



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1387 – OPTIMIZER™ IVs Implantable Pulse Generator (IPG) – cardiac contractility modulation therapy for patients with heart failure

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

An application requesting Medicare Benefits Schedule (MBS) listing of cardiac contractility modulation (CCM) therapy (OPTIMIZER™ IV system), for patients with chronic heart failure, was received from MetaCure Australia Pty Ltd. The evidence for assessment of this application was submitted in February 2015.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of cardiac contractility modulation (CCM) therapy (OPTIMIZER™ IV system) for patients with chronic heart failure, MSAC did not support public funding because of uncertain clinical effectiveness and cost-effectiveness. MSAC considered that the key areas of uncertainty were the magnitude and durability of any effects on symptoms and quality of life, hospitalisation or mortality and whether a treatment-induced improvement in New York Heart Association (NYHA) class would result in a consistent proportional improvement in survival.

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

The comparator for CCM was optimal medical treatment (OMT) i.e. patients whose symptoms have not improved despite optimal medical treatment. MSAC noted that the main argument for the nominated comparator was that there are no alternative treatment options for the patient population with normal QRS duration. MSAC considered this to be appropriate.

However, MSAC acknowledged that there is also an unmet clinical need in patients with prolonged QRS duration.

MSAC considered the clinical effectiveness to be uncertain. Data showed that CCM improved symptoms, quality of life and exercise parameters of up to 12 months; however the durability of this benefit beyond 12 months is unknown. MSAC noted the uncertain effect on mortality and hospitalisation. MSAC further noted:

- The patients and investigators were not blinded in the largest study FIX-HF-5 which is relevant for subjective endpoints despite attempts to minimise the risk of bias.
- Primary efficacy endpoint (VAT) was not achieved in study FIX-HF-5 at 24 weeks.
- FIX-HF-5 used last observation carried forward for remaining lifetime however this is inappropriate given that the LOCF is unlikely to carry forward for the lifetime.
- Study population was likely younger than the real world heart failure population

The application claimed that CCM is non-inferior in terms of safety however MSAC noted that there are device related complications. A summary of device malfunctions from a post-market surveillance study and various other studies demonstrated that device malfunctions were rare (approximately 3%), but further details of these studies and results were limited. MSAC noted that the relative risk for mortality compared to OMT was not statistically significant in the randomised controlled trials.

MSAC noted several issues with the economic model. The application assumed that a 30 year time horizon would encompass the life expectancy of most patients. The pre-MSAC response stated that the 30 year time horizon is standard in heart failure models given the chronic nature of heart failure. However, MSAC considered this claim to be unreasonable as heart failure is primarily a disease seen in older adults. Therefore, MSAC considered the model to be over-extrapolated. Furthermore, MSAC considered it was unreasonable to assume that the NYHA class after 12 months was static in patients (did not worsen) for the remaining 29 years given the progressive nature of heart failure.

MSAC considered there were several other issues with the economic model:

- Rate of implantation failures and peri-operative death should have utilised data from both studies, FIX-HF-5 and FIX-CHF-4;
- Post-discharge complication rate was found by averaging the rates from each trial. MSAC did not consider this reasonable and advised that the rate should be weighted by the number of trial participants;
- Fundamental programming errors in the model leading to an invalid analysis; and
- MBS costs associated with the implantation of the device, such as anaesthesia, radiology and consultant fees, or the removal of the device, have not been factored in the model.

MSAC also considered the financial and budgetary impact was uncertain due to inappropriate proposed values in the number of eligible patients. MSAC considered the proposed growth rate of the patient population to be underestimated as it was based on the Australian population growth rate. This is unreasonable given that the heart failure patient population is expected to rise at a greater rate due to Australia's ageing population.

Whilst there are limited treatment options in the proposed patient population, larger studies are required to determine whether the treatment effect is durable. MSAC advised that any future application should present evidence from a larger study (such as FIX-H5-5C) with

longer term duration in order to adequately evaluate efficacy and durability of treatment effect.

4. Background

CCM therapy has not previously been considered by MSAC.

5. Prerequisites to implementation of any funding advice

The application noted that the implantation procedure must be performed by a Fellow of the Royal Australasian College of Physicians with specialty training in cardiology. An overnight stay is suggested to allow for post-surgery monitoring, with an x-ray generally performed 24 hours after implantation. Anaesthesia and prophylactic antibiotics would also be used with surgery. The application noted that the procedure should only be performed in a hospital equipped for cardiac surgery and it would be assumed that such a hospital would already have the necessary equipment available, so no additional resources would be required.

The components of the OPTIMIZER™ IV systems are TGA registered.

6. Proposal for public funding

Proposal for public funding

The application suggested the following separate MBS item descriptors for the proposed intervention:

- insertion, removal or replacement of the implantable pulse generator;
- insertion, removal or replacement of the three bipolar leads; and
- interrogation of the implantable pulse generator device.

The application stated that CCM therapy is intended for use in patients with symptomatic chronic heart failure due to left ventricular systolic dysfunction despite appropriate medical therapy. The application seeks MBS listing for patients who:

- are at least 18 years of age;
- have a New York Heart Association (NYHA) functional class of III;
- have a QRS duration of < 120 ms; and
- have a LVEF \geq 25% and \leq 45%.

The application noted that CCM therapy should be considered for patients whose symptoms failed to improve despite the use of heart failure medications.

The table below sets out the proposed MBS item descriptor and restrictions on the use of the proposed intervention.

Proposed MBS item descriptor

Category 3 – Therapeutic Procedures
MBS Item number XXXX Permanent Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device insertion, removal or replacement of, for a patient with all of the following: (a) Symptomatic heart failure due to systolic left ventricular dysfunction despite failed Optimal Medical Therapy; (b) NYHA Class III; (c) ≥ 18 years; (d) Normal QRS duration (<120 ms); (e) LVEF $\geq 25\%$ and $\leq 45\%$. Fee: \$255.45 Benefit: 75% = \$191.60
MBS Item number XXXXX The permanent insertion, removal or replacement of three bipolar leads, one in the right atrium and two leads in the right ventricle. All three leads are connected to the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG). Fee: \$1,224.60 Benefit: 75% = \$918.45
MBS Item number XXXXX Interrogation of the Cardiac Contractility Modulation (CCM) Implantable Pulse Generator (IPG) device for the following: (a) Interrogate the IPG device parameters as currently programmed; (b) Modify the IPG device parameters; (c) Read ECG signals from patient and display for analysis; (d) Retrieve statistics accumulated by the IPG device as it operates; (e) Log the activity of the IPG device; (f) Store standard programs for future use; (g) Program the IPG device to safe parameter values in emergency situations. Fee: \$69.75 Benefit: 75% = \$52.35 85% = \$59.30

Source: Table A:2, p11 of the Submission

CCM = cardiac contractility modulation; ECG = electrocardiogram; IPG = implantable pulse generator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

The application stated that insertion of both the implantable pulse generator and bipolar leads would require approximately the same technical complexity and duration as removal. For this reason, it requested that the MBS fees be the same.

7. Summary of Public Consultation Feedback/Consumer Issues

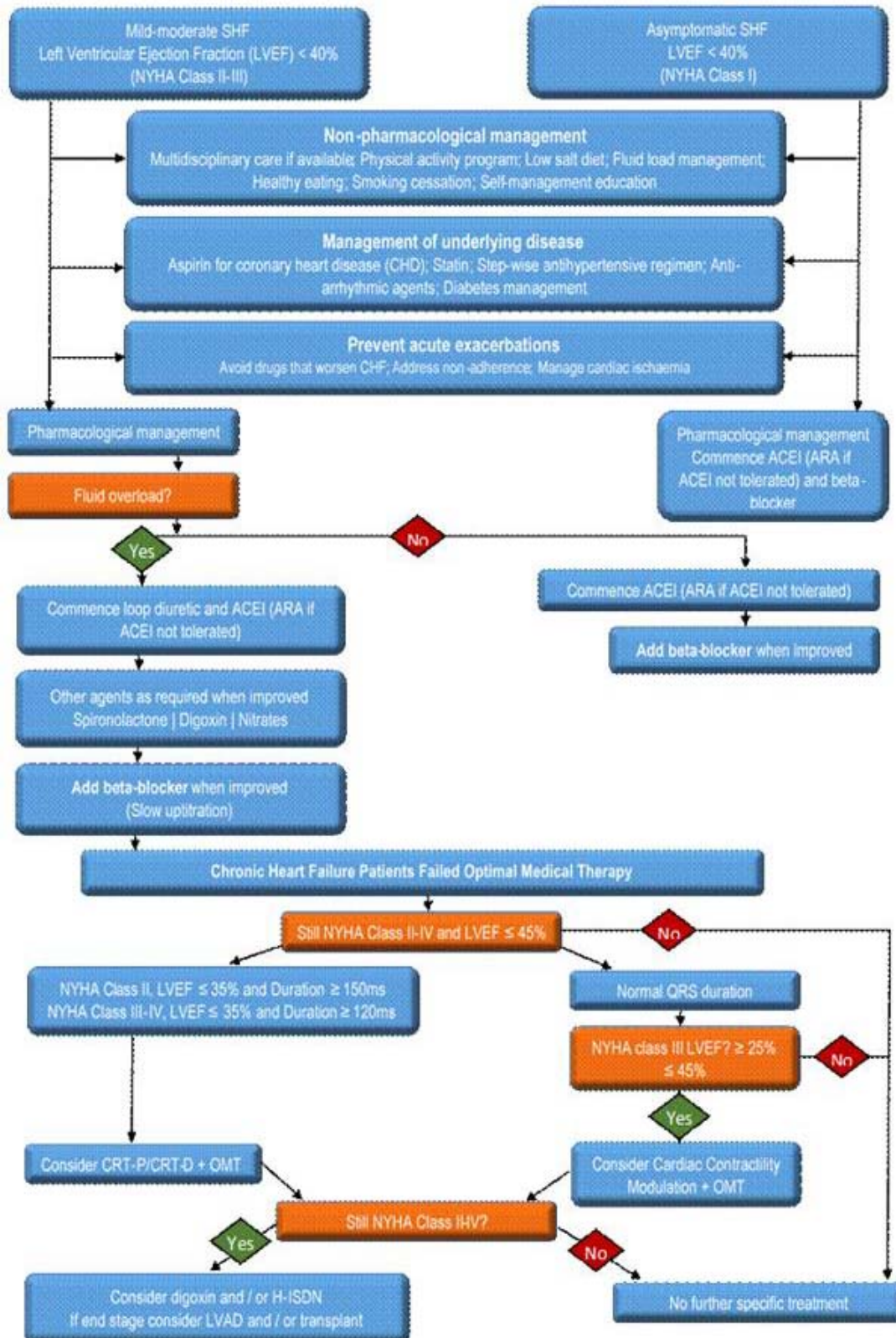
Nil.

8. Proposed intervention's place in clinical management

CCM therapy is delivered by an implantable pulse generator, which senses intracardiac electrical activity, and applies non-excitatory electrical signals to the heart during the absolute refractory period. This intervention is intended to enhance the strength of left ventricular contraction without increasing myocardial oxygen consumption.

The application provided the below clinical management algorithm which is based on the National Heart Foundation of Australia's Chronic Heart Failure Guidelines (2011) and concurs with the management algorithm of the main comparator.

Proposed clinical treatment algorithm for patients with chronic heart failure



9. Comparator

The application nominated ‘failed optimal medical treatment’ (OMT) as the appropriate main comparator.

Failed OMT refers to patients whose symptoms have not improved despite optimal medical treatment. The main argument provided in support of this nomination is that there are no alternative treatment options for the patient population with normal QRS duration.

The application noted that in the proposed intervention, patients received CCM therapy in addition to OMT (CCM+OMT). In the comparator, they received OMT alone.

10. Comparative safety

The application claimed that CCM therapy is non-inferior in terms of safety compared to OMT.

The application noted that serious adverse events are common in this population (~50% in the largest trial); however, there appear to be no overall significant differences between patients treated with CCM therapy or OMT therapy in the short-term (< 6 months) with one exception (sepsis was more common with CCM). The all-cause mortality and all-cause hospitalisation rates from the trials are presented individually, and combined in a meta-analysis. The pooled relative risk for all-cause mortality was 1.19 (95% CI: 0.50, 2.86) for CCM versus OMT and for all-cause hospitalisations was 0.64 (95% CI: 0.38, 1.08).

The application further noted that by December 2014, a total of 1,553 patients were implanted with the OPTIMIZER™ IV system. A summary of device malfunctions was presented in the application using OPTIMIZER™ IV system post-market surveillance data and various studies. Device malfunctions or other problems occurred rarely (44/1553 patients, or 2.8%) and details of these were limited. The implantation failure rate was 0.93% in the largest trial FIX-HF-5.

The application also identified two longer-term safety studies (up to 3 years), Schau (2011) and Röger (2014), which provided supportive safety evidence.

11. Comparative effectiveness

The application presented evidence on efficacy from three prospective randomised trials (two US and one European) and two meta-analyses of the same trials. The evidence mostly relied on a subgroup analysis of one trial for participants most likely to match the proposed MBS population and because this subgroup appears to benefit most from CCM.

The application provided a summary of the outcomes used in the trials in the table below.

Summary of outcomes used in the trials

-	FIX-HF-5 n=428	FIX-HF-5 Pilot n=49	FIX-CHF-4 n=164	Giallauria (2014)	Kwong (2012)
Time point	50 weeks	24 weeks	24 weeks	NA	NA
Efficacy	-	-	-	-	-
Peak VO ₂	✓	✓	✓	✓	-
MLWHFQ	✓	✓	✓	✓	✓ ^a
NYHA classification	✓	✓	✓	-	-
6MWT	✓	✓	✓	✓	-
Safety	-	-	-	-	-
All-cause mortality	✓	✓	✓	-	✓ ^b
All-cause hospitalisation	-	✓	✓	-	✓ ^b

Source: Borggreffe (2008), Giallauria (2014), Kadish (2011), Kwong (2012), Neelaguru (2006), and Application Tables B:21–B:22
 6MWT = six minute walk test; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NA = not applicable; NYHA = New York Heart Association; peak VO₂ = peak oxygen consumption
^a Excluded data from FIX-HF-5, and second half of FIX-CHF-4
^b First arm crossover of FIX-CHF-4 only

The key results from the trials and their subgroups are presented in the table below.

Summary of the results of efficacy outcomes (means) in the trials

Parameter	Trial	Δ CCM	Δ OMT	Δ CCM - ΔOMT	P-value
Peak VO ₂ (mL/(kg/min)) <i>Higher values indicate better exercise tolerance</i>	FIX-HF-5 subgroup ^a (24 weeks)	0.33	-0.98	1.31	0.001
	FIX-HF-5 subgroup (50 weeks)	0.29	-0.80	1.09	NR
	FIX-HF-5 (24 weeks)	0.25	-0.40	0.65	0.024
	FIX-CHF-4 (95% CI)	NR	NR	0.52 (0.04, 0.99)	0.032
	FIX-HF-5 Pilot	-0.80	-1.00	0.2	NR
6MWT (metres) <i>Higher values indicate better exercise tolerance</i>	FIX-HF-5 subgroup (24 weeks)	22	1	21	0.044
	FIX-HF-5 subgroup (50 weeks)	NR	NR	NR	NR
	FIX-HF-5 (24 weeks)	8	19	-11	0.108
	FIX-CHF-4 (95% CI)	NR	NR	19	NR
	FIX-HF-5 Pilot	50	35	15	NR
MLWHFQ (score 0–125) <i>Lower values indicate better quality of life</i>	FIX-HF-5 subgroup (24 weeks)	-17.0	-6.2	-10.8	0.003
	FIX-HF-5 subgroup (50 weeks)	NR	NR	NR	NR
	FIX-HF-5 (24 weeks)	-16.0	-6.0	-10.0	<0.001
	FIX-CHF-4 (95% CI)	NR	NR	-2.9 (-0.3, -5.6)	0.030
	FIX-HF-5 Pilot	-18.3	-16.2	-2.1	NR
NYHA class (ordinal variable, four classes) <i>Lower values indicate lower severity of heart disease</i>	FIX-HF-5 subgroup (24 weeks)	-0.46	-0.17	-0.29	0.002
	FIX-HF-5 subgroup (50 weeks)	-0.62	-0.31	-0.34	0.040
	FIX-HF-5 (24 weeks)	-0.49	-0.34	-0.15	0.003
	FIX-CHF-4 (95% CI)	NR	NR	NR	NR
	FIX-HF-5 Pilot	NR	NR	Improved	NR

Sources: Abraham (2011), Borggreffe (2008), Kadish (2011), Neelaguru (2006), and Section B.6, pp62–77 of the Submission
 6MWT = six minute walk test; CCM = cardiac contractility modulation; CI = confidence interval; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; NR = not reported; OMT = optimal medical therapy; peak VO₂ = peak oxygen consumption
^a The subgroup is 48% of the full sample (n=206) and patients had normal QRS, ejection fraction >25% and NYHA III

12. Economic evaluation

The application noted that a stepped economic evaluation was presented in the form of a cost-utility analysis using an excel spreadsheet developed in the submission. The structure was a Markov cohort model, with six health states:

- NYHA I;
- NYHA II;
- NYHA III;
- NYHA IV;
- hospitalised; and
- dead.

The application noted that patients began in health state ‘NYHA III’, and received either CCM+OMT, or OMT alone. If patients received CCM+OMT, they either died, or their implant failed or succeeded. They then moved between health states and experienced relevant changes in utility level, and costs.

The time horizon in the modelled economic evaluation was 30 years, and each cycle represented one month of life. The surrogate outcome was cost per patient with NYHA class improvement and the final outcomes considered by the model were incremental cost per quality-adjusted life year (QALY) and cost per life year gained.

The application summarised the results of the economic evaluation of CCM therapy and OMT in the following table.

Results of the economic evaluation: Incremental cost-effectiveness ratio (cost per QALY) for CCM therapy versus OMT

Component	CCM+OMT therapy	OMT therapy	Increment
Costs	\$68,758	\$28,955	\$39,803
QALY	4.92	3.77	1.15
ICER	-	\$34,539	-

Source: Table D:20, p120 of the Submission

CCM = cardiac contractility modulation; ICER = incremental cost-effectiveness ratio; OMT = optimal medical therapy; QALY = quality-adjusted life year

The critique noted that there were a number of issues which could impact on the financial and economic analyses; including calculation errors in the estimation of eligible patients and patients receiving CCM therapy; and the lack of costs for additional MBS services associated with the implantation, removal or replacement of the device and other costs such as hospitalisation and the cost of the device.

13. Financial/budgetary impacts

The application estimated that 1,958 patients will receive CCM therapy in the first five years following listing on the MBS. The application noted that the financial estimates assumed that insertion of the implantable pulse generator and bipolar leads occurs once only. Interrogation of the device was assumed to occur twice in the first year, then once annually. Data from the Australian Bureau of Statistics was used to estimate the CCM eligible population. Uptake of the CCM device was based on assumptions

The estimated number of patients receiving CCM therapy and the number of services provided per patient have been summarised by the applicant in the table below.

Estimated number of patients for CCM therapy and the services provided per patient for Years 1 to 5

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Patients accepting CCM therapy	65	263	400	542	688
Total insertions of CCM	65	263	400	542	688
Total insertions of leads	65	263	400	542	688
Total interrogations of CCM	129	590	1,128	1,812	2,647
Total cost of CCM to MBS	\$78,541	\$322,509	\$503,380	\$696,650	\$902,665

Source: Extracted during the evaluation

CCM = cardiac contractility modulation; MBS = Medicare Benefits Scheme

The application assumed that the total cost of CCM therapy to the MBS will total approximately \$2.5 million over the first five years and stated that no other costs are anticipated.

Revised estimated total cost due to implantation of CCM device for Year 1 to Year 5

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Corrected patient numbers	72	294	447	606	769
Proposed MBS costs (insertion of device and leads, and interrogation)	\$87,769	\$360,488	\$562,478	\$778,562	\$1,008,723
Cost of consultant surgeon	\$8,150	\$33,281	\$50,600	\$68,599	\$87,051
Cost of anaesthetist	\$2,322	\$9,482	\$14,416	\$19,544	\$24,800
Cost of anaesthesia initiation	\$7,484	\$30,561	\$46,466	\$62,994	\$79,938
Cost of anaesthesia – 1 hour	\$4,277	\$17,464	\$26,552	\$35,996	\$45,679
Cost of x-ray	\$1,912	\$7,806	\$11,868	\$16,089	\$20,417
Total cost to MBS	\$111,607	\$459,499	\$712,055	\$981,921	\$1,266,312
Cost of hospitalisation	\$27,072	\$110,544	\$168,072	\$227,856	\$289,144
Cost of CCM device	\$2,348,280	\$9,588,810	\$14,578,905	\$19,764,690	\$25,080,935
Total net cost of CCM	\$2,486,959	\$10,158,853	\$15,459,032	\$20,974,467	\$26,636,391

Source: Calculated during the evaluation

CCM = cardiac contractility modulation; MBS = Medicare Benefits Scheme

The critique expected that this estimate would rise further if costs relating to adverse events due to surgery and costs associated with device removal or replacement were included. There may also be some cost reductions to the Pharmaceutical Benefits Scheme, as patients receiving CCM therapy transition to lower severity heart failure classes where less intensive medication treatment of lower cost is required.

14. Key issues from ESC for MSAC

ESC noted that there were a number of errors in the submission which would impact on the financial and economic analyses; including calculation errors in the estimation of eligible patients and patients receiving CCM therapy; and the lack of costs for additional MBS services associated with the implantation, removal or replacement of the device and other costs such as hospitalisation and the cost of the device.

ESC also noted that the evidence put forward for the clinical effectiveness of the device was weak and considered the 30 year time horizon excessive for extrapolating one year trial data. To help MSAC assess the implications of this concern, ESC requested that the applicant

report in its pre-MSAC response the following two Markov traces from its model (with time in years on the x-axis), and on the y-axis:

1. the proportion of people alive in each arm of the model
2. the incremental cost/QALY gained.

ESC noted that the population proposed in the item descriptor was broader than the clinical trial population because it did not include the same exclusion criteria.

15. Other significant factors

Nil.

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

Optimizer addresses a serious unmet need in the management of HF patients. The effectiveness of Optimizer in improving symptoms and quality of life has been evaluated in three clinical trials undertaken in the USA and Europe. Within the context of these, the effects were in most occasions, large in magnitude, statistically and clinically significant and stable over time, which supports the premise of a durable effect. Moreover, an extensive literature indicates that the improvements in the evaluated functional parameters, especially NYHA classification, are associated with long-term improvements in hospitalisation and survival. This is confirmed by investigator initiated observational studies undertaken independently of the manufacturer and published subsequent to this submission. Moreover, economic models are inevitably based on assumptions, which are necessary to synthesize and extrapolate the data and it is natural that different commentators may have different opinions about how this should be done. Nonetheless, the model used was calibrated and tested for its predictive ability based on available observational data and sensitivity analysis and probabilistic analysis showed that the results were stable under many different assumptions and extreme parameter values. Thus, there is enough evidence to indicate that the Optimizer represents a safe, effective and cost-effective treatment option for HF patients.

17. Further information on MSAC

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