Comments on the ACD Received from the Public Through the NICE Website

Name	Graham Wallis
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Following discussions within the PCT, NHS Trafford's comments are as follows: The prevalence estimation is taken at the lower end of the scale (8% to 52%) and in the PCT's view is unrealistic. There are many patients with refractory constipation who put up with their symptoms as there is no treatment that works for them at present. There is likely to be media publicity which will be targeted at this group and result in a significant representation of the clinical problem. Whilst we think it is unlikely that this would be at the upper end of that spectrum a figure of circa 15% is very likely. If the treatment pathway is that this treatment will be considered after assessment by a specialist then there will be an increase in referral and OPD attendance as a consequence with an additional cost implication. The PCT disagrees with the conclusion and feel that more evidence of long term safety and identification of the characteristics of those likely to respond is required. There is a lack of trial data comparing this directly to other treatments. The PCT's view is that this should only be approved in the context of a clinical trial designed to answer these questions.
Section 2 (clinical need and practice)	
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	The PCT already spends '£340,000 on laxative preparations (0.09% of the budget) and as the group we are considering do not respond there is unlikely to be a concomitant reduction in the prescribing of these drugs. Effectiveness evidence does not seem strong. It is only effective for 20% of the target population. The health gain is modest and open to challenge as the weighting to the symptom improvement is debateable. Finally the trial data extends to only 12 weeks and long term safety has not been established. The patients who do respond will be likely to want to continue for a long time as this is a lifelong problem.

Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 5:01:00 PM

Name	Rachael Stevenson
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The statement relief from constipation should be better defined as this could vary wildly depending on the treating clinician and patient. There should be a definition of chronic constipation that includes number of bowel movement and other relevant symptoms such as straining or hard stools etc. It is also felt that the duration of chronic constipation should be longer than 6 months (especially as in the trials the mean duration was 17 to 22 years). There are numerous different types of laxatives with years of safety and efficacy data supporting their use which could be tried before using prucalopride. It is felt that only using at least 2 laxatives is not restricting the use of this drug at all. Need clarification on how long prucalopride should be used for and when it should be stopped if patients do not respond - a lack of satisfactory response by 4 weeks could be a discontinuation criterion.
Section 2 (clinical need and practice)	Laxatives are commonly prescribed drugs and the cost of prucalopride is 8 times more expensive than the cost of some alternatives. Therefore, this could have a great impact on budgets depending on the indications proposed for treatment. Prucalopride should be reserved as a last drug resort after trying all suitable laxative alternatives that have proven safety and efficacy data.
Section 3 (The technologies)	The long term safety data for prucalopride is not clear as the randomised controlled trials (RCTs) only lasted for 12 weeks. The long term efficacy of prucalopride is also unclear and the RCTs did not compare prucalopride against standard therapies or other treatments. In the RCTs excluded patients with drug induced constipation,

	constipation as a result of endocrine, metabolic or neurological disorders and patients with renal and hepatic impairment therefore, it is impossible to assess the efficacy of prucalopride in all the patient groups covered by the license. We do not know if it will only benefit certain groups of patients with certain types of constipation. The cost effectiveness estimates are uncertain and the QALY gains that are estimated appear to be small
Section 4 (Evidence and interpretation)	The RCTs were short and only placebo controlled rather than comparing with active treatments.
Section 5 (implementation)	It is not clear how long treatment with prucalopride will continue or when it will stop in those who fail to respond. The eligibility criteria should also be revised with definitions for chronic constipation - possibly increasing the length of duration with constipation and associated symptoms. These will all have impacts on budgets for a treatment that seems to have small QALYs for the women eligible for this treatment.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 4:52:00 PM

Name	Rasila Shah
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It would be helpful if the NICE committee can define the following: "clinician with experience of treating chronic consitpation" "chronic consitpation" "inadequate relief". It would extremely helful to define stopping crtieria and timeframe for "lack of response" and stopping criteria if there is relapse of response.
Section 2 (clinical need and practice)	The unit cost may seem low at £498 per patient per year but this is at least eight to ten times the cost of many common alternatives. As laxatives are frequently prescribed medications in the NHS, the increase in costs (common laxatives average at £52/ year)and impacts on VERY tight budgets are potentially substantial.
Section 3 (The technologies)	Long-term efficacy and safety against placebo is not known. Prucalopride is similar to Cisapride which was withdrawn after several years in use. Benefits against existing treamtents also not known. Hence, place in therapy, compared to wide range of existing treatments is also not known. Discontinuation of treatment is common. Whilst cost-effectiveness ratio is within thresholds recommended, the QALY gains of this treatment are

	very small not compared to alternatives.
Section 4 (Evidence and interpretation)	The RCTs were short (12 weeks) and lacked standard care control groups (active comparators). The trials included men and people who may not have been considered laxative-refratory. Hence the efficacy results may not be representative of the efficacy in the population in whom the drug is being recommended. Revision of the elgibility criteria for this treatment would be helfpul in the following manner: Defining "inadequate relief from constipation" restricting use in patients with severe constipation (as patients in trials had average duration of consitpation of between 17 -22 years) recommending discontinuation if lack of response by 4 weeks (as trials lasted between 4 -12 weeks)
Section 5 (implementation)	The criteria and definitions used will affect the numbers of eligible people. Estimates of prevalence of constipation in women vary widely and may be as high as 50%. No standard definition exists for "inadequate relief". There is potential for off-license use in men and in women with predominantly irritable bowel syndrome. Lack of clarity on length of treatment to assess response and stopping criteria if relapse - will also result in difficulty in implementing the guidance. The potential impact of the recommendations for NHS Hertfordshire may be signficant and may impact on delivery of services like rehabilation for heart failure/ COPD and for mental health.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 3:27:00 PM

Name	Erin Murphy
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	A number of terms are very open to interpretation and should be defined further: - "failure to provide adequate relief" - what is "adequate" (appreciating that ACD say its difficult to define) - "experience of managing chronic constipation" - how much experience? Most GPs will have some experience. - "tried at least 2 different laxatives for at least 6 months, with no relief" - tried and relief are very subjective.
Section 2 (clinical need and practice)	The unit cost may seem low at £498 per patient per year, but this is at least 8x the cost of some alternatives. Laxatives are frequently prescribed medications in the NHS (3 million items in 2008). Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this

	treatment.
Section 3 (The technologies)	Placebo controlled RCTs show prucalopride increases the proportion of people who achieve 3 or more spontaneous complete bowel movements per week after 12 weeks. Long-term efficacy is not clear. There are no trials comparing prucalopride against standard therapy or other therapies. The long-term safety of prucalpride is unclear and discontinuation is common. Prucalopride showed acceptable safety profile in RCTs lasting 12 weeks. Longer term uncontrolled studies up to 36 months showed an 18% discontinuation rate because of an insufficient treatment response and 9% due to adverse events at 12 months. Prucalopride belongs to a similar class of drugs as cisapride (withdrawn due association with serious cardiovascular events). Prucalopride is reported to be more selective in action than cisapride, with no reported effects on QT interval. The cost effectiveness ratio is within thresholds currently accepted by NICE for recommending NHS funding. The most plausible ICER for prucalopride (compared to placebo plus rescue bisacodyl) was likely to be below £20,000 per QALY. Although the drug is relatively inexpensive, the QOL gains are small, and there is some uncertainty in these estimates.
Section 4 (Evidence and interpretation)	There were limitations to the quality of the research: The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. Further optimisation of these recommendations may be possible: - 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria could be revised further in the optimised recommendation. - Response to treatment: placebo trials have lasted for 4 to 12 weeks. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 5 (implementation)	The exact number of people who will be eligible for prucalopride treatment is unknown. Estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome. It is not clear how long treatment with prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond.
Section 6 (proposed recommendations for further research)	
Section 7	

(related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 3:21:00 PM

Name	Dr Gerry Keysell
Role	NHS Professional
Other role	medicines management
Location	England
Conflict	no
Notes	Apologies re brevity of comments. I had this passed to me rather late.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (clinical need and practice)	
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 3:12:00 PM

Name	Devika Sennik
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	- How is relief from constipation going to be measured/defined? Would it be measured as number of spontaneous complete bowel movements per week (as per the outcome measure used in the trials)? What is the criteria for stopping therapy? This should be
Section 2 (clinical need and practice)	- Although not part of the guidance remit, the licence is fairly restrictive - ie women only. Some clinicians will want to use the drug in men (unlicensed) - what is the stance from NICE on this as this will increase the cost implication? - The price of
Section 3 (The technologies)	

Section 4 (Evidence and interpretation)	- There is limited published long term efficacy and safety data from RCTs -the 3 key RCTs were all short term at 12 weeks in length. In addition these studies were all conducted more than 10 years ago. - None of the RCTs compared prucalopride with other
Section 5 (implementation)	- No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 1:15:00 PM

Name	Dr. Muhammad Usman Khan
Role	NHS Professional
Other role	NICE Coordinator
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Relief from constipation and adequate relief needs to be defined specifically in the guidance later on.
Section 2 (clinical need and practice)	According to the costs stated above , according to prevalence estimate of 8 % at NHS Richmond and 50% uptake , it would cost us £13,598 per year. But looking at the higher end of the spectrum (52%) and based on 50% uptake , the costs would be £88,832 which are quite high compared to the total prescription costs for laxatives per year i.e £161,403, i.e almost 50% more than the existing spend.
Section 3 (The technologies)	Several uncertainities still remain as the studies included were short-term (12 weeks)and the long-term effects are unknown. There is lack of published long-term safety data , cisapride (same drug class) was withdrawn from the GI market in 2001. Lack of comparative data against alternatives treatments because trials to date have been placebo-controlled.
Section 4 (Evidence and interpretation)	The drug does not seem to be cost effective based on our local estimates unless savings are identified from inhospital events avoided.
Section 5 (implementation)	No comments
Section 6 (proposed recommendations for further research)	No comments
Section 7 (related NICE guidance)	No comments
Section 8	

(proposed date of review of guidance)	
Date	8/24/2010 1:06:00 PM

Name	Teresa Salami-Adeti
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Bexley Care trust is happy to note prucalapride as a Â new option in the treatment of chronic constipation in women.
Section 2 (clinical need and practice)	Bexley Care Trust wishes to see the full breadth of side effects and contraindications of prucalapride.
Section 3 (The technologies)	Criteria for discontinuation of this drug should include "a lack of satisfactory response by 4 weeks" as placebo trials have lasted for 4 to 12 weeks.
Section 4 (Evidence and interpretation)	While we welcome the use of a new cost effective drug, which would be helpful in treating severe consitpation locally Bexley Care trust is concerned about the long-term side effects of prucalopride, such as effects on people with cardiovascular conditions. We do however note that the cost effectiveness ratios as advised by NICE are acceptable for this drug but the quality of life gains are small in women (estimated 0.0316QALY). We also note that there were limitations to the quality of the reaserch used, such as short RCTs and the inclusion of men and people who may have not been laxative refractory. We would urge NICE to make this information more explicit. Taking into account the possible ramifications on the efficacy of prucalapride.
Section 5 (implementation)	At this time BCT has no comment on the above and wishes to take this opportunity to consult more widely.
Section 6 (proposed recommendations for further research)	No Comment
Section 7 (related NICE guidance)	No Comment
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 12:40:00 PM

Name	Matthew Whitty
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I disagree with the ecommendatinos. Â The cost is too high for the limited benefit.

Section 2 (clinical need and practice)	If there is no benefit at 4 weeks surely the treatment should be stopped given the enormous cost?
Section 3 (The technologies)	Actual usage is liekly to far exceed the type of patients recruited for the trials
Section 4 (Evidence and interpretation)	More emphasis on the large placebo response and the modest benefits of this treatment vs placebo
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/24/2010 11:12:00 AM

Name	Dr Yan Yiannakou
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	I have agreed to undertake some educational work for the manufacturer for which i will receive payment.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (clinical need and practice)	
Section 3 (The technologies)	I would concur with the manufacturer's submission that a proportion of patients with chronic constipation suffer significant symptoms that greatly affect quality of life and functions of daily living, and that some of these are refractory to laxatives. In our practice patients have experienced their symptoms for a mean of 16 years, and have tried, on average, 6 different laxative regimens (audit data from 278 patients). We have studied QOL in a consecutive series of these patients, using SF-36, and have found that results are worse than those patients attending with active inflammatory bowel disease, and equivalent with the sorts of values seen in chronic rheumatoid arthritis [1]. A large proportion of patients attending secondary care (78% in our series) with constipation feel that laxative therapy is unsatisfactory. It is important to be clear that adequate relief of constipation ? as defined by frequency of complete bowel motions ? can be attained in most patients by upward titration of stimulant laxatives, but in many cases this results in unacceptable urgency, abdominal pain, unpredictability, or even incontinence. Thus, the definition of 'adequate response' relates to patient satisfaction rather than just frequency of bowel motions.

	As many as one third of our patients also fail other conservative therapies, such as biofeedback and rectal irrigation, and require surgical interventions including sacral nerve stimulation, appendicostomy, rectocoele repair, and colectomy [2]. The development and approval of effective drug therapies, based on a physiological enhancement of gut motility, is therefore very welcome. The studies presented by the manufacturer are, for the most part, well designed, with adequate patient numbers, and with valid conclusions regarding efficacy over placebo in patients who are mostly refractory to laxatives. Safety and adverse events seem satisfactory. My only significant reservation is the choice of primary outcome measure, which is essentially based on bowel frequency. In constipation bowel frequency does not correlate with QOL [3], or intestinal transit [4]. As mentioned above, it is fairly easy to produce an increase in frequency of (complete) bowel motions using upward titration of stimulant laxatives, but doing this may not improve 'wellness'. The emphasis on bowel frequency also undermines the definition and understanding of constipation, since many patients perceive themselves to be constipated despite normal bowel frequency [5]. It is interesting to note that in the development of a robust tool for assessing severity (PAC-SYM) bowel frequency was rejected as a predictive factor, and does not appear in the final questionnaire (see below). Experienced clinicians agree that patients with chronic constipation are most bothered by pain and evacuatory disturbance, with little emphasis on bowel frequency. Thus the meaningfulness of this as the primary outcome measure needs to be questioned. Two factors mitigate my reservation. The first is the use of a subjective quality of the defecation ie a sense of complete emptying. More important however, is the use of PAC-SYM and PAC-QOL as secondary outcome measures. These tools have been developed using scientifically robust methodology of patient-derived symptoms [6,7]. They have been well validated, and we have recently assessed validity in a cohort of UK patients, showing good correlation with SF-36 and global assessments, and satisfactory ceiling and floor effects [1]. Averaged scores can theoretically range from 0 to 4, but in practice 0.5 to 3.5, so that a one-point reduction does represent a very significant improvement, and is not easy to achieve. The reductions seen in both PAC-SYM and PAC-QOL in patients treated with prucalopride were significantly greater than those in the placebo group, and do represent strong evidence of efficacy. The point here is not that there is inadequate evidence of efficacy of prucalopride, but that approval of this drug using the studies presented should not act as a precedent for the use of SCBM as a primary outcome measure in future studies in this

	condition, and that care should be taken to use measures which are proven to be meaningful. 1. Cowlam S. Quality of life, physiological evaluation, and novel treatment, in refractory constipation: University of Newcastle 2008. 2. Khan U, Bain I, Green S, Cundall J, Varma J, Yiannakou Y. Evaluation of the range of therapies provided by a specialist constipation clinic. Â Colorectal Disease. 2010 12, supplement 1. 3. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, Hughes AO. Defecation frequency and timing, and stool form in the general population: a prospective study. Gut. 1992 Jun33(6):818-24. 4. Cowlam S, Khan U, Mackie A, Varma JS, Yiannankou Y. Validity of segmental transit studies used in routine clinical practice, to characterize defaecatory disorder in patients with functional constipation. Colorectal Dis. 2008 Oct10(8):818-22. 5. Sandler RS, Drossman DA. Bowel habits in young adults not seeking health care. Digestive diseases and sciences. 1987 Aug32(8):841-5. 6. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scandinavian journal of gastroenterology. 2005 May40(5):540-51. 7. Frank L, Kleinman L, Farup C, Taylor L, Miner P. Psychometric validation of a constipation symptom assessment questionnaire. Scandinavian journal of gastroenterology. 199934:870-7.
Section 4 (Evidence and interpretation)	At the time of writing, I have prescribed prucalopride to 87 patients with chronic laxative-refractory constipation, most of whom have also failed treatment with biofeedback and rectal irrigation. To date, follow-up is short and incomplete, but around 20-25% seem to be responding and continuing with treatment. This is in line with the trial data, and may represent a significant benefit to patients with genuinely refractory symptoms. Those patients who have not responded (or suffered side effects) have stopped treatment before a second prescription, supporting this particular assumption of the economic analysis. The economic calculations seem valid, though one aspect has not been considered. This is the potential increase in healthcare costs as a result of development of minimally invasive, high-tech, high cost therapies, such as laparoscopic appendicostomy and sacral nerve stimulation. The latter has recently been shown to be effective in chronic constipation [8], and though further studies are needed, and NICE approval is some way off, these procedures are being performed in specialist centres on a compassionate basis at a cost of £15-20k for each. With regards to the committee's recommendations, some clarity is required regarding the statement that the treatment should be prescribed in patients who have been 'managed by a clinician with expertise in treating chronic constipation'. I presume this

	means prescription by GPs, since all will have such experience? For reasons noted above, I also feel that clarity could be improved by replacing the statement that Prucalopride be used where "laxatives fail to provide adequate relief" with the phrase "used in chronic constipation in women who find laxative therapy unsatisfactory". The committee mentioned the issue that studies used a placebo comparator rather than standard therapy (ie laxatives). Two points are worth making here. The first is to say that if recommendations are (as they should be) that the drug should only be used in patients who are truly refractory to laxatives, then this concern should have little relevance. The second is that the efficacy and safety of laxatives is poorly characterised. Many patients with more refractory symptoms are taking high doses of laxatives over many years. There has been some evidence in the past that this may be harmful [9-12], and long term safety is unlikely to ever be confirmed. The use of a drug which has been carefully studied, and which will undergo post-marketing surveillance, should therefore be seen as a progressive step. Finally, it is important to state that approval of this drug for use (in specific situations) in chronic constipation may have wider benefits than the specific effect in symptoms and QALYs. Constipation is a 'Cinderella' subject which remains relatively poorly understood and under-researched. Approval of an effective promotility agent will ignite interest in the condition, and may stimulate increased research to help those patients who continue to suffer severe symptoms despite diet and laxative therapy. 8. Kamm MA, Dudding TC, Melenhorst J, Jarrett M, Wang Z, Buntzen S, et al. Sacral nerve stimulation for intractable constipation. Gut. 2010 Mar59(3):333-40. 9. Ziter FM, Jr. Cathartic colon. N Y State J Med. 1967 Feb 1567(4):546-9. 10. Dufour P, Gendre P. Ultrastructure of mouse intestinal mucosa and changes observed after long term anthraquinone administration. Gut. 1984 Dec25(12):1358-63. 11. Dufour P, Gendre P. Long-term mucosal alterations by sennosides and related compounds. Pharmacology. 198836 Suppl 1:194-202. 12. Smith B. Changes in the myenteric plexus in pseudo-obstruction. Gut. 1968 Dec9(6):726.
Section 5 (implementation)	none
Section 6 (proposed recommendations for further research)	none
Section 7 (related NICE guidance)	none

Section 8 (proposed date of review of guidance)	
Date	8/23/2010 1:17:00 PM

Name	Alexis Macherianakis
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Consider the number of potential patients who might be eligible for this new treatment.
Section 2 (clinical need and practice)	The unit cost may seem low at £622/403 per patient per year, but this is at least 8x the cost of some alternatives. Laxatives are frequently prescribed medications in the NHS (3 million items in 2008). Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this treatment.
Section 3 (The technologies)	The evidence from RCTs show that prucalopride increases the proportion of people who achieve three or more spontaneous complete bowel movements (SCBM) per week after 12 weeks of treatment. An increase from about 11% to 24% (Absolute difference 13% NNT 7 to 8). Long-term efficacy is not clear. There are no trials comparing prucalopride against standard therapy or other therapies. The long-term safety of prucalopride is unclear and discontinuation is common. Prucalopride showed acceptable safety profile in RCTs lasting 12 weeks. Longer term uncontrolled studies up to 36 months exist. These showed an 18% discontinuation rate because of an insufficient treatment response and 9% due to adverse events at 12 months. Prucalopride belongs to a similar class of drugs as cisapride, a drug withdrawn due to an association with serious cardiovascular events. Prucalopride is reported to be more selective in action than cisapride, with no reported effects on QT interval. Product characteristics will carry a warning that the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease.
Section 4 (Evidence and interpretation)	There were limitations to the quality of the research: The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. Further optimisation of these recommendations may be possible: NICE say that Prucalopride should only be considered in women who have been managed by a clinician with experience of treating chronic constipation. The women should have tried at least two different types of laxative and lifestyle modification for at least 6 months, but not had relief from

	constipation. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria could be revised further in the optimised recommendation.
Section 5 (implementation)	The exact number of people who will be eligible for prucalopride treatment is unknown. Estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome. It is not clear how long treatment with prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/21/2010 11:12:00 PM

Name	Francois Strydom
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"adequate relief" is not defined properly and is open to various interpretation that could result in prucalopride being prescribed to people for whom it is not intended. All currently available laxitives, including invasive, should be tried first in addition to the lifestyle modifications, instead of at least two
Section 2 (clinical need and practice)	
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	We are not convinced of the cost-effectiveness of prucalopride. If you consider prevalence in upper range, cost for this drug could escalate to over £260,000, and with the poor definition of adequate control it could even be more. This PCT would be forced to cut funding of other proven cost-effective treatments in order to fund prucalopride. In the current cash-strapped climate we should rather concentrate on national and local priorities and continue to manage conditions like constipation with proven cost effective measures. There is also concern about the lack of long term safety and efficacy data.

Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/20/2010 2:24:00 PM

Name	carole boarer
Role	NHS Professional
Other role	NICE sub-committee NHS Surrey
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Clinical trials were carried out over 12 weeks only. There is currently insufficient evidence for treatment beyond this 12 week period. The evidence for prucalopride has not been compared to any active comparators, only with placebo. The evidence is only for treatment over 84 days (not 220 days).
Section 2 (clinical need and practice)	The SPC states uncommon palpitations for cardiac disorders under undesirable effects. The numbers affected as uncommon is given as 1/1000 but 1/100.These may be dose dependent i.e. 1.9% with 4mg, although the QT interval prolongation with prucalopride in clinical studies was reported as low and similar to that with placebo. Similarly there was no reported problem in overdose for cardiac disorders.
Section 3 (The technologies)	There is a wide range on the prevalence of constipation in the female population from 8% to 52%. Current estimates of patients eligible for treatment are based on 8%. Assuming patients receive 2mg for 12 weeks with a cost of 28 tablets at Â£59.52 this gives a 12 week treatment cost of £178.56 For NHS Surrey with a population of roughly 1.2 million, the low estimate will give: 152,200x4x0.08x0.077x0.1375 (i.e. roughly 94x4) 12 weeks 375 patientsX £178.56 £66,960 If the prevalence is actually 52% then the figures are: 152200x4x0.52x0.077x0.12438 (i.e. roughly 4x610) 12 weeks 2438patientsx £178.56 £435,329 Obviously ongoing costs if treatment was not restricted to 12 weeks would be significant (375 patients £267,840 annually, 2438 patients £1,741,317 annually).
Section 4 (Evidence and interpretation)	
Section 5 (implementation)	It is not clear what costs savings, if any, there might be from reduced hospital admissions. The SPC recommends a review after 4 weeks if prucalopride is not effective, however it is not clear how straight forward it

	would be to assess the patient after only 4 weeks, and it is therefore possible that a 12 week trial will be implemented. The comparator during clinical trials was only placebo and an active comparator or comparison to standard care would give more robust evidence. It is not clear how the use of rescue medication with bisacodyl may have impacted on the trial results.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/19/2010 11:38:00 AM

Name	Graham Reader
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Regarding the statement in the proposed NICE recommendation : 'Prucalopride should only be considered in women who have been managed by a clinician with experience of treating chronic constipation. The women should have tried at least two different types of laxative, and lifestyle modification, for at least 6 months, but have not had relief from constipation'. I have concerns over what is meant by 'a clinician with experience of treating chronic constipation'. As it stands it is impossible to know what this means ? it implies a specialist but does this mean a specialist gastroenterologist in a secondary care setting? However it could be interpreted to mean any GP, who all have experience of treating chronic constipation. This will lead to practical difficulties in implementing the guideline. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 2 (clinical need and practice)	
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	I have concerns regarding the fact only short-term trials are available for prucalopride for a product that may be used long-term. I have concerns that the clinical benefit appears very modest. This product was appraised by our Area Medicines Management Committee which recommended prucalopride not be prescribed based on poor evidence of efficacy and increased cost, pending NICE guidance due shortly.

Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/18/2010 3:48:00 PM

Name	June Rogers
Role	other
Other role	patient group representative
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	PromoCon welcomes the committees recomendations regarding the option to be able to offer women an alternative oral treatment for intractable constipation. Currently the only other options are rectal preparations (which many do not find acceptable) or surgery
Section 2 (clinical need and practice)	Would like some clarification on any drug interactions - particularly anticholinergics
Section 3 (The technologies)	We think it is important to take into account not only the cost of the prucalopride treatment but to balance that with the potential savings of hospital admissions and the reduced need for any invasive surgical procedures etc
Section 4 (Evidence and interpretation)	The 2nd paragraph under key conclusions perhaps needs clarification as it could be misinterpreted in 2 different ways. Is the recomendation saying that after 6 mths of trying at least 2 different laxatives Proculapride can be tried or is it saying that each course of different laxative treatment needs to be at least 6 mths meaning that a period of 12 months needs to pass prior to Proculapride being considered?
Section 5 (implementation)	In recent discussions with Primary Care based Continence Services it is envisaged that Proculapride is a treatment that could ultimately be instigated and prescribed in primary care
Section 6 (proposed recommendations for further research)	Many of the women also suffer to some greater or lesser degree with faecal soiling/incontinence. It may be beneficial to link in to the NICE clinical guideline - Faecal incontinence (CG49)
Section 7 (related NICE guidance)	No comment
Section 8 (proposed date of review of guidance)	
Date	8/18/2010 1:47:00 PM

Name	Johanna Taylor
Role	NHS Professional
Other role	
Location	England

Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There is no definition of what "provide adequate relief" is. It is difficult to determine what a "clinician with experience of treating chronic constipation" is, I would state that in most cases as this is a condition primarily managed in primary care, alot of GPs and community nurse prescribers would consider themselves to have "an experience" in managing this condition. Therefore use of this product may not be restricted as much as implied in the NICE TA. Many patients may have tried laxatives for 6 months-however, should this be more specific i.e.regular laxatives, specifying which laxatives? In most cases in practice laxatives are used inappropriately. Lactulose will be prescribed "when required" therefore if comparing prucalopride to this, it is not a fair comparison.Lactulose takes 48 hours to exert and effect and most patients will not take regularly due to other known side effects e.g.bloating,increased wind. Appropriate (maximum tolerated) doses of "standard laxatives" should be used before considering this treatment,in practice this also does not occur. Number of patients expected to use treatment will be greater due to off-license use, therefore increased cost.
Section 2 (clinical need and practice)	Section 2.2. Although detailed that treatment should only be continued for 4 weeks - it does not specifically state treatment should be stopped. Perhaps this could be made more specific: "if once-daily prucalopride is not effective after 4 weeks, the patient should be re-examined and the treatment should be stopped." This would reduce inappropriate continuation of medication that is not working, where the long-term safety/adverse effects are still not known. Section 2.3 The full adverse and long-term effects are not yet known. Perhaps to include any adverse effects should be recorded via the yellow card reporting scheme. Section: 2.4 Although the cost per patient appears low, for the large numbers of patients with constipation this could increase costs signigicantly. I estimate that this product will be used off-label in men also and in women who do not fit the UK marketing authorisation. Most standard treatments for constipation cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the numbers of patients treated. Also difficult to audit use as prescribing data does not provided details of indication.
Section 3 (The technologies)	Evidence from placebo controlled RCTs shows prucalopride increases proportion of people who achieve three or more spontaneous complete bowel movements (SCBM) per week after 12 weeks of treatment. An increase from about 11% to

	24% (Absolute difference 13% NNT 7 to 8). Long-term efficacy is not clear. There are no trials comparing prucalopride against standard therapy or other therapies. Long-term safety of prucalopride is unclear and discontinuation is common. Prucalopride showed acceptable safety profile in RCTs lasting 12 weeks. Longer term uncontrolled studies up to 36 months exist. These showed an 18% discontinuation rate because of an insufficient treatment response and 9% due to adverse events at 12 months. Prucalopride belongs to a similar class of drugs as cisapride, withdrawn due to an association with serious CV events. Prucalopride is reported to be more selective in action than cisapride, with no reported effects on QT interval. Product characteristics will carry a warning that the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease. The cost effectiveness ratio of this technology is within thresholds currently accepted by NICE for recommending NHS funding. The most plausible ICER for prucalopride (compared to placebo plus rescue bisacodyl) was likely to be below £20,000 per QALY. Although the drug is relatively inexpensive, the quality of life gains are small (0.0316 QALY gain estimated for all women), and there is some uncertainty in these estimates.
Section 4 (Evidence and interpretation)	Limitiations: RCT were short (12 weeks), no standard care control groups. Patients groups for which this drug is not licensed are included in the trial analysis (i.e. men, patients who may not have been considered laxative-refractory) therefore efficacy results may not be true to the cohort of patients defined in the licensing. Relief from constipation is not defined in the studies used, by NICE or by manufacturer. Eligibility criteria could be revised further in the optimised recommendation. Placebo trials lasted 4-12 weeks, poor/no response at 4 weeks could be included as criteria to stop treatment as mentioned previously. Rescue medication suggested does not reflect current practice or that stated in Map of Medicine guidance.
Section 5 (implementation)	Need to be clear about who this TA is targeted at. Within primary care, most GPs may deem themself as a "clinician with an experience in treating chronic constipation". Should this be more robust and state "specialist with experience in treating chronic constipation". The number of patients this treatment will be appropriate for will be relatively low, however I expect larger numbers due to off-license use. Difficult to contain prescribing of a new drug particularly in primary care when there are many people with constipation and generally this condition is managed within the primary care setting. Therefore it is difficult to project real population numbers of patients. I am not sure if this drug provides any cost savings directly/indirectly as these are not detailed. Trial data does not support the initiation of this drug in practice, in the suggest cohort of patients and prescribers must be

	mindful of the potential for adverse effects with all new drugs.
Section 6 (proposed recommendations for further research)	No comments
Section 7 (related NICE guidance)	No comments
Section 8 (proposed date of review of guidance)	
Date	8/18/2010 1:43:00 PM

Name	Janet Brember
Role	Healthcare Other
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	There is no indication of the meaning of "adequate relief" or "relief from constipation" and people may have variable views on what these terms mean. I am not sure what is implied by "have been managed by a clinician with experience of treating chronic constipation". There may be many women who have self-treated with OTC laxatives for long periods - would they only be eligible if they have been under medical (specialist?)supervision for constipation for at least six months?
Section 2 (clinical need and practice)	The cost is significant compared with available laxatives. Prucalopride is likely to have an impact on the primary care prescribing budget if used long-term in place of(or in addition to)existing laxatives. Estimates of cost impact may be low if based on an 8% prevalance of constipation and actual impact may be higher. A once daily oral tablet has practical advantages over many other laxative products.
Section 3 (The technologies)	Long-term efficacy and safety are not established. The mode of action indicates that prucalopride may continue to be effective over time but this is not confirmed and discontinuation due to insufficient reponse was common. Although prucalopride appears to be safer than cisapride, rare adverse effects may still emerge.
Section 4 (Evidence and interpretation)	Prucalopride offers an alternative to more invasive or unlicensed options.
Section 5 (implementation)	The exact number of patients who will be eligible for prucalopride is unknown. Due to ease of use there may be off-license prescribing in men, IBS, drug-induced constipation etc. or early use in place of standard laxatives. Stopping criteria may be required, both for non-responders and an indication of how long treatment should continue in those that do respond.
Section 6 (proposed recommendations for further research)	Children are another group where off-license use may occur.
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	

Date	8/18/2010 1:13:00 PM

Name	Debbie Campbell
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please consider the number of patients this guideline may be applicable to. What about lifestyle advice and length of time different laxaitives are tried for.. This is likely to be a GP prescribed drug and potentially numbers could be large
Section 2 (clinical need and practice)	The unit cost may seem low at £498 per patient per year, but this is at least 8x the cost of some alternatives. Laxatives are frequently prescribed medications in the NHS (3 million items in 2008). Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this treatment.
Section 3 (The technologies)	The evidence from placebo controlled RCTs show that prucalopride increases the proportion of people who achieve three or more spontaneous complete bowel movements (SCBM) per week after 12 weeks of treatment. An increase from about 11% to 24% (Absolute difference 13% NNT 7 to 8). Long-term efficacy is not clear. There are no trials comparing prucalopride against standard therapy or other therapies. The long-term safety of prucalpride is unclear and discontinuation is common. Prucalopride did show acceptable safety profile short term however it belongs to a similar class of drugs as cisapride, a drug withdrawn due to an association with serious cardiovascular events.
Section 4 (Evidence and interpretation)	There were limitations to the quality of the research: The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria could be revised further in the optimised recommendation. Response to treatment: placebo trials have lasted for 4 to 12 weeks. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 5 (implementation)	Number is unknown, range 8% to 52%. How can 'inadequate relief' be measured. There is a potential for off-license use in

	men, or in similar conditions such as constipation predominant irritable bowel syndrome. What is recommended length of treatment and when should it be stopped in those that don't respond
Section 6 (proposed recommendations for further research)	Would not expect CG 99 to be applicable
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/16/2010 5:35:00 PM

Name	Diane McGinn
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is difficult to assess the numbers of patients with chronic constipation in a PCT population and what proportion of these are women. At a time when we are faced with difficult prioritisation decisions for conditions which may be life threatening or significantly reduce a patients quality of life, it would be difficult to argue in favour of adopting a treatment which is considerably more expensive than those currently used for a condition which is likely to be deemed by the public as a lower priority. I can imagine that the requirement for specialist initiation will generate considerable increases in outpatient referrals at a time when were trying to reduce pressures in these areas.
Section 2 (clinical need and practice)	The unit cost may seem low at £498 per patient per year, but this is at least 8x the cost of some alternatives. Laxatives are frequently prescribed medications in the NHS (3 million items in 2008). Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this treatment.
Section 3 (The technologies)	Evidence from placebo controled trials shows prucalopride increased the proportion of patients achieving spontaceous complete bowel movements from 11% to 24% over a 12 week period (NNT approximately 8). However there are no head to head trials or evidence of long-term outcome. Long-term safety is also unclear.This is a concern due to prucalopride belonging to a similar class of drugs as cisapride which was withdrawn due to cardiac side-effects. There were no reported instances of QT changes due to prucalopride which is claimed to be more selective. Packs will carry warnings about caution in patients with cardiac arrythmias or uncontrolled cardiac disease. The cost effectiveness ratio of this technology is within thresholds currently accepted by NICE for recommending NHS funding. The most plausible ICER for prucalopride (compared to

	placebo plus rescue bisacodyl) was likely to be below £20,000 per QALY. Although the drug is relatively inexpensive, the quality of life gains are small (0.0316 QALY gain estimated for all women), and there is some uncertainty in these estimates.
Section 4 (Evidence and interpretation)	There were limitations to the quality of the research: The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. Further optimisation of these recommendations may be possible: NICE say that Prucalopride should only be considered in women who have been managed by a clinician with experience of treating chronic constipation. The women should have tried at least two different types of laxative and lifestyle modification for at least 6 months, but not had relief from constipation. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria could be revised further in the optimised recommendation.
Section 5 (implementation)	The exact number of people who will be eligible for prucalopride treatment is unknown. Estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome. It is not clear how long treatment with prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond. Response to treatment: placebo trials have lasted for 4 to 12 weeks. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/16/2010 5:00:00 PM

Name	Neeshma Shah
Role	NHS Professional
Other role	Head of Medicines management and Pharmacy
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1	How will adequate relief be defined, as needs to be both

(Appraisal Committee's preliminary recommendations)	lifestyle + pharmacological? It could potentially apply to many women on weight management programmes whose food and fluid intake is limited, often causing the problem in the first place. GPs would be considered clinicians with experience in treating chronic constipation as this is not considered a secondary care specialist clinician expertise alone. From practical experience, the statement left as it is captured above would lead to unnecessary referral to specialist.
Section 2 (clinical need and practice)	Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on PCT budgets, as the definition would in practice apply to about 50% of women who have tried laxatives (e.g. 3 million prescription items in 2008). Long term effectiveness and safety data is not available to know if the affect continues and there appears to be no on-going trials on the clinical trial registry. Costs would be mainly incurred in primary care where there cannot be negotiated procurement discounts.
Section 3 (The technologies)	As rescue therapy was allowed in the trials, this would be considered in addition (cost) to current therapy - none of the trials compared with treatments used currently, so it is not known for how long current treatments would be continued. Small gain in QALY versus potential cost pressure as the estimates of prevalance of chronic constipation vary widely and the manufacturers may have underestimated the numbers.'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives.
Section 4 (Evidence and interpretation)	Only short term studies upon which this is based concerns that safety, especially as cisapride, in the same class of medicine, was withdrawn after widespread (unlicensed) use and there is inadequate long-term data on safety, especially as the cohort of women to which this technology would apply to is potentially large. Discontinuation criteria need to be strengthened, such as after 4 weeks if no improvement.
Section 5 (implementation)	Taking some of the issues already raised above, estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. It is not clear how long treatment with prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond.
Section 6 (proposed recommendations for further research)	There is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome - again paucity of any long-term serious ADRs (cf. cisapride)
Section 7 (related NICE guidance)	Date is too far away - the marketing of this product is already raising demand (not necessarily need, and likely that larger numbers than that estimated by the manufacturers will be prescribed this product inappropriately, in absence of long-term adverse
Section 8 (proposed date of review	

of guidance)	
Date	8/16/2010 3:35:00 PM

Name	Sasha Beresford
Role	NHS Professional
Other role	NICE manager
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Need more detail in guidance on when this drug should be stopped to prevent its long term prescription and waste of resources.Although the drug is relatively inexpensive,the numbers may be large. Clarify whether each of the 2 different types of laxatives is trialed individually for 6 months.
Section 2 (clinical need and practice)	The unit cost may seem low at £498 per patient per year, but this is at least 8x the cost of some alternatives. Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this treatment.
Section 3 (The technologies)	Long-term efficacy is not clear beyond 12 weeks from placebo controlled RCTs. In addition long-term safety of prucalpride is unclear and discontinuation is common. Longer term uncontrolled studies up to 36 months exist but show 18% discontinuation rate because of an insufficient treatment response and 9% due to adverse events at 12 months. Although the drug is relatively inexpensive, the quality of life gains are small (0.0316 QALY gain estimated for all women), and there is some uncertainty in these estimates.
Section 4 (Evidence and interpretation)	Limitations to quality of the research. The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended.'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria could be revised further in the optimised recommendation. Response to treatment: placebo trials have lasted for 4 to 12 weeks. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 5 (implementation)	The exact number of people who will be eligible for prucalopride treatment is unknown. Estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome. It is not clear how long treatment with prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond.

Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/12/2010 10:47:00 AM

Name	Louise Wilson
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (clinical need and practice)	Unit cost high compared with some laxatives.Common laxatives cost less than £1 per week and an increase in cost per item can have substantial impact on budgets, depending on the indications proposed for this treatment.
Section 3 (The technologies)	The long term efficacy and the safety of this drug is unclear. Life quality gains are low.
Section 4 (Evidence and interpretation)	The RCTs were short (12 weeks) and lacked standard care control groups. The inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. A lack of satisfactory response by 4 weeks could be included as a criterion for discontinuation.
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/12/2010 10:26:00 AM

Name	Caroline Court
Role	NHS Professional
Other role	
Location	England
Conflict	no

Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	How is adequate relief defined? This is very subjective. There is no NICE guidance on treating constipation in adults and therefore alternative treatments and lifestyle modification are not defined. People in the trials had mean duration of constipation of around 17-22 years. Therefore the 6 months recommendation may be too short. The prevalence of constipation and therefore cost to PCTs may be greatly underestimated. The QALY gain is small and therefore this may not be viewed as a priority for funding by PCTs or the public.
Section 2 (clinical need and practice)	Prucalopride is at least 8 times the cost of some alternative treatments.
Section 3 (The technologies)	There are no trials comparing this treatment against other therapies. Long term efficacy is unclear. Quality of life gains are small (0.0316) and there is some uncertainty in this.
Section 4 (Evidence and interpretation)	The RCTs were of short duration. There was no comparison to standard care. Some people in the trials may have been responsive to other laxative therapies.
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/10/2010 1:33:00 PM

Name	Janet Corbett
Role	Healthcare Other
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The recommendations are poorly defined and will lead to confusion in the service. What is the definition of "clinician with experience of treating chronic constipation" - a GP may feel he hits that description. Has both liefstyle modification AND laxative therapy to have been tried for at leats 6 month and failed? What constitutes failure to gain relief? There is likely to be "indication creep".
Section 2 (clinical need and practice)	The unit cost is at least 8 times the cost of some alternatives. Although the unit cost is relatively low, the volume is likely to be high and could have a substantial impact on PCT budgets already under pressure.

Section 3 (The technologies)	The evidence from placebo controlled RCTs show that prucalopride increases the proportion of people who achieve three or more spontaneous complete bowel movements (SCBM) per week after 12 weeks of treatment. The absolute difference 13% (NNT 7 to 8). Long-term efficacy is not clear. There are no trials comparing prucalopride against standard therapy or other therapies. The long-term safety of prucalpride is unclear,discontinuation is common. Prucalopride belongs to a similar class of drugs as cisapride, a drug withdrawn due to an association with serious cardiovascular events. Prucalopride is reported to be more selective in action than cisapride, with no reported effects on QT interval.However, the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease. The quality of life gains are small and uncertain.
Section 4 (Evidence and interpretation)	There are limitations to the quality of research - short RCTs and inclusion criteria that do not match the licensed indications. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. All patients had more than 6 months of constipation however mean duration of constipation in trials was about 17 to 22 years. On average patients had less than 1 SCBM per week, despite treatment with alternatives. Eligibility criteria should be revised further in the optimised recommendation. Response to treatment: placebo trials have lasted for 4 to 12 weeks. A lack of satisfactory response by 4 weeks should be included as a criterion for discontinuation.
Section 5 (implementation)	The number of patients likely to be treated with prucalopride is unknown. Estimates for the prevalence of constipation in women vary from 8% to 52%. There could be off license use in men which would add to the numbers and cost. It is unclear how long treatment should be continued for.
Section 6 (proposed recommendations for further research)	There is a risk that prucalopride may be used off license for these additional indications.
Section 7 (related NICE guidance)	No comment
Section 8 (proposed date of review of guidance)	
Date	8/10/2010 11:57:00 AM

Name	Christopher Ranson
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's	I suspect that if clinicians find this treatment to be effective then it will be used in both women and men even though it only has

preliminary recommendations)	a license for women. There may be a need to define chronic constipation as there will be differing opinions on this issue, if criteria to be used as per clinical trials then this should be specified.
Section 2 (clinical need and practice)	This overall cost is at least eight times the cost of some alternatives. Laxatives are a very frequently prescribed medicine in the NHS so this has a potential to have a significant impact on budgets. It will be difficult to restrict its use when prescribed in practice. It is likely to be recommended by district nurses if found to be effective, so large scope to increase prescribing within primary care.
Section 3 (The technologies)	The evidence from the clinical trials showed that this drug is effective in the short term compared to placebo. Patient with chronic constipation do have a tendency to be on laxatives long term in clinical practice and as this is an oral drug then this is a particular risk. Long term efficacy has not been proven in these clinical trials, although the manufacturer has estimated that patients will be on the drug for an average of 220 days, it is not clear how this assumption was made. Regards to the safety profile the majority of side effects in the clinical trials were mild to moderate in severity. Once again need to take into account that these were relatively short clinical trials compared to how long patients are likely to be on treatment. Prucalopiride belongs to a similar class of drugs as cisapride, a drug withdrawn due to the association with serious cardiovascular events. There has been no reported effects on QT interval in clinical trials which may explained by it being reported to be more selective in action compared to cisapride.
Section 4 (Evidence and interpretation)	The clinical trials were all of short duration, but treatment in practice is likely to be a lot longer. Comparison is with placebo and no comparison was made with other treatment options. The predicted number of patients eligible for treatment is likely to be an underestimate as in clinical practice it will be used in men also. It suggests that treatment should be reviewed after 4 weeks abd only continue if effective. This should be included in the main recommendation.
Section 5 (implementation)	No further comments
Section 6 (proposed recommendations for further research)	No further comments
Section 7 (related NICE guidance)	No further comments
Section 8 (proposed date of review of guidance)	
Date	8/9/2010 4:56:00 PM

Name	Paul McManus
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Implementing these criteria and, in particular, identifying appropriate patients, will be difficult in view of the lack of a definition of adequate relief, the extrapolation of data from trials in which women (and men) had constipation for up to 22 years, the short duration of trials, concerns about long term safety (cf cisapride), and the need for specialist involvement in a largely primary care managed condition.
Section 2 (clinical need and practice)	Compared to other treatments for constipation, this is an expensive product, at around 8-times the cost of common alternatives. Laxatives are frequently prescribed. Use of prucalopride may, therefore, have a signigicant overall cost impact.
Section 3 (The technologies)	The long-term safety and efficacy of prucalopride are not clear and there are no comparisons with standard therapy or other therapies. Discotinuation is common. In uncontrolled studies, 18% of patients discontinued prucalopride because of an insufficient treatment response and 9% due to adverse events at 12 months. Long term safety is particularly relevant since prucalopride is similar to cisapride, a drug withdrawn due to an association with serious cardiovascular events. While the cost effectiveness ratio of this technology is within thresholds currently accepted by NICE for recommending NHS funding, there is uncertainty around the estimates. The most plausible ICER for prucalopride (compared to placebo plus rescue bisacodyl) is likely to be below £20,000 per QALY. Quality of life gains are small for the additional investment required.
Section 4 (Evidence and interpretation)	RCTs were short (12 weeks) and lacked standard care control groups. Inclusion in these trials of men and people who may not have been considered laxative-refractory means that the efficacy results may not be representative of the efficacy in the population in which the drug is being recommended. 'Relief from constipation' is not defined in the studies, by NICE or by the manufacturer. In trials, the mean duration of constipation was about 17 to 22 years - how does this fit with NICE provisional recommendation that includes women with constipation for 6 months? Can the NICE criteria be refined to better reflect the trial populations? Also include discontinuation of treatment after 4 weeks if no response (since trials looked at use for 4-12 weeks).
Section 5 (implementation)	The exact number of people who will be eligible for prucalopride treatment is not known. Estimates of the prevalence of constipation in women vary widely (8% to 52%). No standard definition exists for 'inadequate relief' of constipation the definition used will affect the number of people eligible. In addition there is the potential for off-license use in men, or in similar conditions such as constipation predominant irritable bowel syndrome. It is not clear how long treatment with

	prucalopride is likely to continue in those who respond, or when it will be stopped in those that don't respond.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/9/2010 4:35:00 PM

Name	Vishal Kaushik
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (clinical need and practice)	
Section 3 (The technologies)	Need to clarify type of constipation - is slow transit constipation or patients with obstructive defeacation also an indication?
Section 4 (Evidence and interpretation)	
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/9/2010 3:22:00 PM

Name	raymond macallister
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Do you mean full relief or partial relief i think the indication should be patients who are about to undergo a surgical procedure for constipation. prescribers should report whether the drugs action was suffcient to avoid surgery
Section 2 (clinical need and	

practice)	
Section 3 (The technologies)	i think for a chronic condition the estimates of cost per qualy are worthless the main criterion should be whether there is clear evidence that the drug is better than existing aperients (no there isnt there are no active comparator trials) as its more expensive its place in therapy is uncertain, and it should only be used in hyperspecialist units as a treatment of last resport i.e. to avoid surgical procedures, implants
Section 4 (Evidence and interpretation)	i refer to commentson the usefulness of guessing a cost per qualy in this lifelong condition
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	8/4/2010 11:07:00 AM