Location within the ACD	Comments
Page 3, 1.1	We welcome the committee's recommendation for the use of prucalopride, and for clarity ask that the committee amend their recommendation for prucalopride to; 'an option for the **symptomatic** treatment of chronic constipation in women for whom laxatives fail to provide adequate relief'.
Page 3, 1.2	The following amendment to the text of the committee's recommendation may be considered helpful; Prucalopride should only be considered in women who have been managed by a clinician with experience of treating chronic constipation. During a period of at least six months the female patient should have tried at least two different types of laxatives, and have received advice on lifestyle modification but have failed to achieve adequate relief from constipation.
Page 3, 2.1	We recommend the following amendment: Prucalopride (Resolor, Movetis) is a selective serotonin (5HT4) receptor agonist that predominantly stimulates colonic motility. Prucalopride belongs to the therapeutic and pharmacological WHO ATC subgroup class (AO3AE04) of drugs for the treatment of functional bowel disorders that are acting on serotonin receptors. Prucalopride has a UK marketing authorization for the 'symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief'.
Page 7, 3.6	We request that for clarity the description of PRU INT 12 is amended to: In PRU INT 12, (a study in elderly (>65 years) patients, the proportion of patients treated…
Page 7, 3.8	We suggest that the following clarification may be considered helpful, SF36 data was collected from patients in fewer clinical trials compared to the disease specific PAC QOL data, for this reason alone it was decided by Movetis to use the more abundant PAC QOL for analysis of the quality of life changes associated with treatment with prucalopride. The committee's comment regarding outcomes measured using SF36 data; 'that no trials showed statistically significant greater improvements in SF36 for prucalopride compared with placebo at week 12' is correct, however only so when all patients are considered irrespective of response to treatment. Further analysis shows when the cohort of patients who responded to treatment are compared to placebo a statistically significant difference between prucalopride and placebo exists, with an average qaly gain of 0.04 and a cost per qaly gained of £15,300. This outcome based on SF36 data only shows prucalopride to be cost effective in patients who respond to treatment. Sensitivity analysis of these SF36 based outcomes show that treating all patients irrespective of response produces an average qaly gain of 0.019 and a cost per qaly gained £32,100 whereas treating the

	responder cohort only, produces a qaly gain of 0.040 at a cost per qaly gained of £15,300. Further sensitivity analysis has been conducted varying the acquisition cost by changing the number of days on treatment. The outcome is consistent with work conducted by the ERG.
Page 8, 3.9	We welcome the opportunity to offer further clarification regarding withdrawal and continuation in the long-term open label extension study. All patients who completed the 12 week double blind phase were invited to take part in the extension; approximately 80% of these participants choose to join the open label extension. Therefore the patients who continued in the open label extension study were a mix of responders and none responders, patients on active treatment or placebo. All of the patients in the extension study were put on to active treatment. Approximately 45% of the total patients enrolled in the extension study dropped out as a consequence of the sponsor stopping the studies. Of the remaining patients, the main reasons for drop out were: insufficient response (18%) withdrawal of consent (15%) adverse events (9%). Post hoc analysis shows that 90% of patients who dropped out of the extension due to insufficient response were already non-responders in the previous double blind phase. This confirms that patients who do not respond early in treatment will not respond with continued treatment and patients who do respond will show a sustained response with no loss of efficacy over time.
Page 9, 3.10	We concur with the committee's opinion that the incidence of serious adverse events is low and comparable between treatment and placebo. With regard to the specific adverse events of diarrhoea,, nausea, abdominal pain, and headache we agree with the committee that the incidence of these adverse events in the treatment arm is higher than in the placebo arm for the first two days of treatment then afterwards are comparable. These adverse events are mainly mild transient and do not require medical intervention.
Page 9, 3.11	We would like to clarify a very minor point in the consultation document regarding male data in the HE model. All data from the included trials is incorporated into the model, however the model is run using female data only, in accordance with the licensed indication.
Page 9, 3.11	We request that for the purpose of clarity the text of 3.11 is amended to include: …The model compared prucalopride with placebo. In both arms, bisacodyl as rescue medication was allowed, if bisacodyl was used by a patient any bowel movement in the following 48 hours were not included as these were not counted as spontaneous complete bowel movements…
Page 10, 3.13	Please refer to 3.10

Page 10, 3.14	Please refine the text regarding the description of PAC QOL as follows… …PACQOL is a measure from 1 (mild symptoms) to 4 (severe symptoms). This should read; from 0 (no symptoms) to 4 (VERY severe symptoms) and in fact should not refer to symptoms but to impact of symptoms on HRQOL
Page 10, 3.14	We would like to clarify the purpose of including the various studies in the HE model; The three pivotal studies, PRU-INT-6, PRU-USA-11, PRU-USA-13 the two elderly studies PRU-INT-12 and PRU-USA-26 and the extension studies were used to provide outcomes data and patient characteristics to inform the starting population and disease state in the HE model. Further patient characteristic data was also obtained from other prucalopride trials in chronic constipation – PRU-INT-1, PRU-INT-2, PRU-USA-3, PRU-GBR-4 and PRU-FRA-1.
Page 12, 3.18	We would like to confirm that the rationale for using the studies PRU-INT 6 PRU – USA 11 and PRU USA 13 was that these 3 trials are our pivotal trials, with the largest number of patients and 12 weeks treatment duration. All three studies were of identical design so pooling the data was appropriate. Please refer to 3.9 for clarification regarding how patients were enrolled for follow-up studies. As these patients were rolled over immediately from the double blind pivotal trials their original baseline (start of double blind trial) remained unchanged. (Please see 3.20 and 4.3 with regard to comments on refractory to lazative treatment and inadequate relief). The inclusion of PRU INT 17 (Opioid Induced Trial) does not effect the overall result as the numbers were small (96 out of approximately 2500 patients) and the nature of OIC would if any effect be noticed, reduce the utility gain as these are more challenging with a high level of co-morbidity. Please also see 3.9 for further clarification regarding withdrawal
Page 13, 3.20	The following clarification may be helpful; The patient population in the trials does not completely reflect the patient population covered by the marketing authorization; ‘symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief’, whereas the trail population was approximately 12% male.

	Further, to clarify understanding around the use of the term laxative refractory with regard to the licensed indication for prucalopride. Laxative refractory is metric based on bowel movement frequency alone, if a patient on laxatives has fewer than 3 bowel movements per week they are considered to be laxative refractory. The majority of patients in whom laxatives fail to provide adequate relief report: lack of efficacy on a cohort of symptoms, intolerable adverse events, intolerable dosage regimen and, lack of predictability. It was stated by the clinical experts at the committee meeting that some patients may achieve an increased frequency of bowel movement through the use of laxatives; however they cannot tolerate the laxative or find the unpredictability of the effect of the laxative unacceptable.
Page 14, 3.21	Refer to comments made regarding withdrawal rate in 3.9
Page 14, 3.22	We would like to refer the Committee to the comments made by Professor Whorwell with regard to the choice of comparator for trials of this nature, he advised the committee that trials of this nature are required to use placebo as a comparator, and that the use of an internationally available rescue medication is essential, hence the choice of biscodyl as the rescue medication.
Page 15, 3.24	Movetis acknowledge the committee's comments concerning the use of PAC-QOL and PAC-SYM to elicit quality of life data to produce EQ5D scores through mapping, and that SF36 scores did not directly contribute to the EQ5D scores. We welcome the opportunity offer further explanation of our decision; PAC-QOL and PAC-SYM are validated disease specific tools which were used in many of the prucalopride clinical trials whereas SF36 was used in few of the trials. Movetis acknowledge that from the perspective of expedience and simplicity we could have modeled the cost effectiveness of prucalopride on the available SF36 data. However having established an empirical relationship between the PAC data with SF36 and EQ5D it was appropriate to use the mapping process to translate PAC data to EQ5D directly, this producing a more robust cost effectiveness model drawn from a an abundant pool of individual patient data.
Page 15, 3.26	We accept the criticism that adverse events were not directly accounted for in the HE model, however PAC QOL does account for the effect of any adverse events on the quality of life of the patients on treatment, and that PAC QOL outcomes were mapped to EQ5D in which case the effect of AEs on QoL

	were accounted for. It may also be helpful to refer the committee to comments made by the clinical experts, that it is often difficult to differentiate between the AEs caused by the treatment and symptoms of chronic constipation. We would like to assure the committee that data from the trials shows that the vast majority of Adverse Events are mild to moderate, transient and do not require medical intervention.
Page 15, 3.27	We welcome and support the finding of the ERG in their conclusion that the results from their sensitivity analysis did not differ significantly from those provided by the manufacturer.
Page 17, 4.3	We agree with the committee that the definition of adequate relief requires refinement; the challenge of defining adequate relief is complicated by individual patient preference and circumstance. Expert clinicians suggest that adequate relief is a matter for the patient to decide together with their treating clinician. Setting rigorous criteria for the definition of adequate relief may result in patients being treated unnecessarily or patients who would benefit from prucalopride being excluded from treatment.
Page 18, 4.5	Movetis accept and support the conclusion of the committee that it would be difficult to define a standard laxative regimen as a comparator for patients with chronic constipation. We also feel that we must point out that the pivotal trials were placebo controlled with rescue medication available, and not comparator trials.
Page 19, 4.6	We concur with the committee; the available data demonstrates that prucalopride is clinically effective in providing relief to patients with chronic constipation, consistently from multiple trials.
Page 20, 4.7	We concur with the committees comments and further follow-up is planned. The submission of prucalopride to the EMEA went into considerable detail in evaluating cardio-vascular effects specifically QT prolongation. A thorough QTC study showed that prucalopride had no effect on QTC prolongation in contrast to the positive control (moxifloxacin).
Page 20, 4.8	We agree with the committee's comments that the SF36 data taken directly from the trials does not show a statistically significant improvement for prucalopride compared with placebo when all patients are included in the analysis. The mean of all SF36 patient data shows that the average qaly gained is 0.014 which would produce a cost per qaly of £33,400. However this is an unrealistic scenario as this includes continued treatment for all patients irrespective of effect. If the qaly is based on continued treatment for responders only, with the cost of none responder carried by the responder, using SF36 data the qaly gained by the under 65 cohort is 0.04 with a cost per qaly of £15,300.
Page 21, 4.9	We support the conclusion of the committee that the use of prucalopride could conceivably reduce the secondary care costs of treating chronic constipation; this opinion is also supported by clinical experts.

	We would like to bring to the attention of the committee that in 2008/09 in England and Wales in excess of £60 million cost were incurred by the NHS treating patients admitted as emergencies for treatment for fecal impaction associated with chronic constipation. We anticipate that a significant proportion of these patients, if treated with prucalopride would not attend at accident and emergency to be admitted.
Page 21, 4.10	We support the conclusion of the committee and the ERG
Page 22, 4.11	We support the conclusion of the committee