PUBLIC SUMMARY DOCUMENT
Product: Macrogol 3350, sachet containing 13.125 g powder, 30, Movicol®; sachet containing 6.563 g powder, 30, Movicol-Half®
Sponsor: Norgine Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

To seek the following:

a. an extension to the current listing to include the treatment of faecal impaction in adults, where conventional therapies have failed, and the alternative treatments may require hospitalisation; and

b. a similar listing for a lower strength product that can be used in adults and children for the treatment of faecal impaction, where conventional therapies have failed, and the alternative treatments may require hospitalisation.

2. Background

At the June 2002 PBAC meeting, Macrogol 3350 (13.125 g, sachet) was recommended for a restricted benefit listing for the treatment of constipation in patients with malignant neoplasia, on the basis of acceptable cost-effectiveness compared to lactulose. PBS listing was implemented on 1 November 2002.

3. Registration Status

Movicol is TGA approved for the following indications:

- treatment of constipation.
- faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon confirmed by physical examination of abdomen and rectum.

Movicol-Half is TGA approved for the following indications:

- effective relief from chronic constipation in adults and children over 12 years.
- resolving faecal impaction in adults and children. Faecal impaction is defined as refractory constipation with faecal loading of the rectum and/or colon confirmed by physical examination of abdomen and rectum.

4. Listing Requested and PBAC's View

Restricted benefit

The treatment of faecal impaction, where conventional therapies have failed, and alternative treatments may require hospital admission.

For PBAC's view, *see Recommendation and Reasons.*

5. Clinical Place for the Proposed Therapy

Macrogol 3350 with electrolytes provides an alternative treatment for faecal impaction in adults and children aged 2 years and over. Current treatment for faecal impaction in adults and children includes repeat enemas and suppositories or large volumes of lavage solution or manual disimpaction requiring hospitalisation.

6. Comparator

The submission nominated conventional therapy as the appropriate main comparator. Conventional therapy was stated in the submission to include: (i) hospital admission; and

(ii) either repeated enemas and suppositories, lavage solutions or manual disimpaction, associated with inpatient admission.

The choice of comparator was partially accepted by the PBAC. *See Recommendation and Reasons for further details.*

7. Clinical Trials

The submission presented four single-arm, open-label studies as the key evidence. The details of the published key studies, forming the foundation of the submission, are tabulated below.

Trial/first author	Protocol title	Publication citation
Culbert P	Highly effective oral therapy (polyethylene glycol/electrolyte solution) for faecal impaction and severe constipation. (prospective study)	Clin Drug Invest 1998;16(5):355-9.
Vincent R	Movicol for the treatment of faecal impaction in children. (retrospective study)	Gastroenterology Today 2001;11(2):1-4.

8. Results of Trials

The four key studies, involving mostly hospital patients, were single-arm, open-label studies with small sample size and short duration. In the study by Vincent and Candy, data was collected retrospectively by chart review.

All key studies enrolled patients who had previously used laxatives in an attempt to resolve faecal impaction/severe constipation prior to study commencement.

9. Clinical Claim

The submission described Movicol and Movicol-Half as having similar effectiveness to conventional therapy, but with less toxicity.

The PBAC did not accept the submission claim. For PBAC's view, *see Recommendation and Reasons.*

10. Economic Analysis

No formal economic evaluation was included in the submission. The economic case presented assumed a 90% effectiveness rate for adults and children for Movicol and Movicol-Half.

For PBAC's view, *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The PBAC believed the likely number of patients per year: up to 2,000-10,000 in Year 3 of listing, a poorly justified and likely underestimate in the submission.

The cost per year to the PBS was estimated in the submission to be well under $1 million in the first three years of listing. PBAC was of the opinion that the cost per year to the PBS in Year 3 was a poorly justified and likely under-estimate in the submission.

The PBAC considered that the overall market was expected to grow more rapidly if Movicol and Movicol-Half were listed on the PBS; ease of convenience associated with both products was expected to expand the market. The PBAC noted that there was also considerable potential for usage beyond the requested restriction – for example, nursing home patients.

12. Recommendation and Reasons

The PBAC considered there was potential for the inappropriate use of Movicol and Movicol-Half if they were listed as a restricted benefit as requested. This potential for widespread usage arises for several reasons, including that faecal impaction and severe constipation are similar conditions of differing severity (two of the studies presented investigated both conditions) and variations may therefore exist among clinicians in differentially diagnosing between them.

The PBAC noted the choice of comparator implicitly assumed hospitalisation alone, however, other oral laxatives: are employed outside hospital and are more commonly used than manual disimpaction; are in a similar therapeutic class as Movicol; and are in liquid formulation similar to reconstituted Movicol. Further, faecal impaction may be treated in outpatients' departments without requiring inpatient admission.

The PBAC did not accept that the evidence based solely on single-arm, open-label studies is adequate to support the comparative effectiveness of Movicol and Movicol-Half in the treatment of faecal impaction against other alternative interventions for PBS listing. Overall, the PBAC considered the measures taken by investigators to minimise bias in the studies were inadequate.

All key studies presented were single-arm, open-label studies with small sample size and short duration. The PBAC noted comparisons across these studies were potentially subject to important sources of bias such as selection and observer bias because there were no randomisation, blinding or comparative arm. The assessment of the patient-relevant outcomes was considered by the PBAC to be highly subjective; often based on patient's self-report.

All four studies enrolled patients who had previously used laxatives in an attempt to resolve faecal impaction/severe constipation prior to study commencement. In the absence of a comparative arm, the PBAC considered that it is difficult to differentiate the effects of Movicol from previous laxatives and it was also uncertain whether the reported adverse events can be attributed to Movicol or faecal impaction.

Nevertheless, the PBAC considered there is clinical place for Movicol and Movicol-Half in the treatment of chronic constipation not responding to conventional therapies. However, evidence demonstrating comparative effectiveness in this patient group had not been presented.

There was no formal economic evaluation included in the submission, and the PBAC agreed the assumptions on which the estimates for the costs to the PBS and offsets to government health budgets were based were poorly justified. The PBAC also noted that because all key studies are single-arm, open-label studies, the results of any economic evaluation, if performed, would be difficult to interpret. In the absence of any clinical data to suggest

Movicol and Movicol-Half are more effective than paraffin oil or lavage solutions of polyethylene glycol (PEG), any off-sets to the budgets of public hospital (and hence state and territory government) budgets based on an assumption that Movicol and Movicol-Half could further reduce hospitalisations was likely to be overestimated. Further the extent to which these claimed reduced hospitalisation episodes are realised as financial savings to government health budgets was not discussed and was also a source of overestimation.

The PBAC did not accept data from the AIHW National Hospital Morbidity Database on hospital separations for constipation as a measure of the extent of, and costs associated with, hospitalisation for faecal impaction. In particular, patients with other co-morbidities may be hospitalised anyway.

Therefore, the PBAC rejected the submission because clinical and economic uncertainties and inadequately demonstrated cost-effectiveness.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor wishes to note that whilst other oral laxatives may be more commonly used than manual disimpaction for the treatment of faecal impaction, none of these treatments are approved by the Therapeutic Goods Administration (TGA) for use for this purpose.