



Australian Government
Department of Health and Ageing



Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summaries

Optimizer™ cardiac contractility modulation (CCM) system

June 2006



ASERNIPs

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**



© Commonwealth of Australia [2006]

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at <http://www.ag.gov.au/cca>

Electronic copies can be obtained from <http://www.horizonscanning.gov.au>

Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

DISCLAIMER: This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements to health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The Commonwealth does not guarantee the accuracy, currency or completeness of the information in this report. This report is not intended to be used as medical advice and it is not intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Commonwealth does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by staff from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

**Name of Technology:**

Optimizer™ cardiac contractility modulation (CCM) system (Impulse Dynamics Inc., New Jersey, USA).

Purpose and Target Group:

The Optimizer System is indicated for patients suffering from severe drug-refractory chronic systolic heart failure.

Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Not yet emerged

The Optimizer System is currently not available in Australia. Hence it is not listed or registered in the Australian Register of Therapeutic Goods database.

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely diffused
Italy	✓		
Germany	✓		
United States	✓		
Austria	✓		

Impact Summary:***Background***

Heart failure is a condition in which the heart pumps blood inadequately, leading to reduced blood flow, congestion of blood in the veins and lungs and other changes that may further weaken the heart. Heart failure has two main forms: systolic dysfunction and diastolic dysfunction. In systolic dysfunction, which is more common, the heart contracts less forcefully and pumps out less blood than it receives. This results in the accumulation of blood in the ventricles, which in turn causes accumulation of blood in the veins. Systolic



dysfunction can arise from coronary artery disease, myocarditis (inflammation of heart muscle), heart valve disorders (e.g. stenosis), disorders that affect the heart's electrical conduction system and pulmonary embolism. Diastolic dysfunction, which occurs when the heart becomes stiff and can no longer expand to receive a normal volume of blood, is usually caused by chronic high blood pressure (Merck Manual 2006).

A range of treatments are utilised to slow or halt the progression of heart failure, including lifestyle modifications, pharmacological treatments (e.g. loop diuretics, angiotensin-converting enzyme inhibitors, digitalis) and surgical interventions (Merck Manual 2006). Modern heart failure therapy, in the form of oral medications, has improved symptom control and prolonged the survival of congestive heart failure patients. However, heart failure is a progressive disorder and eventually the patient will die.

The state of weakened contractility in failing heart muscle cells (myocytes) is believed to result from an abnormally low amount of calcium ions (Ca^{2+}) delivered to the myofilaments during each beat, independent of disease aetiology (Gomez *et al.* 1997). This knowledge, combined with the discovery of depressed Ca^{2+} transients with a shift from intracellular to extracellular ion fluxes in failing hearts, resulted in the idea of modulating these ion fluxes (Pappone *et al.* 2004). One form of treatment, known as inotropic therapy, utilises drugs (e.g. dobutamine, milrinone) that increase intracellular levels of cyclic adenosine monophosphate (cAMP), which regulates the passage of Ca^{2+} into cells. This increases Ca^{2+} uptake and leads to stronger cardiac contractions (Callans *et al.* 2001). These agents have been used frequently to treat heart failure with encouraging results. Unfortunately, almost all chronically administered inotropic agents, except for digitalis, increase mortality in heart failure patients. This is attributed to an increase in ventricular arrhythmias, which may be due to the systemic increase of intracellular Ca^{2+} levels (Callans *et al.* 2001; Willems and Sipido 2004).

Knowledge of the role of Ca^{2+} in myocardial contractility has spurred the development of cardiac contractility modulation (CCM). CCM involves the application of a biphasic pulse within the refractory period of myocytes, with the aim of prolonging the action potential, increasing intracellular Ca^{2+} levels and producing stronger cardiac contractions (Willems and Sipido 2004). Unlike inotropic therapy, which induces systemic reactions, CCM therapy is localised to the target site and is, therefore, presumably safer.

The concept of CCM was the basis for the development of the Optimizer System, which consists of a programmable implantable pulse generator, a portable programmer, a charger and percutaneous pacemaker leads (Impulse Dynamics 2006). All leads are implanted transvenously while the Optimizer device itself is implanted using a routine pacemaker-like approach where it will be placed in a pocket created under the skin in the upper chest (Stix *et al.* 2004).



Clinical Need and Burden of Disease

An estimated 300,000 Australians are afflicted with chronic heart failure, with approximately 30,000 new cases diagnosed every year (AIHW 2003). Between 2003 and 2004, the number of patients suffering from congestive heart failure or left ventricular failure was 29,346 and 10,957, respectively (AIHW 2005). Direct healthcare costs for chronic heart failure in Australia were estimated to be AU\$411 million in 2001, including AU\$140 million for hospitalisation and AU\$135 million for nursing home costs (National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, Chronic Heart Failure Clinical Practice Guidelines Writing Panel 2001).

Estimated Speed and Geographic and Practitioner Use Patterns of Diffusion in the Health System

The Optimizer System is currently undergoing trials in Italy, Germany, the United States and Austria. If proven safe and efficacious and approved for use in Australia, the Optimizer System would provide a new way of treating systolic dysfunction in patients who are unresponsive to conventional pharmacological treatments.

Existing Comparators

There are no other devices that provide CCM to treat systolic dysfunction. However, other devices/procedures that are utilised to treat systolic dysfunction include the following.

- CorCap™ Cardiac Support Device (Acorn Cardiovascular, Inc., St. Paul, MN, USA)
- Aortic valve replacement
- Ventricular assist devices (Left ventricular assist devices and biventricular assist devices)
 - HeartMate® Left Ventricular Assist System (Thoratec Corporation, Pleasanton, CA, USA)
 - Novacor® Left Ventricular Assist Device (Baxter Healthcare, Oakland, CA, USA)
 - Thoratec® Ventricular Assist Device System (Thoratec Corporation, Pleasanton, CA, USA)
- Cardiac resynchronisation therapy
- Inotropic therapy

Estimated Cost Impact

The cost of the Optimizer System is not known. However, the Medicare Benefits Schedule reimbursement fees for related procedures are listed in Table 1.

**Table 1 Medical Benefits Schedule of fees for procedures related to heart failure (Medicare Australia 2006)**

Category	Item Number	Benefit (AUD)	Number of Claims (July 2004 to June 2005)
Valve replacement with bioprosthesis or mechanical prosthesis	38488	1652.70	1905
Valve replacement with allograft (subcoronary or cylindrical implant), or unstented xenograft	38489	1965.50	101
Insertion of a left or right ventricular assist device	38615	1325.90	24
Insertion of a left and right ventricular assist device	38618	1652.70	11
Restoration of cardiac rhythm by electrical stimulation (cardioversion), other than in the course of cardiac surgery	13400	83.80	3936
Insertion, removal or replacement of a permanent cardiac synchronisation device for patients who have moderate to severe chronic heart failure	38365	221.10	0
Insertion, removal or replacement of a permanent transvenous left ventricular electrode through the coronary sinus for the purpose of cardiac resynchronisation therapy for patients who have moderate to severe chronic heart failure	38368	1059.85	0
Insertion, removal or replacement of a permanent left ventricular electrode via open thoracotomy for the purpose of cardiac resynchronisation therapy for patients who have moderate to severe chronic heart failure	38654	1059.85	0

Efficacy and Safety Issues

List of Studies Found

Total number of studies	2
-------------------------	---

Case series studies	2
---------------------	---

The studies included in this summary are highlighted in bold in the reference list. Safety and efficacy data from two case series studies have been selected for inclusion in this summary as no randomised controlled trials or comparative studies were available. It is important to note that there is patient overlap between these two studies.

Efficacy

The multicentre trial conducted by Pappone *et al.* (2004) enrolled 13 New York Heart Association (NYHA) class III patients with left ventricular ejection fraction (LVEF) < 35% and left ventricular end-diastolic diameter > 55 mm despite 3 months of optimal



pharmacological treatment. This study consisted of two phases: the first phase (FIX HF-3) encompassed an 8-week period with daily 3-hour CCM therapy, while in the second phase (FIX HF-3 extension) CCM was applied 7 hours a day during seven equally spaced 1-hour periods for 24 weeks. Stix *et al.* (2004) reported on 23 patients who underwent daily 3-hour CCM therapy for 8 weeks, 13 of whom were included in the Pappone *et al.* (2004) study.

Pappone *et al.* (2004) stated that implantation of the device averaged 80 minutes (standard deviation (SD) \pm 34.0), with successful implantation of the atrial lead and two right ventricular leads in all patients. No serious complications occurred during lead implantation and there were no cases of lead dislodgement over the course of the study. Four patients achieved at least a 5% increase in maximal rate of pressure (dP/dtmax), a measure of the acute haemodynamic effectiveness of CCM therapy and the minimum threshold required to continue with the treatment, and therefore did not require lead repositioning during the procedure. The remaining 9 patients, however, required repositioning of leads in mid-septal positions to achieve this threshold. The average dP/dtmax achieved was 7% (SD \pm 2.0) (Pappone *et al.* 2004).

Stix *et al.* (2004) successfully implanted the Optimizer System in 92% (23/25) of patients. One patient had an insufficient increase in dP/dtmax, which could not be resolved with lead repositioning. The second patient suffered from intolerable symptoms of phrenic stimulation. Both patients were excluded from CCM treatment. During the course of CCM therapy, 8/23 (35%) patients complained of mild sensations, while one patient (4%) suffered intolerable symptoms and required lead repositioning. A mean increase in dP/dtmax of 7% (SD \pm 2.7) was recorded during acute testing (Stix *et al.* 2004).[‡]

Table 2 Summary of results from case series studies of the Optimizer System

Outcome measure	Pappone <i>et al.</i> (2004) n = 13			Stix <i>et al.</i> (2004)* n = 23	
	Baseline	FIX HF-3 phase FU = 8 weeks	FIX HF-3 extension phase FU = 24 weeks	Baseline	FU = 8 weeks
Mean left ventricular ejection fraction	22.7% [7.0]	28% [7.0] [†]	36.9% [12.5] [†]	22% [7]	28% [8] [†]
LVESV (mL)	136 [15]	116 [16] [†]	96 [21] [†]	N/A	N/A
LVEDV (mL)	176 [13]	163 [11]	149 [15] [†]	N/A	N/A
LVEDD (mL)	68 [4]	66 [5]	62 [6] [†]	N/A	N/A
Mean peak VO ₂ (mL/kg/minute)	13.7 [1.1]	14.9 [1.9] [‡]	16.2 [16.2] [‡]	N/A	N/A
Mean distance walked in 6 minutes (m)	418 [99]	477 [96] [‡]	510 [97] [†]	411 [86]	465 [82] [‡]

*This study and Pappone *et al.* (2004) are based on a common core of patients; [†] indicates $p < 0.01$ compared to baseline; [‡] indicates $p < 0.04$ compared to baseline; [] = standard deviation; FU – follow-up;



VO₂ – peak oxygen uptake; LVESV – left ventricular end-systolic volume; LVEDV – left ventricular end-diastolic volume; LVEDD – left ventricular end-diastolic diameter.

Both Pappone *et al.* (2004) and Stix *et al.* (2004) reported significant improvements in mean left ventricular ejection fraction (Table 2). In addition, Pappone and colleagues stated that end-diastolic and end-systolic dimensions gradually decreased at the end of each study phase compared to baseline values (Table 2) (Pappone *et al.* 2004). In line with the significant increase in peak VO₂, patients achieved a significant increase in mean distance walked within 6 minutes (Pappone *et al.* 2004). Similarly, Stix *et al.* (2004) also reported a significant increase in mean walking distance after CCM therapy.

Pappone *et al.* (2004) reported that patients experienced an improvement in NYHA functional class at the end of the FIX HF-3 phase (3 to 1.8 ± 0.4) and the FIX HF-3 extension phase (3 to 1.5 ± 0.7) ($p < 0.001$ for both pairwise comparison with baseline). In addition, quality of life improved by 49% (from 36 ± 21 to 18 ± 12 , $p = 0.06$) by the end of the FIX HF-3 phase while a further improvement was noted at the end of the FIX HF-3 extension phase (absolute reduction of 29 and 11 points compared to baseline and previous study phase) ($p = 0.02$ for both). All patients reported a better quality of life after the first study phase (3 hours CCM per day); however 2 patients reported a slightly worse quality of life when comparing the first and second study phases (Pappone *et al.* 2004). These results indicate that CCM therapy may have different effects on patients depending on the dose administered, highlighting the importance of patient-tailored CCM treatments.

Throughout the study period, one patient (4%) in the Pappone *et al.* (2004) study was admitted to the hospital for symptoms of worsening heart failure, which included significant rest dyspnoea and signs of fluid retention. In addition, the patient reported CCM generator pocket swelling that was managed with an 8-week course of antibiotics. The patient recovered well and did not require additional hospitalisation. Overall, 92% of patients were free from heart failure related hospitalisations over the mean follow-up period of 8.8 months; an absolute risk reduction which approached 54% ($P = 0.002$) (Pappone *et al.* 2004).

Safety

There was no increase in the mean number of premature ventricular or supraventricular arrhythmias per day in either study (Pappone *et al.* 2004; Stix *et al.* 2004). Conversely, post hoc calculations by Pappone *et al.* (2004) revealed that there was a trend towards a reduction of ventricular and supraventricular complexes ($P = 0.05$), as well as non-sustained ventricular tachycardia ($P = 0.01$). CCM therapy did not alter the duration of the QRS- or QT-interval (Pappone *et al.* 2004).



In the Pappone *et al.* (2004) study, the Optimizer device was replaced in all patients after a mean of 7 months (SD \pm 3.0). Only one patient (4%) experienced an infection at the pocket infection site after replacement. One patient required ventricular lead repositioning due to phrenic stimulation, while another patient experienced pocket stimulation that was resolved by decreasing the Optimizer output (Pappone *et al.* 2004). Stix *et al.* (2004) reported one case (4%) of device and defibrillator pocket haematoma that required surgical revision. Pappone *et al.* (2004) stated that more than 70% of normal sinus beats were achieved during CCM therapy, with no evidence of CCM signal delivery outside the QRS complex. No device failure occurred (other than end-of-battery life) (Pappone *et al.* 2004).

The most alarming finding in these studies was the two deaths (8.7%) due to ventricular fibrillation and asystole reported by Stix *et al.* (2004). Despite the fact that sudden death rates are high for these patients, an 8.7% death rate in 2 months exceeds the 8-week all-cause mortality rate in the COPERNICUS trial in NYHA III and IV patients (Krum *et al.* 2003). Stix *et al.* (2004) stated that these deaths occurred when the Optimizer was turned off, but this does not rule out the possibility that CCM therapy may have caused persistent changes that lasted beyond the time frame of treatment.

One patient in the Stix *et al.* (2004) study was a heart transplant recipient. Three weeks after Optimizer implantation, this patient experienced atrial undersensing, with automatic device inhibition, followed by clinical deterioration. The device was reprogrammed and LVEF improved from 36% to 46% after 8 weeks (Stix *et al.* 2004).

Ethical Issues

No issues were identified from the retrieved material.

Cultural or Religious Considerations

No issues were identified from the retrieved material.

Other Issues

The Optimizer II System was used in the included studies. The Optimizer System is now in its third revision, known as the Optimizer III. Recently, Impulse Dynamics announced the start of a clinical trial for the Optimizer III System, which is expected to enrol 420 patients in 50 centres in the United States (Impulse Dynamics 2006). Specific differences between the Optimizer II and III were not revealed in our searches, but both devices appear to function in the same way. The energy requirements for the Optimizer System are quite high and thus may necessitate frequent, possibly annual, battery replacement. This is a significant cost on top of the implantation of the device itself.



Both studies included in this summary were funded by Impulse Dynamics.

Recommendation

The evidence available on the safety and efficacy of CCM therapy with the Optimizer System is limited to small case series studies with medium-length follow-up. It is unlikely that the Optimizer System will be used as the sole treatment for systolic heart failure. In addition to this, the appropriate dosing regimen for CCM therapy has not been determined. However, it provides a novel method of treatment that can be used in conjunction with existing procedures and medication to improve patient outcomes. A large randomised study would be required before this device is widely accepted. It is proposed that the Optimizer System should be monitored for 12 months.

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

References:

AIHW. Australian Institute of Health and Welfare Bulletin, Issue 6. Last updated June 2003.
<http://www.aihw.gov.au/publications/aus/bulletin06/bulletin06.pdf> [Accessed April 2006].

AIHW. National Hospital Morbidity Database. Last updated 2005.
<http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0304> [Accessed April 2006].

Callans DJ, Fuchs S, Mika Y, Shemer I, Aviv R, Haddad W, Darvish N, Ben-Haim SA, Kornowski R. Global improvement in left ventricular performance observed with cardiac contractility modulation is the result of changes in regional contractility. *Heart Failure Reviews* 2001; **6**(1): 35-44.

Gomez AM, Valvidia HH, Cheng H, Lederer MR, Santana LF, Cannell MB, McCune SA, Altschuld RA, Lederer WJ. Defective excitation-contraction coupling in experimental heart failure. *Science* 1997;276: 800-806.

Impulse Dynamics. Last updated 2006.

http://www.impulse-dynamics.com/int_optimizer.asp [Accessed April 2006].

National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, Chronic Heart Failure Clinical Practice Guidelines Writing Panel. Guidelines for



management of patients with chronic heart failure in Australia. *Medical Journal of Australia* 2001; **174**(9): 459-466.

Medicare Australia. Medicare Benefits Schedule - 1 May 2006. Last updated 2006.
<http://www9.health.gov.au/mbs/> [Accessed April 2006].

Merck Manuals: Online Medical Library. Last updated 2006.
<http://www.merck.com/mmhe/sec03/ch025/ch025a.html> [Accessed April 2006].

Pappone C, Augello G, Rosanio S, Vicedomini G, Santinelli V, Romano M, Agricola E, Maggi F, Buchmayr G, Moretti G, Mika Y, Ben-Haim SA, Woltz M, Stix G, Schmidinger H. First human chronic experience with cardiac contractility modulation by nonexcitatory electrical currents for treating systolic heart failure: mid-term safety and efficacy results from a multicentre study. *Journal of Cardiovascular Electrophysiology* 2004; **15(4): 418-427.**

Stix G, Borggreffe M, Wolpert C, Hindricks G, Kottkamp H, Bocker D, Wichter T, Mika Y, Ben-Haim S, Burkhoff D, Woltz M, Schmidinger H. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. *European Heart Journal* 2004; **25(8): 650-655.**

Willems R, Sipido KR. Nonexcitatory stimulation as a novel treatment for heart failure: cause for excitement? *European Heart Journal* 2004; **25**(8): 626-628.

Search Criteria:

A search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the UK National Research Register, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted in April 2006.

Search terms used were: 'Optimizer system', 'cardiac contractility modulation', 'CCM', 'electrical stimulation during absolute refractory period', 'nonexcitatory stimulation for heart failure'.

This Horizon Scanning Prioritising Summary was prepared by Mr. Irving Lee from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).