Reviewer's report

Title: Efficacy and tolerability of PEG-only laxative on faecal impaction and chronic constipation in children: a randomized controlled study vs a standard PEG-electrolyte laxative.

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Reviewer: Mike Geraint

Reviewer's comments: Dr Mike Geraint BSc MB ChB MFPM

Major compulsory revisions.

1. This study is comparing two products, Movicol Bambini and Onligol and the primary outcome measure is stated to be stool frequency over the 4 weeks of treatment. A major concern in interpretation of the results is that the recommended dose of Onligol for treating constipation is significantly higher than the dose of Movicol Bambini. For example in a 5 year old child weighing 20Kg the recommended daily dose of Onligol would be around 14g PEG compared to 6.9g PEG for Movicol Bambini. Therefore it is totally predictable that if a child is treated with Onligol the weekly stool frequency would be higher than with Movicol Bambini. This serious limitation regarding the interpretation of the results obtained from is not made sufficiently clear in the discussion of the results. Also the abstract does therefore not accurately convey the results where it states that “…patients in the PEG-only group had higher and more regular soft stool frequency.” The abstract needs to make clear that this higher stool frequency was solely due to the higher dose of PEG administered, as the discussion section does.

2. For the treatment of faecal impaction the authors correctly note in the results section that there were not enough children with faecal impaction entered into the study to allow a statistical comparison to be made. Nevertheless, in the discussion section they comment that: "PEG-only was apparently faster as more than 2/3 of patients resolved the faecal obstruction at the second day of treatment as compared to only 1/3 in the PEG-EL group". This is implying a clinical difference between the two products which has not been confirmed by statistical analysis, so I would suggest that the authors justify reference to this statement in the discussion section, or remove it.

3. In the discussion section the authors state that: "the efficacy of the two PEG formulations for the treatment of chronic constipation in children cannot be
considered equivalent.” This statement implies that if they cannot be considered equivalent, then one product must be considered to be superior or inferior, and by clear implication this would imply that Onligol was superior. As pointed out previously the difference in stool frequency seen between the products was a function of the different doses of PEG administered not due to any inherently superior efficacy of Onligol. Either this statement needs to be qualified to refer to the difference in dosing, or it should be removed. Also the authors need to address the fact that absolute stool frequency alone is not necessarily a measure of how clinical effective a laxative is, it is possible for patients to experience too many stools a week as well as too few.

4. One of the outcomes of the study that is reported in the results (and the abstract) is acceptability and compliance. Also the report states that PEG-only solution is tasteless. That is somewhat misleading, although the PEG-only product has no added flavours, PEG solution made up in water is not tasteless, it has a slightly soapy or oily taste to it and in the case of PEG-EL the taste is slightly salty as well as being slightly oily or soapy. Children are notoriously fussy about the taste of liquid medicines and what they will or will not take. Therefore parents will do whatever they need to do in order to get their children to take a PEG based laxative, and this usually involves adding additional concentrated fruit drinks to the solution, or dissolving the PEG powder in the child’s favourite soft drink. This means that in clinical practice it is very unusual for PEG laxatives to be dissolved in water alone, so that any comparison of the acceptability from the point of view of taste or amount taken is probably not valid. The authors need to address this issue.

5. In the conclusion section, the authors conclude that The PEG-alone laxative may be superior to the PEG-EL formulation in terms of tolerability, preference and ease of administration. In respect of tolerability, this is only true for the symptom of nausea but not for the only other measure of tolerability which was abdominal discomfort. Therefore it is probably too much of a generalisation to state that the tolerability of one product is superior to the other just on the basis of one of many possible measurements to assess tolerability. Furthermore, the point made above is relevant to this conclusion as to the preference of one product over another, In actual clinical practice flavour masking using various strategies is adopted by parents anxious that their children should comply with the dosing requirements. Also the words ‘preference’ and ‘ease of administration’ are used in the conclusion but these words do not appear elsewhere in the manuscript so it is unclear what is meant by the choice of words. The authors should comment on these points.

Minor essential revisions

1. Further to the comparison of doses between the two products, the manuscript is unclear about the dosage that is actually recommended for the PEG-only product. It refers to the constipation dose for Onligol being: “In children <20Kg 0.7g/kg/day; in children >20Kg the daily dose was up to 30g daily.” Is it that for children >20Kg the dose is still calculated on the basis of 0.7g/Kg/day but with the dose not to exceed 30g per day? This needs clarifying.

2. The manuscript does not make clear at what stage the children were
considered as being eligible for entry into the study? Presumably they were only enrolled if they fitted the Rome criteria and they were only formally entered at visit 2 in which the bowel diaries for the previous 7 – 10 days were assessed to confirm their eligibility? The authors need to clarify this.

3. The authors state that PEG is the only active ingredient in both formulations. This is not correct, as the electrolytes contained in Movicol Bambini are listed as active ingredients in the SmPC. This needs amending.

4. The authors also state that the function of the electrolytes is to make the solution iso-osmotic. This is also not correct. It is the dissolving of the constituents of Movicol Bambini in a 125ml of water that produces an iso-osmotic solution.

5. The authors state that there is “increasing evidence that electrolytes are only important when the amount of PEG is very high”. This statement needs to be supported by references.

6. Similarly the authors refer to “some studies” which have indicated that PEG-EL and PEG-only do not induce tolerance. They need to support this statement with references.

7. Figure 2 presents a graphical representation of ‘responders’ over the course of the study, but nowhere in the manuscript is the term ‘responders’ defined. This needs correction either in the body of the text or on the figure itself.

Discretionary revisions.

1. The manuscript states: “We evaluated the use of PEG products in children aged 4 years and older …” but the patient demographics show that children from the age of 2 were entered into the study. This needs correcting.

2. The trial flow chart is unclear as to the population analysed. The results suggest that this was the ITT population (49/42 patients) but the flow chart suggests that analysis was performed on 48/39 patients, which does not seem to be correct.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I am employed as Medical Director of Norgine Pharmaceuticals Ltd in the UK. Norgine market Movicol Bambini in Italy which was the comparator PEG-EL product used in this trial.