PUBLIC SUMMARY DOCUMENT
Product: MACROGOL 3350 plus electrolytes, sachets containing powder for solution, 13.125 g and 6.563 g, Movicol®, Movicol®-Half
Sponsor: Norgine Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought to amend the current listing of macrogol 3350 to an unrestricted benefit and to list a new, half strength macrogol 3350 on the Schedule of Pharmaceutical Benefits.

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 of macrogol 3350 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.

At its March 2006 meeting, the PBAC considered a request from the Palliative Care Medications Working Group to list macrogol 3350 for palliative care patients where constipation is a problem. The PBAC agreed to the request that macrogol 3350 sachets be included in the Palliative Care Schedule to allow access for palliative care patients who were unable to access the medication via the current restricted benefit listing.

At its March 2007 meeting, the PBAC considered a request to extend macrogol 3350's listing to include the treatment of patients with chronic constipation due to neurogenic causes not responding to other oral therapies. The PBAC recommended listing for this indication on the grounds that listing would meet an important clinical need and that macrogol 3350 was superior to other oral therapies.

3. Registration Status

Macrogol 3350's TGA registration commenced on 21 August 1997. Macrogol 3350 is registered for the relief of constipation, treatment of chronic constipation and resolution of faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon confirmed by physical examination of the abdomen and rectum.

Half strength macrogol 3350's TGA registration commenced on the 23 September 2004. Half strength macrogol 3350 is registered for the relief of constipation in adults, the treatment of chronic constipation, and resolving or preventing recurrence of faecal impaction, defined as refractory constipation with faecal loading of the rectum and/or colon, confirmed by physical examination of abdomen and rectum, in adults and children aged 2 years and older.

4. Listing Requested and PBAC's View

The submission proposed two listing options as follows:
Option 1: Unrestricted benefit listing.

Option 2:
Restricted Benefit
Patients with chronic constipation or faecal impaction who are refractory to the first line interventions.

The PBAC considered that a restricted benefit listing was more appropriate than an unrestricted listing (see *Recommendation and Reasons).*

5. Clinical Place for the Proposed Therapy

Macrogol 3350 provides a second-line treatment option for constipation after dietary management and oral bulk forming agents. Half-strength macrogol 3350 provides a non-invasive treatment option for managing chronic constipation in children.

6. Comparator

The submission did not specify any particular comparator. In the five randomised comparative studies submitted, the comparators were lactulose (2 studies), placebo (2 studies) and ispaghula husk (1 study). Neither of the active comparators are PBS listed for the indication sought in the submission.

7. Clinical Trials

The submission presented the results of five randomised, comparative studies of macrogol 3350 in chronic constipation and faecal impaction in adults and children as primary evidence (Attar (1999), MOV-PARK (2001), Lenmann (1994), Wang (2004) and Thomson (2004)). Attar (1999) and MOV-PARK (2001) were double blind parallel group studies of macrogol 3350 versus lactulose in 115 and 9 patients respectively. Lenmann (1994) was a double-blind cross over study of macrogol 3350 versus placebo in an unreported number of patients. Wang (2004) was an open label parallel group study of macrogol 3350 versus ispaghula husk in 116 patients and Thomson (2004) was a cross over study of half strength macrogol 3350 versus placebo in 51 children aged from 2-11 years. The Attar (1999), Lenmann (1994) and Wang (2004) studies were presented in the submission considered by the PBAC in March 2007.

One comparative study with macrogol 3350 as a lead-in therapy, 10 non-comparative studies and one before-and-after study of macrogol 3350 in chronic constipation were also presented as supportive evidence.

These trials were published at the time of submission as follows:

Trial/First author	Protocol 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 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 20:A21.

Trial/First author	Protocol title	Publication citation
Candy et al (2002)	A study of Movicol (macrogol 3350 plus electrolytes) for the treatment of faecal impaction in children.	Journal of Paediatric Gastroenterology & Nutrition 34:462
Candy et al (2006)	Treatment of faecal impaction with polyethelene glycol plus electrolytes (PGE+E) followed by a double-blind comparison of PEG+E versus lactulose as maintenance therapy	J Pediatr Gastroenterol Nutr 43:65-70
Chen CC et al (2005)	Evaluation of polyethlylene glycol plus electrolytes in the treatment of severe constipation and faecal impaction in adults.	Current Medical Research & Opinio n 21 (10):1595-602
Culbert P et al (1998a)	Highly effective new oral therapy for faecal impaction.	British Journal of General Practice 48(434):1599-600
Culbert P et al (1998b)	Highly effective oral therapy (polyethylene glycol/electrolyte solution) for faecal impaction and severe constipation.	Clinical Drug Investigation 16(5):355-360
Eichhorn TE et al (2001)	Macrogol 3350/electrolyte improves constipation in Parkinson's disease and multiple system atrophy.	Movement Disorders 16(6):1176–7.
Ferguson A et al (1999)	New polyethylene glycol electrolyte solution for the treatment of constipation and faecal impaction.	Italian Journal of Gastroenterology & Hepatology 31 Suppl 3:S249-52
Gruss H-J et al (1999)	Treatment of chronic constipation. Results of a multi-centre observation period on the use of polyethylene glycol 3350 plus electrolytes.	Der Allgemeinarzt 21:1342–1350.
Gruss H-J et al (2004).	Efficacy and tolerability of PEG 3350 plus electrolytes (Movicol) in chronic constipation associated with Parkinson's disease.	European Journal of Geriatrics 6:143–149.
Hanson S et al (2006)	The clinical effectiveness of Movicol in children with severe constipation: an outcome audit	Paediatric Nursing 18(2):24-8
Hardikar W et al (2007)	Macrogol 3350 plus electrolytes for chronic constipation in children: A single-centre, open-label study.	Journal of Paediatrics and Child Health.43;527-531
Lemann M, et al (1994)	Efficacy of low dose polyethylene glycol (PEG) 3350 (Movicol) in idiopathic constipation: double blind crossover study against placebo.	Gastroenterol Clin Biol 18:B256.
Mingeon-Duballet I et al (2006).	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 22:P1-P9
Schlosser A et al (1998)	The use of Movicol in the treatment of severe, treatment-refractory constipation in the intellectually disabled.	Medical Aspects of Mental Handicap Conference, June 1998.
Thomson M (2004)	A placebo controlled crossover study of Movicol in the treatment of childhood constipation.	Journal of Pediatric Gastroenterology & Nutrition 39:S16
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 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	Drugs in R&D 6 (4):221–5.

Trial/First author	Protocol title	Publication citation
	chronic functional constipation.	
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 11:483–486.

8. Results of Trials

Adults – As noted above, three of the four randomised comparative studies were considered by the PBAC in March 2007 in respect of the sponsor's application to list macrogol 3350 for chronic constipation due to neurogenic causes and not responding to other oral therapies. The fourth study, MOV-PARK (2001) recruited only 9 patients and therefore did not substantially change the evidence base previously considered by the PBAC.

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.

Results of the selected 'primary evidence' trials - macrogol

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

None of the results presented by the submission were actually reported in the trials, with the exception of the proportion of patients using suppositories or enemas in Attar et al (1999) and the proportion of patients with ≥3 stools/week in Wang et al (2005). The remaining results were based on what appeared to be post-hoc outcomes created by the submission. Given that the majority of evidence presented by the submission was not based on 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 3350.

However, in March 2007, the PBAC concluded that "superiority [of macrogol 3350] over other oral therapies had been more convincingly demonstrated in other conditions [than constipation due to neurogenic causes] 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 proposed".

Children – In a randomised controlled cross-over trial of macrogol 3350 in the treatment of chronic constipation in children, Thomson et al (2004) reported the mean number of complete defecations per week as its primary efficacy outcome. After two weeks, patients taking macrogol 3350 had significantly more complete defecations per week compared to placebo (see table below).

Mean number of complete defecations per week

Study	Treatment	Time-point	N	Complete defecation[a] (SD)	P value
Thomson 2004	Macrogol 3350	2 weeks	25	3.6 (2.3)	<0.001
	Placebo	2 weeks	23	1.6 (1.1)	

[a] Mean number of complete defecations per week is the summary value calculated for each patient.

There are currently no other oral therapies PBS listed for use in chronic constipation in children.

9. Clinical Claim

The submission claimed that macrogol 3350 is significantly more effective than other second-line therapy such as lactulose and ispaghula husk in the treatment of chronic constipation whilst having similar or less toxicity.

10. Economic Analysis

The submission cited the results of five pharmacoeconomic studies on macrogol 3350 (Christie et al (2002), Guest & Varney (2004), Migeon-Duballet et al (2006), Guest & Cleggg (2006) and Guest et al (2007)). No economic evaluation generated by the sponsor was presented.

11. Estimated PBS Usage and Financial Implications

The submission estimated that under Option 1 (unrestricted benefit), the number of additional macrogol 3350 packs dispensed in Year 1 of listing would be greater than 200,000 and would increase further by Year 3. Half strength macrogol 3350 use was estimated to be in the range of 10,000 – 50,000 packs in Year 1, increasing to a figure somewhere in between 50,000 – 100,000 in Year 3. Under Option 2 (restricted benefit), the number of additional macrogol 3350 packs dispensed was estimated to be in the range of 100,000 – 200,000 in Year 1, increasing to greater than 200,000 by Year 3. Half

strength macrogol 3350 use was estimated to be in the range of 10,000 – 50,000 packs in Year 1, increasing further by Year 3 of listing.

The net financial implications were estimated to be an additional value of less than $10 million in Year 1 of listing and remaining less than $10 million by Year 3 under Option 1. Under Option 2, these figures were also estimated to be less than $10 million.

12. Recommendation and Reasons

The PBAC recommended the listing of half strength macrogol 3350 on the PBS and an extension to the listing for macrogol 3350 both for chronic constipation or faecal impaction not adequately controlled with first line interventions such as bulk-forming agents. The PBAC considered that a restricted benefit listing was more appropriate than an unrestricted listing for both macrogol 3350 and half strength macrogol 3350, due to concern over first line use in children if the listing was changed to unrestricted. The PBAC accepted the wording as proposed by the sponsor in its pre-PBAC response.

Recommendation

Amend the general listing restriction for macrogol 3350 by adding the following restriction:

Restriction:	Restricted Benefit Constipation in patients with malignant neoplasia; Paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function not responding to other oral therapies; Chronic constipation or faecal impaction not adequately controlled with first line interventions such as bulk-forming agents.
Maximum quantity:	1
Repeats:	5

List the half-strength macrogol 3350 product as follows:

Restriction:	Restricted Benefit Constipation in patients with malignant neoplasia; Paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function not responding to other oral therapies; Chronic constipation or faecal impaction not adequately controlled with first line interventions such as bulk-forming agents.
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

Sponsor agrees that this is an accurate summary of the history of macrogol 3350 & electrolytes (Movicol and Movicol-Half) on the PBS including the evidence presented and the decisions reached by the PBAC.