Wednesday 28th April 2010

NHS
National Institute for
Health and Clinical Excellence

NICE
Level 1A
City Tower
Piccadilly Plaza
Manchester
M1 4BD

Tel: 0161 870 3152
Fax: 0207 0619764

Email: lori.farrar@nice.org.uk

www.nice.org.uk

Dear [redacted]

Single Technology Appraisal – Prucalopride for the treatment of chronic constipation in women

The Evidence Review Group West Midlands Health Technology Assessment Collaboration and the technical team at NICE have now had an opportunity to take a look at submission received on the 29th March by Movetis Pharmaceuticals. The ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data. The questions for clarification are listed at the end of this document.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, Wednesday 12th May 2010.**Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Raphael Yugi – Technical Lead (raphael.yugi@nice.org.uk)

Any procedural questions should be addressed to Lori Farrar – Project Manager (lori.farrar@nice.org.uk)

We would appreciate it if you alert us to any queries you have as soon as possible.

The clarification phase of this appraisal is referenced in section 3.4:Phase 2/ evidence review/ evidence submission and clarification/ section 3.4.2,
available in the NICE guide to the methods of technology appraisal, available from the NICE website and via the link below

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http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp

Yours sincerely

pp ***Dr*** **Frances Sutcliffe**

Associate Director – Technology Appraisals Committee C
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Literature searching

A1. In appendix 2 (page 204), the submission states that a systematic review for clinical effectiveness studies was not conducted. Please provide details of how clinical effectiveness literature searches were done, the dates and databases searched. Please clarify if any searches of ongoing trials registers were conducted and whether any company databases were searched.

A2. In appendix 10 Section 9.10 (page 205), please supply the date on which the cost effectiveness search was conducted, the date span of the search and clarify which databases were searched (if only MEDLINE was searched, please state).

A3. In appendix 13 Section 9.13 (page 214) the introductory text of this section states that searches are outlined at the end of the section but no searches appear to be included. Please provide the searches completed to identify resource use.

Clinical trials

A4. Page 36 of the submission states that in the pivotal studies, laxatives were not allowed but a rescue therapy (bisacodyl (a type of laxative) or enema) could be given.

- Please define the laxatives used in trials for banned medication

- Please describe the criteria for allowing rescue therapy and the process by which patients could receive that therapy

A5. Please clarify what medications were allowed during the run-in period and whether in the run-in period spontaneous complete bowel movements (SCBM) were classed only as those >24 hours after the use of laxative.

A6. In tables 12, 13 and 15 (pages 41-4) combined data for patients' previous laxative and enema use are provided. Please provide separate data for previous laxative use and enemas that patients used before they took part in the pivotal. Please provide data for the pivotal, elderly and retreatment populations for each study arm separately.

A7. Pages 45-48 of the submission present results in terms of spontaneous bowel movements so that all bowel movements occurring due to the comparator treatment (biscodyl) are discounted. Please provide data for the total number of bowel movements (spontaneous and non-spontaneous) in each arm of pivotal, elderly and retreatment trials

A8. Page 58 of the submission states that data from the last 7 diary days were used to fill in missing diary days.

- Please provide a full description of how this was done
- Please provide data for the number of days that patients filled in their diaries in the different treatment arms for the pivotal, elderly and retreatment studies.

A9. It is stated on page 79 that meta-analysis was not conducted. However, pooled results are described in the summary of section 5.5 and elsewhere in the submission. Please provide details of the methods used to pool results from the three pivotal trials.

A10. It is stated in page 60 that 50 patients were excluded from PRU-USA-11 trial (Camilleri 2008) for the pooled efficacy pivotal trial results.

- Please explain why these patients appear to be excluded from the analysis of pivotal trials (table 25, page 62) but included in the economic modelling (table 53, page 124)
- Please provide details and results of the additional analysis referred to on page 60.

A11. On pages 62-63, all data for the three pivotal clinical trials appear to have informed the analysis of pooled efficacy. Please clarify whether male patients and those who had not previously taken laxatives were included in the pooled analysis of pivotal trials.

A12. Section 5.5 of the submission (pages 62-68) provides combined data for laxative and enema use during the clinical trial. Please provide separate data for the number of days with bisacodyl use and days with enemas in the pivotal, elderly and retreatment trials in each study arm.

A13. On page 62 of the submission, the change between run in and week 4 for the primary efficacy endpoint (% patients with > 3 SCBMs/week) in the placebo arm rises in the three pivotal trials, for example, for PRU-INT-6 the increase is from 0.8% to 10.4%. This appears counterintuitive for a situation in which laxative availability has been withdrawn and only “rescue therapy” is available. Please provide a discussion and explanation for the increases observed.

A14. Table 25 (page 63), describes patients’ rating of their treatment. Please clarify whether patients were asked to rate only the study intervention part of their treatment that is, prucalopride or placebo, or whether this rating also included the rescue therapy.

A15. Adverse events are only given for those occurring ≥5% of patients (pages 99-103). Please provide full data for adverse events for each study arm in the pivotal, elderly and retreatment trials.

Section B: Clarification on cost-effectiveness data

Economic model structure

A16. Please clarify whether data for a comparator group are included in the economic model. Further, please confirm whether the estimates of NET_COST and EQ5D change in columns F and J of the spreadsheets are intended to represent differences between the results with and without prucalopride

A17. Please clarify whether figure 8 (page 118) is purely illustrative of utility profiles for the two compared groups. If so, please supply a corresponding graph that is generated by the model in the base case situation (after any model changes following from clarification) with utility quantified on the vertical axis.

A18. Please clarify what items of PAC Q are represented in figure 9 (page 119). If this graph is based on the dissatisfaction subscale please clarify stability of other scale values between 12 and 52 weeks.

A19. Please confirm whether the CEAC curves in figures 11-13 (pages 148-150) represent variability between individual patient or uncertainty around parameters?

Economic model spreadsheets

A20. On each spreadsheet, please clarify whether columns: B (=Age), C (=Gender), D (=Baseline) represent individual patient data? In addition please clarify the source of the values used in the spreadsheet? In particular, please clarify what is driving the number of rows in each sheet

A21. Please clarify how the stopping rule (that is, patients who after 4 weeks do not continue the therapy or patients who experienced free symptoms period and taking it only when they needed) is incorporated into the model and how non-responders are included in the model.

A22. If the model only considers responders, please provide an estimation of costs and QALYs for non-responders.

A23. Please clarify why [mean (standard error)] is considered instead of [mean (standard deviation)] for the variables applied in the economic model.

Data in the economic model

A24. Table 52 (page 121), describes 3 cycles one at 4 weeks, 12 weeks and 52 weeks. For each cycle please describe:

- The details (including source, characteristics and values) of the exact data used for the prucalopride arm
- The details of the exact data used for the placebo arm
- How the data were incorporated into each of the cycles

A25. Page 118 states that 12 week data were used in the economic model. However, it appears that some of the trials only lasted for 4 weeks (pages 27-31, table 1). Please describe how data were used where studies only lasted 4 weeks.

A26. **T**able 53 (page 124) describes the clinical trial data chosen for inclusion in the economic model. Please clarify the rationale for:

- The trials that were selected
- The individual patient data taken from those trials.

A27. On page 129, please explain how the baseline utility of 82.22 was derived. Please clarify which trials were used for this estimate

A28. On page 140, the submission describes how some people will take prucalopride on an intermittent basis while others will take it on a continuous basis. Please clarify how these two regimens are handled in the economic model:

- in terms of costs, and

- in terms of health related quality of life, is there a reduction in HRQOL for people who take the treatment intermittently and only take further treatment when symptoms reoccur?

A29. Page 142 describes the cost assumptions in the economic model. The summary of product characteristics states that the 1mg dose may be increased to 2mg for the elderly population if required. Please clarify how this incorporated into the economic model

A30. The description of the economic model on page 142 of the submission suggests that it includes no costs for monitoring, administration or for medications that are not prucalopride. The summary of product characteristics states that in cases of prolonged treatment the benefit of prucalopride should be reassessed at regular intervals. Please provide cost estimates (including unit costs, and annual costs) for monitoring and follow up for people on prucalopride and standard care, including costs of interventions and medications (for example rescue medications or invasive procedures) that may be required for non-responders. Please incorporate these into an economic analysis or provide further rationale for their exclusion from the model.

Economic model assumptions

A31. Please clarify whether the key assumptions listed in section 6.3.8 (page 130) of the submission represent all the assumptions in the economic model. If not please list all the assumptions along with a justification for each.

A32. In figure 9 (page 119), please clarify whether in the assumptions of the economic model, patients in the comparator arm continue on the withdrawal from laxatives/rescue therapy regimen or whether they revert to their run in/pre-trial regimen. If the latter is the case, please clarify if the utility values for this arm would be expected to revert to baseline values

A33. In section 6.3.8 (page 130), bullet-point 1 states that: "*Placebo data from the prucalopride clinical trial were taken as an approximation for the efficacy of response for patients on laxatives*." On page 156 (section entitled placebo response as comparator) the submission states: "*One of the key assumptions underlying the analysis equates to the efficiency of laxatives with placebo response in the clinical trials. Such an assumption requires further examination and justification*". Please clarify the justification for this assumption. It appears counterintuitive that withdrawing laxative and making it available only as "rescue therapy" would equate with continued use of laxative. Please supply/clarify any evidence that may justify this assumption.

A34. For figure 14 (page 159), please describe the basis for the assumption that, of people with chronic constipation, 10% will fail to respond to laxatives.

Population in the economic model:

A35. Table 53 (page 124) of the submission suggests that all patients in the pivotal studies were included in the cost effectiveness model but some of these patients were men and some appear not to have had previous laxative treatment. Please clarify whether male patients and those who had undergone no previous laxative treatments were excluded from economic modelling.

A36. In table 53 (page 124), no overall data for the patients included in the economic model appears to have been provided. Please provide the following data for the treatment and placebo arms for patients included in the economic model:

- Demographics
- Duration of constipation
- Ave frequency of stools per week at baseline
- Previous laxative use

- Overall assessment of therapeutic efficacy of previous treatment for constipation
- Current treatments
- SCBM ≥3/week
- Average increase of ≥1 SCBM/week
- Average increase of ≥SBM/week
- Average number of SCBM/week
- Total number of BM (spontaneous and non-spontaneous)
- Number of days with bisacodyl use
- Number of days with enemas
- Patient assessment of constipation severity
- Patients rating their treatment as quite a bit or extremely or extremely effective

Treatment continuation and stopping rules

A37. On page 122, the submission states "*As such the treatment continuation rule suggests reassessment of the patient after four weeks by a general practitioner and discontinuation of treatment for patients who fail to achieve 3 or more spontaneous (i.e. not laxative generated) and complete bowel movements (SCBMs*)". Please clarify if and how the costs of these reassessments were incorporated into the model

A38. With reference to the 4 week stopping rule on page 123, the submission states: "…*patients who fail to respond adequately to prucalopride at any particular are rapidly and easily identified in order to discontinue therapy and explore alternative (and perhaps more life threatening) potential causes of their chronic constipation*". If the 4 week stopping rule identifies patients that potentially have other conditions that require investigation then these are likely to occur almost exclusively in the intervention arm (since the placebo arm has no stopping rule). Please clarify if, in the pivotal trials and in extension follow-up to 52 weeks, any of these patients actually received such investigations and if so what investigations.

Sensitivity analyses

A39. On page 144, the submission states that an alternative process mapping SF-36 to SF-6D was undertaken and compared to the mapping used in the base-case analysis. Please clarify the nature of this analysis and present the results.

Section C: Textual clarifications and additional points

A40. Please provide protocols for the pivotal, elderly and retreatment trials