



**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 Summary**

## **Laparoscopic Diaphragm Pacing Stimulation System**

**April 2010**



**ASERNIP/S**

**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
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# PRIORITISING SUMMARY

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**REGISTER ID** S000105

**NAME OF TECHNOLOGY** LAPAROSCOPIC DIAPHRAGM PACING  
STIMULATION SYSTEM

**PURPOSE AND TARGET GROUP** PROVIDES VENTILATORY SUPPORT IN PATIENTS  
WITH DIAPHRAGM DYSFUNCTION OF  
NEUROMUSCULAR ORIGIN, INCLUDING PATIENTS  
WITH SPINAL CORD INJURIES AND PATIENTS WITH  
AMYOTROPHIC LATERAL SCLEROSIS

## STAGE OF DEVELOPMENT (IN AUSTRALIA)

- |                                     |                    |                          |   |
|-------------------------------------|--------------------|--------------------------|---|
| <input type="checkbox"/>            | Yet to emerge      | <input type="checkbox"/> | Established   |
| <input type="checkbox"/>            | Experimental       | <input type="checkbox"/> | Established <i>but</i> changed indication<br>or modification of technique |
| <input checked="" type="checkbox"/> | Investigational    | <input type="checkbox"/> | Should be taken out of use  |
| <input type="checkbox"/>            | Nearly established |                          |   |

## AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- |                                     |                |             |               |
|-------------------------------------|----------------|-------------|---------------|
| <input checked="" type="checkbox"/> | Yes            | ARTG number | <b>158648</b> |
| <input type="checkbox"/>            | No             |             |               |
| <input type="checkbox"/>            | Not applicable |             |               |

## INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Canada		✓	
Iceland		✓	
USA		✓	

## IMPACT SUMMARY

The current diaphragm pacing stimulation (DPS) system (NeuRx RA/4 system) is manufactured by Synapse Biomedical (Oberlin, OH, USA) with the aim of providing a minimally invasive alternative to mechanical ventilation. The technology can be implanted laparoscopically, and is intended to provide ventilatory support in patients with diaphragm dysfunction of neuromuscular origin, including spinal cord injury (SCI) patients and patients with amyotrophic lateral sclerosis (ALS).

## BACKGROUND

Spinal cord injury can be defined as the occurrence of an acute, traumatic lesion of neural elements in the spinal canal (spinal cord and cauda equina) resulting in temporary or permanent sensory deficit, motor deficit, or bladder/bowel dysfunction (Cripps 2008). Traumatic causes of SCI include motor vehicle accidents, falls, penetrating injuries, and sports accidents (Onders et al 2009a). A high SCI (cervical spine C1-C5) will typically result in quadriplegia and loss of respiratory function (Onders et al 2004).

Another cause of respiratory failure is ALS, a form of motor neurone disease. ALS is a progressive and fatal disease, with the average lifespan of patients diagnosed with ALS only 3 to 5 years. The disease is characterized by motor neurone degeneration of the cerebral cortex, brainstem and spinal cord, although the cause is unknown (Onders et al 2009b). ALS causes progressive muscle weakening and wasting, and loss of ability to initiate and control voluntary movement. As the disease progresses, the mechanical function of the respiratory system is impaired, and pulmonary complications are a major cause of death in ALS (Onders et al 2009b).

Diaphragm movement is essential for adequate ventilation. Patients with diaphragm dysfunction, including high SCI patients and respiratory compromised patients with ALS, traditionally require lifelong positive pressure mechanical ventilation via a tracheostomy (Onders et al 2009a). While effective in maintaining life support, mechanical ventilation is uncomfortable, limits mobility, impairs speech and smell, and is associated with complications such as pneumonia, atelectasis (lack of gas exchange in an area of the lung), barotrauma (damage to tissues due to pressure changes), diaphragm injury, and with high rates of hospitalisation (DiMarco 2009). An alternative, for patients with sufficient phrenic nerve, lung and diaphragm function to accommodate electrical stimulation, is direct phrenic nerve stimulation to restore diaphragm movement (FDA 2008). The phrenic nerve originates from the C3-C5 cervical nerves, and provides the motor supply to the diaphragm (DiMarco 2009). During the past 50 years, phrenic nerve pacers have been developed that use electrodes placed in direct contact with the phrenic nerve. These are placed through an open cervical or thoracic approach (Onders et al 2004). The procedure is invasive, requires a long period of hospitalisation, and risks damage to the phrenic nerve (Onders et al 2004). Advantages over mechanical ventilation include a sense of more normal breathing, elimination of ventilator tubing and ventilator noise leading to improved comfort and mobility, improved speech and smell, and reduced costs (reduction of ventilator supplies and reduced caregiver support requirements) (DiMarco 2009).

A recent development aims to overcome the risks associated with direct phrenic nerve stimulation. From 2000, a new laparoscopic technique has been trialled which involves placement of intramuscular electrodes in the diaphragm, which stimulate movement without requiring direct contact with the phrenic nerve (Onders et al 2004). This technique avoids injury to the phrenic nerve, and can reduce surgical and recovery time in a high-risk patient group (Dimarco 2009). The laparoscopic procedure makes use of a

marketed diaphragm pacing stimulation (DPS) device (the NeuRx RA/4 system, Synapse Biomedical, Oberlin, OH, USA).

**Figure 1: NeuRx DPS**



**(Image used with permission from Synapse Biomedical)**

The DPS surgery consists of diaphragm mapping and electrode implantation. During the laparoscopic procedure, a total of four ports are used. Mapping involves finding the phrenic nerve motor point of the diaphragm where stimulation causes the greatest contraction (Onders et al 2009a). The mapping probe is held onto the diaphragm by suction, stimulation is performed, and both qualitative and quantitative data regarding the contraction strength are obtained. The stronger the observed contraction, the closer the mapping probe is to the motor point of the diaphragm. Software assists in rapid motor point location using a grid-mapping algorithm (Onders et al 2004). Two electrodes are then implanted in each diaphragm, one at a primary site and one at a secondary site to capture additional diaphragm movement. This ensures all branches of the phrenic nerve are stimulated optimally (Onders et al 2004). An electrode implant instrument is used, with the needle at the end of the instrument placed into the diaphragm muscle. On withdrawal, the barb at the end of the electrode releases, allowing the exposed electrode to stay in the muscle (Onders et al 2009a). Each electrode is tested after implantation to ensure it is optimally stimulating, and is adjusted if necessary (Onders et al 2004). The four implanted intramuscular diaphragm electrodes along with an anode are then tunneled to an appropriate spot on the chest or abdominal wall, and connected to a four-channelled external stimulator at a percutaneous exit site. The stimulator delivers a pulse charge, and can be programmed by a clinician (Onders et al 2009a). The DPS is usually programmed to provide a stimulus that would provide a tidal volume of 15% over basal needs (Onders et al 2009a). Patients begin with short pacing sessions to condition their diaphragms, with the eventual aim to achieve at least four hours of continuous pacing every day, free of a ventilator (Onders et al 2009a).

## **CLINICAL NEED AND BURDEN OF DISEASE**

There are an estimated 200,000 SCI patients living in the USA, with 11,000 new SCI patients each year. Over one-half of injuries result in quadriplegia, and 4% require long term mechanical ventilation (Onders et al 2009a). Each year in Australia, about 300 to 400 new cases of SCI from traumatic and non-traumatic causes are added to an estimated prevalent SCI population of approximately 9,000 (Cripps 2008). Between 1999 and 2005, incident rates for males were generally significantly higher than for females across all age groups (3245 versus 1347 cases), and almost half of all incident cases sustained an injury to the cervical spinal cord (48% of incident cases [n = 2,190]) (Henley 2009). Between 1999 and 2005, there were 19,912 hospital separations in Australia involving SCI, with more than half of these separations involving readmissions related to complications of SCI sustained at an earlier time (Henley 2009). Based on 2005 estimates, the ongoing costs associated with the long-term care of the SCI population in Australia are estimated to be nearly A\$500 million per year (Cripps 2008).

In the USA, there are slightly more than 5,000 new cases of ALS diagnosed each year (Onders et al 2009b). In Australia, motor neurone disease (including ALS) is the third largest cause of nervous system mortality after Alzheimer's disease and Parkinson's disease (responsible for 11% of the 4,622 deaths from nervous system disorders in 2002) (AIHW 2004). Incidence and prevalence data are not readily available, but due to the rapid progression of the disease, mortality is likely to reflect patterns of incidence (AIHW 2004). By one estimate, motor neurone disease (including ALS) affects approximately 1300 people in Australia (MND Australia 2009). Mortality from MND has increased significantly in Western countries since the 1950s and the reasons for this are not known (AIHW 2004).

For SCI and ALS patients with respiratory failure, the burden of disease is greater than for those who are not ventilator dependant (DiMarco 2009). Respiratory failure results in significant inconvenience to the patient and caregiver, greater health care costs, and increased morbidity and mortality (DiMarco 2009).

## **DIFFUSION**

Trials of the DPS system have been conducted predominantly in the USA. US Food and Drug Administration (FDA) approval for the NeuRx RA/4 DPS system was obtained in June 2008, under a Humanitarian Device Exemption (FDA 2008). In 2009, the NeuRx RA/4 DPS system was also approved in Australia by the Therapeutic Goods Administration (TGA) and listed on the Australian Register of Therapeutic Goods (ARTG) (TGA 2009). The device was recently introduced for use in one Australian hospital (Austin Hospital, Melbourne) (Vic DHS 2009).

## **COMPARATORS**

The conventional therapy for high SCI patients and for ALS patients with respiratory failure is positive pressure mechanical ventilation via a tracheostomy (FDA 2008). An

alternative to mechanical ventilation, for patients with sufficient phrenic nerve, lung and diaphragm function to accommodate electrical stimulation, is direct phrenic nerve stimulation (FDA 2008). Commercially available phrenic pacers use electrodes placed in direct contact with the phrenic nerves through an open cervical or thoracic approach (Onders et al 2004). This is different from the NeuRx DPS system which is placed laparoscopically into the diaphragm, with the electrodes implanted intramuscularly rather than in direct contact with the phrenic nerve (Onders et al 2004). Other non-invasive alternatives to mechanical ventilation, which may be used in some patients to provide periods of time off mechanical ventilation, include continuous positive pressure ventilation (CPAP) or bilevel positive pressure ventilation (BiPAP) via a mask, nasal occlusion device, or tracheostomy adapter, a pneumobelt which inflates and deflates allowing lung movement, or a rocker bed which shifts abdominal contents (FDA 2008).

## **SAFETY AND EFFECTIVENESS ISSUES**

### *Study Description*

A study by Onders et al (2009a) presents the combined results from prospective FDA trials of all patients who underwent laparoscopic intramuscular implantation of the NeuRx DPS system between March 2000 and September 2007. Eighty-eight patients (50 SCI and 38 ALS) were implanted with the DPS system, at five sites. Patient ages ranged from 18 to 74 years. For the SCI trial patients, criteria for DPS implantation included a high-level SCI, chronic ventilator dependence, and a stimlatable diaphragm with intact phrenic nerves. There were 37 males and 13 females in the SCI trial, with time from SCI to implantation ranged from 3 months to 27 years (mean 5.6 years). Average follow up in this trial was  $2 \pm \text{SD}1.5$  years (Onders et al 2009a). The ALS patients were involved in three separate trials, with the criteria for DPS implantation including a forced vital capacity (FVC) above 50% predicted at enrolment and 45% at implantation. The first ALS trial included 13 males and 3 females with a mean FVC of  $59 \pm \text{SD}13\%$ , who presented on average 23 months post diagnosis. The most recent trial included 14 males and 6 females with a mean FVC of  $60 \pm \text{SD}12\%$ , who presented on average 22 months post diagnosis. Two additional ALS patients had a low FVC and did not meet the criteria, but were implanted for compassionate use. Unlike the SCI patients, for the ALS patients the goal of DPS implantation was not to replace mechanical ventilation, but to delay the need for it (Onders et al 2009a). The DPS surgery included diaphragm mapping and electrode implantation, as described in the background section. For SPI patients the DPS was programmed to provide a stimulus that would provide a tidal volume of 15% over basal needs, and for ALS patients the highest setting within safe parameters that caused no discomfort was used. Patients conditioned their diaphragm using initial short pacing sessions, which were gradually extended (Onders et al 2009a).

Results presented in earlier papers (Onders et al 2004; Onders et al 2005; DiMarco et al 2005; Onders et al 2007; and Alsheklee et al 2008) were included in the study by Onders et al (2009a). Another study by Onders et al (2009b) presents the results of 51 ALS patients implanted from March 2005 to March 2008, from three separate trials. There is duplication with patients reported in Onders et al (2009a) and Onders et al (2009b); however, Onders et al (2009b) includes additional patients implanted after

September 2007. This study presents safety results but no new effectiveness results. Patient ages ranged from 32 to 72 years. The criteria for implantation and the surgical technique was the same as that presented above for Onders et al (2009a).

### *Safety*

In the study by Onders et al (2009a) there was no perioperative mortality in either the SCI or the ALS groups. SCI patients were easily returned to their ventilators postoperatively with no respiratory events. The ALS patients who were on noninvasive positive-pressure ventilation (NIPPV) preoperatively were immediately placed back on NIPPV in the recovery room. All were safely extubated postoperatively. There were no diaphragm injuries, solid-organ injuries, bleeding, bowel injuries, or lung injuries leading to pneumothoraxes, and no conversions to open operations. There was one delayed suture granuloma causing an infection at the epigastric port site where the diaphragm electrodes were connected to separate electrodes that were tunnelled through the skin. This was treated by externalizing the electrodes. There were two superficial wound infections along the tunnelled wires, one in a SCI patient and one in an ALS patient. Both infections were resolved with oral antibiotics and shortening and retermination of the tunnelled electrodes. In 21/50 SCI patients (42%) and 5/38 ALS patients (13%), intraoperative chest x-rays showed air above the diaphragm (capnothorax). This was treated by observation or simple aspiration, and the capnothorax caused no hemodynamic or respiratory problems. There were no electrode erosions to structures in the abdomen, no electrode migrations, no late change in electrode impedance, and no electrode breakages (Onders et al 2009a).

Onders et al (2009b) also reports that the ALS patients were extubated more easily than expected postoperatively, with the DPS assisting this process. There were no failures to extubate, no 30-day mortalities, no perioperative respiratory infections, and no prolonged hospitalizations. Most patients were discharged in less than one day. Three patients returned for second unrelated operations (2 gastrostomies and 1 colon cancer resection), and the DPS was used to monitor and stimulate respirations, to increase safety during these operations (Onders et al 2009b).

### *Effectiveness*

Onders et al (2009a) reports that in 87 of 88 patients the diaphragm motor point was identified with subsequent implantation of the electrodes. In one patient (the second SCI patient), the electrodes were implanted but stimulated tidal volume was never achieved. This patient was found to have a preoperative test result that was false-positive for phrenic nerve function. For the SCI patients (implanted from March 2000), the endpoint for demonstration of benefit was the ability of the DPS system to provide clinically acceptable tidal volume (7ml/kg body weight for males and 6ml/kg body weight for females) for at least four continuous hours of pacing. After conditioning of the diaphragm, 98% of the SCI patients were able to produce tidal volume with DPS of 15% over their basal requirements, and 96% of the patients used DPS for greater than four continuous hours. Over 50% had utilised DPS for over 24 continuous hours. At latest follow-up, 44 patients were actively using the device, five had died from unrelated causes, and one was never able to use the device to pace. For the initial pilot ALS trial of

16 patients (implanted March 2005 to March 2007), the DPS was shown to improve diaphragm movement. After conditioning the diaphragm was thicker when assessed with ultrasound ( $P = 0.02$ ), and the average rate of decline of FVC with the DPS was 0.9% per month, compared with the pre-implantation decline of 2.4% per month. The study extrapolates this to an additional 24 months of ventilator-free survival for the implanted ALS patients. The most recent ALS trial assessed benefit in 20 patients (implanted March 2007 to September 2007) by assessing the rate of decline of FVC pre and post DPS implantation and assessing the effect of DPS. The effectiveness results of these patients continue to be monitored, and are not presented in this study (Onders et al 2009a).

### **COST IMPACT**

The study by Onders et al (2004) outlines the cost savings that can be obtained through use of the DPS system. The average cost of a ventilator dependant patient was estimated to be three times that of a ventilator independent patient. An example was given of one nursing home patient whose health care costs decreased by US\$13,000 a month because he no longer had to stay in a ventilator unit. The study also compared the costs of the implanting the laparoscopic DPS system, which cost less than US\$20,000, with that of implanting the direct phrenic nerve pacing device, which had hospital costs of more than US\$120,000 (Onders et al 2004).

### **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

One study indicated that for ALS patients, ‘tracheostomy and mechanical ventilators would be the usual end result of respiratory failure, but most ALS patients in the United States choose death over this option’ (Onders et al 2009b). The DPS system offers an alternative to mechanical ventilation, at least temporarily in ALS patients, and has the potential to prolong life. However, this raises ethical considerations, and the DPS may not always be a suitable option.

### **OTHER ISSUES**

No other issues were identified from the retrieved literature.

### **SUMMARY OF FINDINGS**

There is limited high level evidence available on the use of the laparoscopic DPS system. Case series evidence demonstrates that the laparoscopic procedure allows for safe implantation of the device in both SCI and ALS patients. There were no serious complications reported. In the majority of SCI patients, the device was effective in providing an alternative to mechanical ventilation (for at least four hours per day), and for ALS patients, the device has been shown to delay the need for mechanical ventilation (Onders et al 2009a). Additional studies in larger patient groups are required to provide further evidence of safety and effectiveness.

### **HEALTHPACT ACTION**

Based on the potential benefit of the DPS technology and given that it is currently being introduced in Australia, HealthPACT will note the development of this technology but additional assessment is not necessary at this time. In future, if required, HealthPACT may supplement this summary with data from Victoria.

#### NUMBER OF STUDIES INCLUDED

Total number of studies	2
Level IV evidence	2

#### REFERENCES

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#### **SOURCES OF FURTHER INFORMATION**

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#### **SEARCH CRITERIA TO BE USED**

Diaphragm pacing