimate the true benefits of laxative treatment. The Committee concluded from the results of the various scenario analyses that the ICERs for lubiprostone compared with placebo were highly unstable; it observed that this was a result of the particularly small absolute differences in QALYs and overall costs.

- 4.22 The Committee concluded that, in a fully incremental analysis, there was insufficient evidence to demonstrate that lubiprostone was cost effective compared with placebo. However, it was sufficiently satisfied that the incremental costs and benefits of lubiprostone compared with placebo were comparable to those for prucalopride compared with placebo. The Committee therefore concluded that lubiprostone was cost effective compared with prucalopride in the population for whom prucalopride is currently recommended. In reaching this conclusion, the Committee noted that although there was insufficient evidence to claim clinical superiority for lubiprostone compared with prucalopride, the 2 treatments were at least of comparable effectiveness. Furthermore, the Committee noted the slightly lower drug acquisition cost of lubiprostone compared with prucalopride, and the benefit that it has a marketing authorisation that covers men as well as women.
- 4.23 The Committee considered the time point at which response to lubiprostone should be assessed. It noted that the UK marketing authorisation specifies a 2 week course of treatment, which was the length of a single cycle in the economic model. The Committee agreed that treatment with lubiprostone should be assessed after one course of lubiprostone, that is at 2 weeks. If treatment is not effective after 2 weeks, the person should be re-examined and the benefit of continuing treatment reconsidered. The Committee concluded that lubiprostone represents a cost-effective use of NHS resources but it should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments.
- 4.24 The Committee considered the potential equality issues raised during the appraisal process. It noted that in its approved formulation, the lubiprostone soft capsule contains gelatine of bovine origin, which may represent a potential equality issue for those with particular religious beliefs, vegetarians and vegans. The Committee noted that the manufacturer is developing a liquid formulation to address this problem.
- 4.25 The Committee considered whether lubiprostone is an innovative treatment. It considered the fact that lubiprostone works through a different mechanism of action to prucalopride, and has a UK marketing authorisation for use in men as

well as women. It also considered that additional treatment options would be of value to people with chronic idiopathic constipation whose condition has not responded to laxative therapy. The Committee concluded that although lubiprostone works through a novel mechanism of action, it was not a step change in the treatment pathway. However, the Committee did not consider that there were any health-related benefits that had not been captured in the economic model.

## ***Summary of Appraisal Committee's key conclusions***

<b>TA318</b>	<b>Appraisal title: lubiprostone for treating chronic idiopathic constipation</b>	<b>Section</b>
<b>Key conclusion</b>		

<p>Guidance:</p> <p>1.1. Lubiprostone is recommended as an option for treating chronic idiopathic constipation, that is, for adults in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered.</p> <p>1.2. If treatment with lubiprostone is not effective after 2 weeks, the person should be re-examined and the benefit of continuing treatment reconsidered.</p> <p>1.3. Lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments specified in 1.1.</p> <p>The Committee understood the manufacturer had positioned lubiprostone in the treatment pathway after failure of 2 standard laxatives. It concluded that the population assessed in the manufacturer's submission was appropriate for its decision-making.</p> <p>The Committee agreed with the clinical specialists and the manufacturer, that people considered for treatment with lubiprostone would have already had an inadequate response to laxative therapies, and that therefore prucalopride was the most relevant comparator for most patients. The Committee concluded that the exclusion of laxative treatment as a comparator was acceptable.</p> <p>The Committee concluded that additional treatment options would be of value to people with chronic idiopathic constipation whose condition has not responded to laxative therapy, and considered lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, who has carefully reviewed the person's previous courses of laxative treatments.</p> <p>The Committee concluded from the results of the various scenario analyses that the ICERs for lubiprostone compared with placebo were highly unstable; it observed that this was a result of the particularly small absolute differences in QALYs and overall costs.</p> <p>The Committee concluded that, in a fully incremental analysis, there was insufficient evidence to demonstrate that lubiprostone was cost effective compared with placebo. However, it was sufficiently satisfied that the incremental costs and benefits of lubiprostone compared with placebo were comparable to those for prucalopride compared with placebo. The Committee therefore concluded that</p>	<p>1, 4.1, 4.13, 4.2, 4.4, 4.21, 4.22</p>
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<p>lubiprostone was cost effective compared with prucalopride in the population for whom prucalopride is currently recommended. In reaching this conclusion, the Committee noted that although there was insufficient evidence to claim clinical superiority for lubiprostone compared with prucalopride, the 2 treatments were at least of comparable effectiveness. Furthermore, the Committee noted the slightly lower drug acquisition cost of lubiprostone compared with prucalopride, and the benefit that it has a marketing authorisation that covers men as well as women.</p>		
<p><b>Current practice</b></p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from clinical specialists and a patient expert that chronic idiopathic 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.</p> <p>The Committee considered the management of chronic idiopathic constipation in clinical practice in England. It understood that current practice is a stepped approach, starting with lifestyle and dietary changes. However, if these changes provide inadequate relief, different classes of oral laxatives are available. The Committee heard that the condition is often poorly managed by people taking over-the-counter medication or more than 1 laxative of the same class in an attempt to restore bowel function; often leading to faecal incontinence. The Committee heard from clinical specialists that surgical interventions would only be offered as a last resort. The Committee concluded that additional treatment options would be of value to people with chronic idiopathic constipation whose condition has not responded to laxative therapy.</p>	<p>4.3, 4.4</p>
<p><b>The technology</b></p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee noted that lubiprostone has a different mechanism of action to prucalopride, as it activates chloride channels in gastrointestinal epithelial cells, relieving symptoms of chronic constipation by improving intestinal secretion.</p> <p>The Committee concluded that although lubiprostone works through a novel mechanism of action, it was not a step change in the treatment pathway. The Committee did not consider that there were any health-related benefits that had not been captured in the economic model.</p>	<p>4.4, 4.25</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee noted the manufacturer's intended position for lubiprostone in the care pathway, which is also where clinicians would likely use it, and is the same as prucalopride (<a href="#">NICE technology appraisal guidance 211</a>), that is, after 2 different types of laxative have failed.</p>	<p>4.4</p>
<p>Adverse reactions</p>	<p>The Committee heard from clinical specialists that there were differences in the adverse reaction profiles of lubiprostone and prucalopride and that lubiprostone may be more tolerable for some people. The Committee concluded that the adverse reaction profile of lubiprostone was manageable.</p>	<p>4.8</p>

**Evidence for clinical effectiveness**

<p>Availability, nature and quality of evidence</p>	<p>The Committee noted that lubiprostone is associated with a statistically significant improvement in treating chronic idiopathic constipation compared with placebo for the primary and secondary outcomes (with the exception of abdominal bloating). It concluded that lubiprostone is clinically effective compared with placebo.</p> <p>The Committee noted that an indirect analysis was carried out because of the absence of any head-to-head randomised controlled trials comparing lubiprostone with prucalopride. The Committee concluded that, on balance, lubiprostone and prucalopride were similarly effective.</p>	<p>4.5, 4.6</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee agreed with the clinical specialists and the manufacturer that people considered for lubiprostone would have already had an inadequate response to laxative therapies, and that therefore prucalopride was the most relevant comparator for most patients.</p> <p>The Committee considered that additional treatment options would be of value to people with chronic idiopathic constipation whose condition has not responded to laxative therapy.</p>	<p>4.13, 4.25</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee observed that the relative clinical effectiveness of lubiprostone compared with prucalopride depended on the specific outcome used in the indirect analysis, noting that 7 different outcomes were used, but that there was no statistically significant difference in 5 of these outcomes.</p>	<p>4.6</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee considered the clinical evidence presented by the manufacturer for a 'previously treated' subgroup of people who had received previous treatment within 90 days of trial enrolment. It understood that the manufacturer had explored this subgroup because it more closely matched a population that had failed 2 lines of laxative. The Committee noted that the baseline characteristics between the intention-to-treat and previously treated populations appeared very similar, and that the Evidence Review Group meta-analysis outcomes were similar. The Committee concluded there was no evidence to show the 2 populations were clinically different.</p>	<p>4.7</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that lubiprostone is associated with a statistically significant improvement in treating chronic idiopathic constipation compared with placebo for the primary and secondary outcomes (with the exception of abdominal bloating).</p> <p>The Committee concluded that, on balance, lubiprostone and prucalopride were similarly effective.</p>	<p>4.5, 4.6</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The Committee heard from clinical specialists that the structure of the economic model was relevant to the typical treatment pathway in clinical practice. The Committee concluded that the model structure was appropriate to capture the main aspects of chronic idiopathic constipation.</p>	<p>4.9</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee considered assumptions about the proportion of patients who have colonoscopy as an investigation, discontinuation of treatment, utility values used in the model, and the inclusion of a placebo as a comparator.</p> <p>The Committee concluded that the clinical assumptions made in the economic model were appropriate.</p> <p>The Committee concluded there was uncertainty as to the number of people who could be maintained on long-term treatment.</p>	<p>4.10, 4.11, 4.12</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>The Committee heard from the clinical specialists that people with severe chronic idiopathic constipation would not have the relatively high utility values observed by Huang et al. (2012). However, the Committee was aware that the experiences of people with severe symptoms as described by the clinical specialists may not be representative of the 'average' patient. As a result of the larger population size and the use of the EQ-5D, the Committee concluded that the utility values derived from Huang et al. were an appropriate and reasonable input into the economic model, although it considered the 'true' difference in utility was likely to be somewhere between those from the studies by Huang et al. and Guest et al. (2008).</p>	<p>4.14</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>There are no specific groups for whom lubiprostone is particularly cost effective. The Committee concluded that there was very little difference between the previously treated subgroup and the intention-to-treat population.</p>	<p>4.16</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee noted the results of the manufacturer's one-way sensitivity analysis, which showed that the ICER was most sensitive to the relative efficacy of lubiprostone and prucalopride based on the mean change in frequency of spontaneous bowel movement from baseline at weeks 1–4.</p>	<p>4.15</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered the incremental cost effectiveness of lubiprostone compared with prucalopride, noting the small absolute difference between lubiprostone and prucalopride in terms of the total cost (£22) and QALYs (0.0007) in the probabilistic base case. This resulted in pairwise ICERs compared with placebo that were particularly sensitive in many of the scenario analyses.</p> <p>The Committee considered the impact of exploratory analyses conducted by the ERG on the continuous dosing of lubiprostone, different source of utility data and the inclusion of a placebo response in the placebo arm on the ICER.</p> <p>The Committee noted that the inclusion of continuous dosing of lubiprostone increased the ICER of lubiprostone compared with placebo from £64,646 to £75,808 per QALY gained. The Committee noted the ICER was particularly sensitive to assumptions about the long-term maintenance of health-related quality of life benefits attributed to the short-term placebo response rates seen in the phase III trials.</p> <p>The Committee considered the impact of different sources of utility data on the ICER and considered the true ICER was likely to be somewhere between that from the study by Huang et al. (ICER for lubiprostone compared with placebo of £75,808 per QALY gained) and that from the study by Guest et al. (ICER for lubiprostone compared with placebo of £30,693 per QALY gained).</p> <p>The Committee considered the impact of the inclusion of laxative costs and different placebo responses in the placebo arm. It noted that in all scenarios lubiprostone always dominated prucalopride, however the ICERs of lubiprostone compared with placebo varied depending on the magnitude and duration of placebo response. The ICER for lubiprostone compared with placebo was 16,061 per QALY gained when the placebo benefit was limited to 2 weeks. When the placebo response was combined with increased utility in the unresolved health state ICERs were £20,256 per QALY gained when a full placebo response rate was assumed and £30,953 per QALY gained when a 50% placebo response rate was assumed.</p>	<p>4.20, 4.21, 4.22, 4.17, 4.18, 4.19</p>
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	<p>The Committee considered that the additional scenario analyses demonstrated the ICER for lubiprostone compared with placebo was particularly sensitive. In scenarios where these placebo benefits were considered to be transitory, the ICER for lubiprostone compared with placebo was shown to be lower than the range that would normally be considered cost effective.</p> <p>The Committee concluded that, in a fully incremental analysis, there was insufficient evidence to demonstrate that lubiprostone was cost effective compared with placebo. However, it was sufficiently satisfied that the incremental costs and benefits of lubiprostone compared with placebo were comparable to those for prucalopride compared with placebo.</p>	
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable to this appraisal.	
End-of-life considerations	Not applicable to this appraisal.	
Equalities considerations and social value judgements	The Committee noted that in its approved formulation, the lubiprostone soft capsule contains gelatine of bovine origin, which may represent a potential equality issue for those with particular religious beliefs, vegetarians and vegans.	4.24

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## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic idiopathic constipation and the doctor responsible for their care thinks that lubiprostone is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.3 NICE has developed a [costing statement](#) explaining the resource impact of this guidance, to help organisations put this guidance into practice.

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## 6 Review of guidance

The guidance on this technology will be considered for review in June 2017. 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 Dillon  
Chief Executive  
July 2014

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## 7 Appraisal Committee members and NICE project team

### 7.1 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 4 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.

#### **Professor Andrew Stevens**

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

#### **Professor Eugene Milne**

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

#### **Dr David Black**

Medical Director, NHS South Yorkshire and Bassetlaw

#### **David Chandler**

Lay Member

#### **Gail Coster**

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

#### **Professor Peter Crome**

Honorary Professor, Dept of Primary Care and Population Health, University College London

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**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Greg Fell**

Consultant in Public Health, Bradford Metropolitan Borough Council

**Dr Janice Kohler**

Formerly Senior lecturer and consultant in paediatric oncology, Southampton University Hospitals Trust

**Emily Lam**

Lay Member

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

**Dr Allyson Lipp**

Principal Lecturer, University of South Wales

**Dr Claire McKenna**

Research Fellow in Health Economics, University of York

**Professor Gary McVeigh**

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

**Dr Andrea Manca**

Health Economist and Senior Research Fellow, University of York

**Professor Stephen O'Brien**

Professor of Haematology, Newcastle University

**Dr Anna O'Neill**

Deputy Head of Nursing & Healthcare School / Senior Clinical University Teacher, University of Glasgow

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**Alan Rigby**

Academic Reader, University of Hull

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Professor Matt Stevenson**

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

**Dr Paul Tappenden**

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

**Professor Robert Walton**

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine & Dentistry

**Dr Judith Wardle**

Lay Member

## ***7.2 NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Chris Chesters**

Technical Lead(s)

**Eleanor Donegan**

Technical Adviser

**Nicole Fisher**

Project Manager

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## 8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York:

- Giannopoulou C, Rice, S, Moe-Byrne T et al. Lubiprostone for treating chronic idiopathic constipation. March 2014

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. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on lubiprostone by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

### I. Manufacturer/sponsor

- Sucampo Pharma Europe

### II. Professional/specialist and patient/carer groups:

- Association for Continence Advice
- Bladder and Bowel Foundation
- Primary Care Society for Gastroenterology
- Promocon
- Royal College of Nursing
- Royal College of Physicians
- The IBS Network

### III. Other consultees:

- Department of Health
- NHS England

- Welsh Government

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

- Centre for Reviews and Dissemination and Centre for Health Economics - York
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Institute for Health and Care Excellence – Public Health Group
- National Institute for Health research Health Technology Assessment Programme
- Norgine Limited
- Shire Pharmaceuticals

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on lubiprostone by providing oral evidence to the Committee.

- Dr Ayesha Akbar, consultant gastroenterologist, nominated by Sucampo – clinical specialist
- Professor Paul Skaife, consultant gastroenterologist, nominated by Sucampo – clinical specialist
- Debbie Gordon, nominated by Bladder and Bowel Foundation – patient expert

D. 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.

- Sucampo Pharma Europe

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## About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE [single technology appraisal](#) process.

It has been incorporated into the NICE pathway on [constipation](#) along with other related guidance and products.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

### Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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