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18th June 2010

Dear [redacted]

Regarding: ERG Report on Prucalopride for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief

Thank you for providing a copy of the ERG report on prucalopride for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. Movetis appreciates the opportunity to correct some misunderstandings and correct a number of statements that occur throughout the review report that are not supported by the evidence.

We agree and concur with the analysis of the ERG that prucalopride is a cost effective treatment for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. We are concerned that the ERG have misunderstood the actual licensed indication and have not appreciated that symptomatic relief and improving health-related quality of life is the primary objective when treating chronic constipation in the target group of female patients. Only measuring increasing bowel movement frequency is oversimplifying a complex symptomatic disease. While complete spontaneous bowel movements are the better endpoint for randomized controlled trials, clinical practice dictates that an increase in bowel movement frequency is insufficient to obtain adequate relief of the broader chronic constipation symptomatology.

It is inferred in the report that the licensed indication is not supported by the robust clinical evidence provided with the submission, specifically the three identical pivotal randomized controlled trials, due to the inclusion of males and laxative naïve patients. We want to refer to the official EMA documentation that clearly states that the license restriction for use in women only was a formal request by EMA *after* the licensing authorities' analysis of the population recruited in the three pivotal trials, and not an outcome desired or planned by Movetis. The approval was based upon a unanimous vote with all EU member stating that 1) the licensed indication represents the highest area of unmet need, 2) that the majority of patients in the studies are indeed well described by the licensed indication and 3) that the evidence provided by the trials supports that -in the licensed indication- the drug obtains the best benefit/risk ratio. It is very disappointing to note that this evidence-based, broadly advocated and conservative approach of not only presenting the best case (only females) but show all original trial data in full transparency is now used to critique the submission.

In the same spirit, the health authorities have imposed upon Movetis the use of *short term* rescue laxatives as the required way to provide some incomplete relief for treatment of *chronic patients* with placebo. The statement that a short term increase in bowel movement is associated with adequate relief in chronic constipation is inaccurate and not in line with existing medical literature on this topic.

The relatively low number of males recruited to the trials, less than 15%, is proportionate to the burden of disease falling on the female gender and consistent with all other trials in this indication. We feel it is inaccurate to define the trials as inappropriate for the licensed indication because the trials were the basis for the indication and include more than 85 % females and only a small number of male patients. A similar misunderstanding and inaccuracy is extended with regard to the inclusion in the trials of a small number of patients who were not laxative refractory. While it is correct that a small proportion of patients recruited to the trials were laxative naïve, they would however have met the recruitment criteria of having symptomatic chronic constipation for at least 6 months with dietary, lifestyle or non-pharmacological interventions and upon analysis do not impact the outcome of the trials.

It is also important to recognize that for the purposes of economic modeling the male patients were excluded from the modeled population and the model was built in such a way that patients who were adequately relieved with laxatives could also be excluded (Counter-intuitively, excluding these patients enhances the cost effectiveness of prucalopride).

The ERG report states that the benefit provided by prucalopride in the economic model is overestimated based on the criticisms above, however when the economic model is run in a mode that excludes the disputed population, the cost effectiveness of prucalopride is seen to improve, supporting the conservative approach taken by the applicant.

The ERG report questions the validity of the economic model based on the unconventional approach, using an evidence based individual patient level model instead of a conventional Markov model approach. The advantage of this individual patient-level based model is that it contains minimal assumptions (each data point is an actual patient in the trials); cost is kept solely to drug acquisition cost. With the main variable being patient self-reported outcomes, there is no possibility to manipulate the outcome, further supporting the robustness of the modeling approach taken by Movetis. The ERG report is critical of the lack of transparency of the mapping process used to convert the patient reported outcome in PAC QOL and PAC SYM to EQ5D. The algorithms used for mapping PAC-QOL and PAC-SYM to SF-36 and from SF-36 to EQ5D have been independently reviewed and validated by Professor John Brazier, an acknowledged expert in this discipline. The

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mapping of SF-36 onto EQ5D has already been published and the study that describes the mapping of PAC-QOL and PAC –SYM to EQ5D has now been accepted for peer-reviewed publication.

We are concerned that the ERG in the evaluation of the economic model outcome may have discounted the patient benefit gained through treatment with prucalopride, to the detriment of the cost effectiveness as measured by cost per QALY gained. All the evidence shows that when prucalopride is used in women with chronic constipation who have failed to achieve adequate relief with laxatives, the cost effectiveness of prucalopride is under the threshold range of £ 20,000 to 30,000 per QALY gained.

Yours sincerely

[redacted]
Movetis UK