PUBLIC SUMMARY DOCUMENT

Product: Macrogol 3350, sachet containing 13.125 g powder, 30, Movicol®

Sponsor: Norgine Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The submission sought an extension to the current restricted benefit listing to include the treatment of patients with chronic constipation due to neurogenic causes not responding to other oral therapies.

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.

At the November 2005 PBAC meeting the Committee considered a request for 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 to request a similar listing for a lower strength product (Movicol Half) 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. The PBAC rejected the submission because of clinical and economic uncertainties and inadequately demonstrated cost-effectiveness.

3. Registration Status

Macrogol 3350 is registered on the ARTG for effective relief from constipation and treatment of chronic constipation. Macrogol 3350 is also effective in resolving faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon confirmed by physical examination of the abdomen and rectum.

4. Listing Requested and PBAC's View

Restricted benefit
Paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function not responding to other oral therapies.

See Recommendation and Reasons for the PBAC's view

5. Clinical Place for the Proposed Therapy

The listing of macrogol 3350 would provide patients with neurogenic causes of constipation access to an osmotic therapy if unresponsive to other oral treatments.

6. Comparator

The submission nominated rectal interventions such as suppositories and enemas as appropriate comparators.

7. Clinical Trials

The submission presented results from four randomised comparative studies of macrogol 3350 in chronic constipation as primary evidence. The submission also presented six non-comparative studies and one before-and-after study of macrogol 3350 in chronic constipation as supportive evidence. There were no trials comparing macrogol with the submissions chosen comparator, rectal interventions.

These trials had been published at the time of submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Attar A et al, 1999	Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation.	Gut 1999; 44(2): 226–30.
Attar A et al, 1996	A randomized study comparing a low-dose polyethylene glycol solution (PEG) 3350 and lactulose in chronic idiopathic constipation.	Gastroenterologie Clinique et Biologique 1996; 20: A21.
Eichhorn TE et al	Macrogol 3350/electrolyte improves constipation in Parkinson's disease and multiple system atrophy.	Movement Disorders 2001; 16(6): 1176–7.
Gruss H-J et al	Treatment of chronic constipation. Results of a multi-centre observation period on the use of polyethylene glycol 3350 plus electrolytes.	Der Allgemeinarzt 1999; 21:1342–1350.
Gruss H-J et al	Efficacy and tolerability of PEG 3350 plus electrolytes (Movicol) in chronic constipation associated with Parkinson's disease.	European Journal of Geriatrics 2004; 6:143–149.
Kalke YB et al.	Study to assess the efficacy, safety and tolerability of Macrogol 3350 plus electrolytes (Movicol) to manage the treatment of bowel dysfunction in patients with spinal cord injuries/disease.	Annual congress of the German-Speaking Medical Society for Paraplegia (DMGP). 2002
Lemann M et al	Efficacy of low dose polyethylene glycol (PEG) 3350 (Movicol) in idiopathic constipation: double blind crossover study against placebo.	Gastroenterol Clin Biol 1994 ; 18: B256.
Mingeon-Duballet I et al	Long-term efficacy and cost-effectiveness of polyethylene glycol 3350 plus electrolytes in chronic constipation: a retrospective study in a disabled population.	Current Medical Research and Opinion 2006; 22: P1-P9
Schlosser A et al	The use of Movicol in the treatment of severe, treatment-refractory constipation in the intellectually disabled.	Medical Aspects of Mental Handicap Conference, June 1998.
Wang HJ et al, 2004	A randomised, controlled comparison of low-dose polyethylene glycol 3350 plus electrolytes with ispaghula husk in the treatment of adults with chronic functional constipation.	Clin Drug Invest 2004; 24: 556–579.
Wang HJ et al, 2005	A randomised, controlled comparison of low-dose polyethylene glycol 3350 plus electrolytes with ispaghula husk in the treatment of adults with chronic functional constipation.	Drugs in R&D 2005; 6 (4): 221–5.
Wang HJ et al, 2002	Efficacy and safety of polyethylene glycol 3350 in the treatment of human functional chronic constipation.	Chinese Journal of New Drugs 2002; 11: 483–486.

8. Results of Trials

Given that the majority of evidence presented by the submission was not trial outcomes, and the submission did not consistently provide the results of statistical analyses, it was difficult to draw definitive conclusions regarding the efficacy of macrogol.

In its calculation of the outcomes presented for the 'primary evidence' macrogol trials, the submission calculated 'best' and 'worst' case scenarios. In the 'best case' scenario for a beneficial outcome, all discontinued patients were assumed to be successful, except those specifically noted as treatment failures, and were added to those patients defined as having a positive response. In the worst case scenario for a beneficial outcome all discontinued patients were assumed to have failed treatment. The opposite was used for detrimental outcomes.

The results of the selected 'primary evidence' macrogol trials, as presented by the submission, are summarised in the table below:

Trial	Timepoint	Proportion with ≥3 stools/wk		Proportion using suppository/enema	
		Worst case[a]	Best case[b]	Worst case[c]	Best case[d]
Attar					
macrogol	baseline	6/60 (10%)	6/60 (10%)	NR	NR
	4 weeks	45/60 (75%)	53/60 (88.3%)	17/60 (28.3%)	7/60 (11.7%)
lactulose	baseline	9/55 (16.4%)	9/55 (16.4%)	NR	NR
	4 weeks	42/55 (76.4%)	46/55 (83.6%)	23/55 (41.8%)	17/55 (30.9%)
Lemann					
macrogol	baseline	NR	NR	NR	NR
	2 weeks	28/39 (71.8%)	35/39 (89.7%)	11/39 (28.2%)	4/39 (10.3%)
placebo	baseline	NR	NR	NR	NR
	2 weeks	18/39 (46.2%)	25/39 (64.1%)	22/39 (56.4%)	15/39 (38.5%)
MOV-PARK	baseline	0/3 (0%)	-	-	-
macrogol	3 weeks	3/3 (100%)	-	-	-
	baseline	3/6 (50%)	-	-	-
lactulose	3 weeks	4/6 (66.7%)	-	-	-
Wang					
macrogol	baseline	0/63 (0%)	0/63 (0%)	-	-
	2 weeks	50/63 (79.4%)	58/63 (92.1%)	-	-
ispaghula	baseline	0/63 (0%)	0/63 (0%)	-	-
husk	2 weeks	26/63 (41.3%)	46/63 (73%)	-	-

NR=not reported

[a] all discontinued patients were assumed to have failed treatment

[b] all discontinued patients were assumed to be successful, except those specifically noted as treatment failures, and were added to those patients defined as having a positive response

[c] all discontinued patients were assumed to have used suppositories or enemas

[b] all discontinued patients were assumed to have not used suppositories or enemas

The pooled results presented by the submission were merely proportions from each included trial added together. Given that the trials pooled together were of different design, included different patient populations and compared different outcomes across the macrogol and rectal intervention trials, it was difficult to draw definitive conclusions about the comparative efficacy of macrogol and rectal interventions.

9. Clinical Claim

The submission claimed that macrogol 3350 had a similar efficacy to rectal interventions, but had greater effectiveness (i.e. a greater number of patients were willing to use macrogol 3350).

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

A preliminary economic evaluation using a cost-effectiveness approach and including only drug costs was presented.

A modelled economic evaluation was presented.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients treated with macrogol per year would be < 10,000 in Year 3 of listing while the financial cost per year to the PBS, after accounting for the savings from the reduced number of rectal interventions, would be < $10 million per year in Year 3.

12. Recommendation and Reasons

The PBAC considered that the evidence presented in the submission to be poor and unconvincing and acknowledged the difficulties associated with collecting data in this patient group. Despite this, the PBAC recognised that access to macrogol 3350 by this patient group would meet an important clinical need, that superiority over other oral therapies had been more convincingly demonstrated in other conditions impairing bowel function to a similar extent sufficient to justify the price advantage for macrogol 3350 over these other oral therapies and recommended listing on this basis at the price requested.

The PBAC also suggested that the sponsor consider submitting an application in the future to change the listing to an unrestricted benefit.

Recommendation
MACROGOL 3350, sachet containing 13.125 g powder, 30,

Add the following to the restriction:

Restricted benefit
Paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function not responding to other oral therapies.

Maximum Quantity: 1
Repeats: 5

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