



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1386 – gastric contractility modulation (GCM) therapy for patients with type 2 diabetes and obesity

Applicant: MetaCure Australia Pty Ltd

Date of MSAC consideration: MSAC 64th Meeting, 30-31 July 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

In February 2015, an application requesting Medicare Benefits Schedule (MBS) listing of gastric contractility modulation (GCM) therapy (DIAMOND™ system) for patients with inadequately controlled type 2 diabetes mellitus (T2DM) and obesity was received from MetaCure Australia Pty Ltd.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of Gastric Contractility Modulation (GCM) therapy (DIAMOND™ system), MSAC did not support public funding for this technology for adult patients with type 2 diabetes mellitus (T2DM) who have:

- obesity (body mass index, BMI, of 30-45 kg/m²);
- inadequate diabetic control on standard oral glucose lowering (anti-diabetic) therapy;
- normal triglyceride levels (fasting plasma triglycerides \leq 1.7 mmol/L); and
- elevated glycated haemoglobin (HbA_{1c} \geq 7.5% and \leq 10%).

MSAC considered that the clinical need and effects of DIAMOND were uncertain and also found uncertainties regarding the financial impact of listing on the MBS.

3. Summary of consideration and rationale for MSAC's advice

MSAC recognised the public health importance of optimal management of T2DM. MSAC noted that the GCM therapy would be considered after the failure of a combination of at least three PBS-listed therapies. Furthermore, GCM therapy would be an alternative to

injected pharmacological agents, continued inadequately controlled oral pharmacological agents, or bariatric surgery. Although all comparators were considered informative, the committee considered that bariatric surgery was most likely to be the usual comparator in clinical practice.

MSAC noted there was uncertainty about whether there was unmet clinical need given the available publicly subsidised effective therapies. MSAC also noted the potential for substantial use beyond the proposed patient population, making the budgetary impact very uncertain.

MSAC noted that there was a lack of robust comparative efficacy and safety data and therefore there was substantial uncertainty surrounding the long-term safety and efficacy of the GCM.

MSAC noted the difficulty associated with extrapolating from a few, small trials, and over a short term period, involving cross-over comparisons, to the likely effects in what may be a large number of patients treated. It was noted that there was sparse safety data, with data derived largely from the applicant's internal database only.

MSAC noted that the comparative effectiveness was also highly uncertain, as randomised comparisons against some comparators, such as injectable agents and bariatric surgery, were limited or not presented.

In summary, MSAC noted that the long-term, comparative effects of DIAMOND on patient-relevant outcomes, were highly uncertain and substantially more data are required to demonstrate the clinical place of this intervention before any resubmission. Such data would need to include comparisons against other surgical interventions, and as an add-on to maximal pharmacological therapy and life style interventions (including the newer blood glucose-lowering agents of SGLT2 inhibitors and GLP-1 agonists).

MSAC noted that the economic evaluation was very premature. MSAC expressed concerns that the economic modelling was based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes model as UKPDS patients are likely to be different from eligible MBS subjects. It was unclear to the committee as to the derivation of the costs compared to insulin.

MSAC questioned whether that was based on data from the small-scale insulin comparison study. MSAC further noted that the costs of the GCM to the MBS and health budget were underestimated.

4. Background

GCM therapy has not been previously considered by MSAC.

5. Prerequisites to implementation of any funding advice

The GCM device and its associated components were registered with the Australian Register of Therapeutic Goods in 2012.

The applicant stated that laparoscopic surgeons performing the procedure would undergo formal training by MetaCure at specialised centres.

6. Proposal for public funding

The applicant sought MBS funding for the implantation, removal, replacement and interrogation of a GCM device for the treatment of obese patients with inadequately controlled T2DM on standard oral anti-diabetic medication. GCM therapy uses an implanted electro-stimulator to deliver meal-dependent gastric stimulation to induce early satiety. Once implanted, the device can remain in the patient for 15 years.

MBS listing was sought for adult patients with T2DM who have:

- obesity (body mass index, BMI, of $\geq 30 \text{ kg/m}^2$ and $< 45 \text{ kg/m}^2$);
- inadequate diabetic control on standard oral glucose lowering (anti-diabetic) therapy;
- normal triglyceride levels (fasting plasma triglycerides $\leq 1.7 \text{ mmol/L}$); and
- elevated glycated haemoglobin ($\text{HbA}_{1c} \geq 7.5\%$ and $\leq 10\%$).

The applicant stated that GCM therapy should be considered after the failure of a pharmacological agent combination of at least three Pharmaceutical Benefits Scheme (PBS) listed therapies, and is an alternative to injected pharmacological agents, continued inadequately controlled oral pharmacological agents and bariatric surgery.

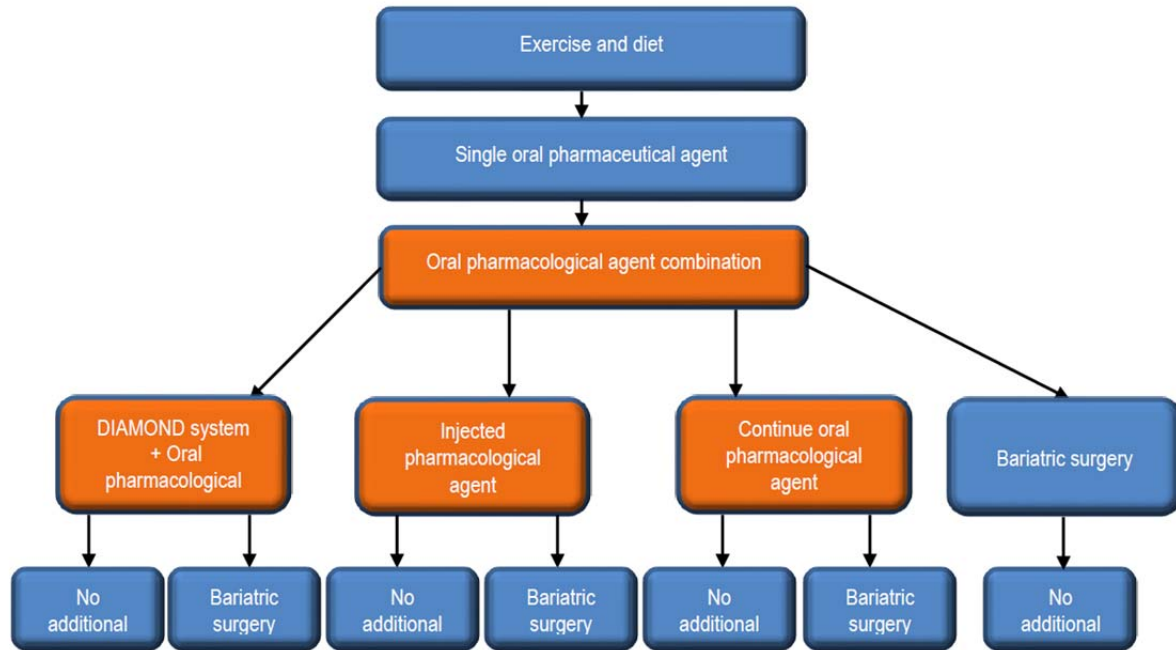
7. Summary of Public Consultation Feedback/Consumer Issues

Consumers concluded it was difficult to support the intervention as there were issues with the safety and efficacy of the intervention, in particular the short term and long term adverse events.

8. Proposed intervention's place in clinical management

The applicant provided the following clinical management algorithm for GCM therapy.

Figure 1: Clinical management algorithm for patients with T2DM and obesity and the place of GCM therapy



Source: Figure A:7, p26 of the submission

DIAMOND system = gastric contractility modulation system; GCM = gastric contractility modulation; T2DM = type 2 diabetes mellitus

9. Comparator

The applicant nominated two primary comparators:

- injectable anti-diabetic therapy, including insulins and exenatide
- oral anti-diabetic therapy, which includes all PBS available oral medications. In the economic modelling, metformin, a sulfonylurea and a dipeptidyl peptidase-4 inhibitor were used.

The applicant noted that bariatric surgery was recommended as an appropriate comparator by the Protocol Advisory Sub-Committee (PASC). Although the submission did not consider bariatric surgery an appropriate comparator, a secondary analysis of GCM therapy compared to adjustable gastric banding was provided as an appendix.

ESC noted that although the nominated comparators, oral and injectable anti-diabetic agents, are appropriate, the clinical evidence presented in the submission does not adequately compare GCM therapy to either of the comparators.

10. Comparative safety

The applicant noted that, as safety was not an outcome of the trial or studies evaluated in the submission, no comparative safety information was presented. Instead, data from 138 patients implanted with the GCM device from the applicant's internal database were analysed. This identified that 43% of adverse events were related to the implantation procedure and included events such as abdominal vibration, pressure pain from the device, infection and bloating, and 85% of adverse events were mild or moderate.

The applicant indicated that, while safety data from the clinical trials was not presented in the submission, an analysis of all adverse events for the DIAMOND™ system was presented in

Section B.7 of the submission. One of the analyses included 138 patients, and the results showed that the majority of AEs were mild to moderate (85%), anticipated and resolved without sequelae.

Additionally, the period of 3 years is considered reasonable. Even though treatment will be used for more than 3 years, it is uncommon for chronic treatment to have trials of longer durations, and the 3-year period is considered sufficient to assess the overall safety and efficacy of GCM therapy. Three years of data is in line with other data sets provided by former devices approved by MSAC. Furthermore, the three year data provides significantly longer data than recently approved T2DM medications on the PBS.

11. Comparative effectiveness

The applicant noted that the basis of the assessment of GCM therapy effectiveness was formed by three studies: one cross-over trial, one case-control study and a long-term retrospective study. The applicant claimed that GCM therapy is superior in terms of efficacy compared to oral and injectable anti-diabetic agents.

The applicant stated the primary outcome of all the studies reviewed in the submission was change in HbA_{1c} from baseline. The pivotal cross-over trial compared active GCM therapy to a control of no GCM therapy in patients who were ‘inadequately treated’ and no information was provided about what constituted inadequate treatment; however, the submission used this trial to compare GCM therapy with oral anti-diabetic agents. The results are provided in the table below.

Table 1: Results of change in HbA_{1c} from baseline in the randomised cross-over trial

HbA _{1c}	Group A ^a (active/control) n = 19	Group B ^b (control/active) n = 24	Difference (group A – group B)	p-value
HbA_{1c} level; % (SE)	-	-	-	-
Baseline	8.33% (0.16)	8.40% (0.14)	-0.07%	0.76
Week 24	7.52% (0.29)	7.55% (0.19)	-0.03%	0.46
Week 48	8.04% (0.32)	7.47% (0.15)	0.57%	0.05
Change in HbA_{1c}; % (SE)	-	-	-	-
Week 24 – baseline	-0.81% (0.33)	-0.85% (0.23)	0.04%	NS
Week 48 – week 24	0.52% (0.29)	-0.08% (0.14)	0.60%	0.05
Week 48 – baseline	-0.29% (0.35)	-0.93% (0.19)	0.64%	0.05

a Group A: GCM therapy ON for weeks 1–24 (active) and OFF for weeks 25–48 (control)

b Group B: GCM therapy OFF for weeks 1–24 (control) and ON for weeks 25–48 (active)

Source: Table B:21, p64 of the submission

HbA_{1c} = glycated haemoglobin; NS = non-significant; SE = standard error

The insulin study compares GCM therapy to insulin therapy and the applicant has provided the results in the table below.

Table 2: Results of change in HbA_{1c} from baseline in the insulin study

HbA _{1c}	GCM group n = 8	Insulin group n = 8	p-value ^a
HbA_{1c} level; % (SEM)	-	-	-
Baseline	9.1% (0.3)	8.9% (0.3)	0.798
6 months	7.5% (0.3)	8.3% (0.5)	0.130

12 months	8.2% (0.5) ^b	8.4% (0.5)	0.959
Change in HbA_{1c}; % (p-value)	-	-	-
6 months – baseline	-1.6% (p = 0.011)	-0.6%	NC
12 months – 6 months	0.7%	0.1%	NC
12 months – baseline	-0.9% (p < 0.05)	-0.5%	NC

a p-value between groups estimated by Mann-Whitey U test

b p-value < 0.05 within group estimated by repeated measures analysis of variance (rANOVA)

Source: Table B:22, p66; Section B.6.1, p65 of the submission; and calculated during the evaluation

GCM = gastric contractility modulation; HbA_{1c} = glycated haemoglobin; NC = not calculated; SEM = standard error of the mean

The triglyceride study compared the effect of GCM therapy in patients with normal (≤ 1.7 mmol/L) and high (> 1.7 mmol/L) baseline fasting triglyceride levels using data from several studies with almost identical protocols. The results (presented in Table 3) suggest that GCM is more effective in patients with normal fasting triglyceride levels at baseline.

Table 3: Results of change in HbA_{1c} from baseline in the triglyceride study

	GCM + normal TG level (≤ 1.7 mmol/L)			GCM + high TG level (> 1.7 mmol/L)		
Time	n	HbA _{1c} ; % (SE)	Change from baseline; % (SE)	n	HbA _{1c} ; % (SE)	Change from baseline; % (SE)
Baseline	32	8.30% (0.14)	-	38	8.40% (0.19)	-
6 months	32	7.12% (0.16)	-1.18% (0.17) ^{a,e}	36	7.80% (0.21)	-0.67% (0.19) ^d
12 months	28	7.25% (0.20)	-1.12% (0.25) ^{a,f}	26	7.80% (0.18)	-0.37% (0.17) ^d
18 months	15	7.24% (0.36)	-1.15% (0.44) ^b	21	7.74% (0.19)	-0.41% (0.22) ^d
24 months	14	7.45% (0.32)	-1.23% (0.43) ^b	17	8.08% (0.38)	-0.21% (0.32)
30 months	8	7.36% (0.39)	-1.63% (0.37) ^b	5	8.89% (0.53)	0.44% (0.78)
36 months	8	7.55% (0.64)	-1.04% (0.46) ^c	-	-	-

Significance from baseline: a p-value < 0.0001; b p-value < 0.005; c p-value < 0.025; d p-value < 0.05

Significance between normal and high triglyceride groups: e p-value < 0.02; f p-value < 0.05

Source: Table B:23, p67 of the submission

GCM = gastric contractility modulation; HbA_{1c} = glycated haemoglobin; SE = standard error; TG = triglyceride; **Bold** = statistically significant result

The critique noted that due to the overall patient population being relatively small, there is potential bias and there was a lack of a common comparator; making it therefore difficult to assess the efficacy of GCM therapy on reducing HbA_{1c} levels. In addition, the critique noted that there is insufficient clinical evidence to support the listing as the clinical evidence in which the applicant relied on has not been published.

12. Economic evaluation

The applicant provided a stepped economic evaluation in the form of a cost-utility analysis, with modelling based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model. The applicant noted that the model is an individual-patient simulation analysis which comprised three broad health states:

1. alive without a diabetes-related event;
2. alive with a diabetes-related event; and
3. dead.

According to the applicant, all patients entered the model in the health state ‘alive without a diabetes-related event’. Patients could remain in this state, transition to ‘alive with a diabetes-related event’, or transition to ‘dead’. In subsequent cycles, patients in the ‘alive with a diabetes-related event’ could remain in this state if they experienced another event, return to ‘alive without a diabetes-related event’ or transitioned to ‘dead’.

The applicant used a 15 year time horizon in the modelled economic evaluation with each cycle representing one year of life. The final outcomes considered by the model are incremental cost per quality-adjusted life year (QALY) and cost per life year gained. These surrogate outcomes were translated from: cost per 1% change in HbA_{1c} for the comparison between GCM therapy and oral anti-diabetic agents, and cost per hypoglycaemic event avoided for the comparison between GCM therapy and insulin. The incremental cost-effectiveness ratios were weighted based on assumed oral and injectable anti-diabetic use.

The critique noted that while the model structure was appropriate, there were issues with a number of the inputs which resulted in the outcomes not being accurate. The key issues included:

- The trial-based analysis, which formed the basis of the stepped economic analysis, was not appropriate as the cross-over trial did not compare GCM therapy to oral anti-diabetic therapy.
 - In its Pre-ESC response (page 4), the applicant agreed that the trial based analysis was not strictly a pure trial based analysis and that the analysis made some minor adjustments to make it more relevant for consideration by MSAC. This included adjusting triglyceride levels using the TG study in the comparison against OMT.
- The critique also noted that assumptions made surrounding the number of patients on oral and injectable anti-diabetic therapies were unfounded and unsupported as the assumptions were based on clinical opinion but no information about the how the clinical opinion was garnered was provided.
- Further, the critique stated that the model did not consider all the MBS costs associated with the implantation of the GCM device and that there was no provision for costs associated with the removal or replacement of the GCM device.
 - In its Pre-ESC response (page 4), the applicant noted that the model did consider costs associated with the implantation: insertion of implantable pulse generator (\$192); insertion of leads (\$918); and interrogation of implantable pulse generator (\$105), which are all the costs included in the prosthesis list application for the DIAMOND. However, the applicant noted that the model did not include costs associated with the removal or replacement of the device because the duration of the model is within the manufacturer recommended lifetime of the device and other costs would have a small impact on the economic evaluation.
- The baseline population is not representative of the trial or study populations, the Australian population or the proposed MBS population. Additionally, failure to incorporate baseline triglyceride levels into the model means the model population does not match the proposed MBS population.

The results of the economic evaluation of GCM therapy and oral and injectable anti-diabetic agents are summarised in the table below.

Table 4: Results of the economic evaluation: Incremental cost-effectiveness ratio (cost per QALY) for GCM therapy versus OAD and insulin therapy

Component	GCM therapy	OAD and insulin therapy	Increment
Costs	\$35,576	\$35,598	\$-22
QALY	5.56	5.37	0.19
ICER	-	-	Dominant

Source: Table D:20, p120 of the submission

GCM = gastric contractility modulation; ICER = incremental cost-effectiveness ratio; OAD = oral anti-diabetic; QALY = quality-adjusted life year

ESC considered that in order to achieve a small positive incremental cost-effectiveness the data had to be extrapolated out to 15 years.

13. Financial/budgetary impacts

The applicant estimated that 5,865 people would choose GCM therapy in the first five years following its listing on the MBS.

The financial estimates provided by the applicant (Table 5), assumed that insertion of the implantable pulse generator and gastric leads would occur once only with interrogation of the device assumed to occur twice in the first year, then once annually.

Table 5: Estimated number of patients accepting GCM therapy and the services provided for year 1 to year 5

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Patients accepting GCM therapy	388	768	1,161	1,565	1,983
Total insertions of GCM	388	768	1,161	1,565	1,983
Total insertions of leads	388	768	1,161	1,565	1,983
Total interrogations of GCM	776	1,925	3,478	5,448	7,847
Total cost of GCM to MBS	\$471,189	\$953,629	\$1,470,458	\$2,022,643	\$2,611,173

Source: Extracted during the evaluation

GCM = gastric contractility modulation; MBS = Medicare Benefits Scheme

The applicant stated the total cost of GCM therapy to the MBS would total approximately \$7.5 million over the first five years. The applicant did not anticipate any other costs.

The critique found a number of calculation errors in the estimation of patients receiving GCM therapy, despite the calculations surrounding the number of MBS services provided per estimated patient being correct. As such, the critique considered the total cost of GCM therapy to the MBS and health budget provided in the submission an underestimation especially given that other factors such as additional MBS items which are associated with GCM implantation (e.g. consultation, anaesthesia and endoscopy fees) or the cost of the device were not taken into consideration.

The assessment group provided the revised table below summarising the additional cost using corrected patient numbers.

Table 6: Revised estimated total cost due to implantation of GCM device for year 1 to year 5

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Corrected patient numbers	389	754	1,096	1,394	1,633
Proposed MBS costs (insertion of device and leads, and interrogation)	\$461,946	\$936,755	\$1,391,078	\$1,810,349	\$2,173,637

Cost of consultant surgeon (MBS 110)	\$43,983	\$85,407	\$124,069	\$157,800	\$184,861
Cost of anaesthetist (MBS 17610)	\$12,530	\$24,332	\$35,347	\$44,956	\$52,666
Cost of anaesthesia initiation (MBS 20706)	\$40,389	\$78,428	\$113,931	\$144,905	\$169,755
Cost of anaesthesia – 2 hours (MBS 23083)	\$46,159	\$89,632	\$130,207	\$165,606	\$194,006
Cost of endoscopy (MBS 36860)	\$48,587	\$94,347	\$137,057	\$174,319	\$204,212
Cost of hospitalisation (Vic. Government)	\$146,092	\$283,683	\$412,102	\$524,141	\$614,025
Cost of GCM device (submission)	\$8,767,451	\$17,024,724	\$24,731,600	\$31,455,415	\$36,849,649
Total net cost of GCM	\$9,577,138	\$18,617,306	\$27,075,390	\$34,477,492	\$40,442,811

Source: Calculated during the evaluation

GCM = gastric contractility modulation; MBS = Medicare Benefits Scheme; Vic = Victorian State

The critique anticipated that the estimate would rise further if pharmaceutical costs, costs relating to adverse events due to surgery, and costs associated with device removal or replacement were included.

14. Key issues from ESC for MSAC

ESC noted that a number of issues had not been addressed in the submission and concluded that there was a lack of clinical evidence supporting clinical effectiveness. ESC noted that the clinical evidence referred to in the submission was largely unpublished internal data available only to the applicant, which was of uncertain quality. ESC also considered that the clinical evidence presented did not adequately compare the effectiveness or safety CGM therapy to either of the comparators.

ESC noted that the proposed MBS population did not match the pivotal cross-over trial population and was broader than the population used in the economic model.

ESC noted that the submission's claim of clinical effectiveness and cost effectiveness of the device was not proven. ESC considered the 15 year time horizon inappropriate and noted that costs associated with the implantation and removal of the device were not included. From a consumer perspective, it was also noted that it was difficult to support the intervention as the larger cost to the community outweighed the benefit.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

GCM therapy is a novel treatment which has been demonstrated in a randomized controlled trial to reduce HbA1c in an at-need diabetic population who have failed oral therapy. It is the view of the sponsor that the committees have applied an excessively high evidence hurdle in their assessment of this device. It is also unfortunate that evaluators for the DIAMOND application have chosen to label differences in approaches to rounding and the selection of references as errors. The sponsor would appreciate the opportunity to continue to work within the MSAC process to ensure that GCM therapy is not denied to those Australians who choose to benefit from this therapy.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at:
www.msac.gov.au.