NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Axonics sacral neuromodulation system for treating refractory overactive bladder

The National Institute for Health and Care Excellence (NICE) is producing guidance on using Axonics sacral neuromodulation system for treating refractory overactive bladder in the NHS in England. The medical technologies advisory committee has considered the evidence submitted by the company and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the public. This document should be read along with the evidence (see the committee papers).

The advisory committee is interested in receiving comments on the following:

- Has all the relevant evidence been taken into account?
- Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on Axonics sacral neuromodulation system for treating refractory overactive bladder. The recommendations in section 1 may change after consultation.

After consultation the committee will meet again to consider the evidence, this document and comments from the public consultation. After considering the comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England. For further details, see the medical technologies evaluation programme process and methods guides.

The key dates for this guidance topic are:

Closing date for comments: 13 March 2020

Second committee meeting: 20 March 2020

Details of the advisory committee are given in section 5.

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology in the NHS but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 Evidence supports the case for adopting Axonics sacral neuromodulation (SNM) system for treating refractory overactive bladder in the NHS. Axonics SNM system improves symptoms and quality of life. It also has a longer battery life than the non-rechargeable system used in NHS clinical practice.

1.2 Axonics SNM system should be considered as an option for people with refractory overactive bladder, that is, when conservative treatment or drug therapy has not worked, in line with NICE's guidelines on urinary incontinence and pelvic organ prolapse and lower urinary tract symptoms. Axonics SNM system is small and does not need to be removed for MRI, so it may be useful for people with a low body mass index (BMI) or when a full body MRI is likely.

1.3 Cost modelling suggests that, over 15 years, Axonics SNM system is cost saving compared with the non-rechargeable system by about £6,200 per person. Cost savings are estimated to begin 6 years after implant. This is

because the device needs to be replaced less frequently than the non-rechargeable system, assuming Axonics has a life span of at least 15 years. For more details, see the NICE resource impact report.

Why the committee made these recommendations

Axonics SNM system uses electrical impulses to stimulate the sacral nerves in the pelvic floor or groin area, to help bladder control. The system is implanted surgically and has a small stimulator that uses a rechargeable battery.

Axonics SNM system has a longer battery life than the non-rechargeable system used in NHS practice. This means that it needs replacing less frequently, so people need surgery less often. Also, the small size and shape of the stimulator makes it more suitable for people with a lower BMI. The system does not need to be removed in people needing a full body MRI.

Evidence from clinical trials shows that Axonics SNM system improves symptoms of refractory overactive bladder and quality of life.

The cost analysis suggests that using Axonics SNM system may lead to cost savings, but this depends on the length of time the battery lasts. The battery is expected to last at least 6 years, at which point Axonics SNM system becomes cost saving to the NHS.

2 The technology

Technology

2.1 Axonics sacral neuromodulation (SNM) system stimulates the sacral nerve through an implantable pulse generator implanted subcutaneously in the upper buttock. Lead electrodes implanted through the corresponding sacral foramen transmit pulses from the stimulator to the sacral nerves. The stimulator is powered by a rechargeable battery.

2.2 A handheld remote control activates the stimulator, adjusts the stimulation amplitude, and checks the battery status. A wireless charger, attachable to the skin over the implanted stimulator is used to charge the stimulator.

The company claims that the battery needs recharging every 1 to 2 weeks for 30 minutes to 1 hour. The implanted device is programmed by a clinician in an outpatient setting using a portable tablet. Axonics SNM system received a CE mark as a class 3 medical device in June 2016.

Innovative aspects

2.3 The rechargeable battery that powers the stimulator has an expected life span which the company claims is longer than the comparable non-rechargeable device (up to 15 years). The stimulator is compatible with full body MRI and is smaller than existing non-rechargeable SNM devices, making it more suitable for people with a low body mass index.

Intended use

2.4 The Axonics SNM system is intended to treat symptoms of overactive bladder, urinary retention and chronic fecal incontinence, specifically when conservative therapy and drug treatment have not worked or are not suitable. Urinary retention and fecal incontinence are outside the scope of this evaluation. Axonics SNM system is recommended by multidisciplinary teams including surgeons, specialist nurses and physiotherapists, and implanted by surgeons specialising in bladder dysfunction. Limited surgical and patient training is needed.

Costs

2.5 The Axonics SNM device costs £9,660 for the permanent implant.

For more details, see the website for Axonics SNM system.

3 Evidence

Clinical evidence

The main clinical evidence comes from 2 single-arm trials

3.1 Two studies met the inclusion criteria defined by the scope:

- ARTISAN-SNM (McCrery 2019 and Lane 2020; n=129 patients), which included 19 centres in the US and Europe (the Netherlands, Belgium, France and the UK) and had a follow up of 12 months.
- RELAX-OAB (Blok 2018a and b, Blok 2019a and c; n=51 patients), which included 7 centres in Europe (the Netherlands, Belgium, France, and the UK) and had a follow up of 2 years.

Both studies were non-comparative, before and after, intra-patient, observational studies reporting patient outcomes as a change from baseline. Both studies had design and reporting weaknesses. The company also submitted evidence for the non-rechargeable comparator system.

The population and definitions of response to therapy and test responder vary in both studies

3.2 ARTISAN-SNM included people with urinary urge incontinence. Response to therapy was defined as at least a 50% reduction in urinary urge incontinence (episodes of urinary leaks) per day according to 3-day urinary diary entries at 6 months. RELAX-OAB included people with urinary urge incontinence (n=37) and all except one had symptoms of urinary frequency (n=50). Although not considered a primary outcome, response to therapy in RELAX-OAB was defined as at least a 50% reduction in episodes of urinary leaks for people with urinary urge incontinence and at least a 50% reduction in voids or reduction to less than 8 voids per day for people with urinary frequency. ARTISAN-SNM defined test responders as people whose symptoms responded to therapy at 1 month after implant. RELAX-OAB defined test responders as people whose symptoms responded to therapy at 2 weeks or 1 month after implant.

Clinical outcome data show that Axonics SNM system is effective at improving symptoms of overactive bladder

3.3 ARTISAN-SNM reported a statistically significant reduction in:

- mean daily urinary urge incontinence (episodes of urinary leaks) from 5.6±0.3 at baseline to 1.3±0.3 after 6 months, and 1.4±0.2 at 1 year ($p<0.0001$)
- urinary frequency episodes (average voids per day) from 11.6±0.3 at baseline to 8.7±0.2 at 6 months ($p<0.0001$).

RELAX-OAB reported a reduction in:

- mean daily urinary urge incontinence (episodes of urinary leaks) from 8.3±0.8 at baseline to 1.8±0.5 after 1 year and to 1.7±0.5 at 2 years ($p<0.0001$)
- urinary frequency episodes (average voids per day) from 14.3±1.1 at baseline to 8.0±0.5 by 1 year and 7.3±0.4 at 2 years ($p<0.0001$).

The evidence suggested that symptoms of urinary urge incontinence were more likely to improve than urinary frequency symptoms, but this depended on how improvement was defined. The clinical effectiveness of Axonics sacral neuromodulation (SNM) system was not assessed beyond 2 years.

Studies report an improved quality of life

3.4 Both studies reported scores for the domains of the quality-of-life measure ICIQ-OABqol before and after treatment. ARTISAN-SNM reported an average score improvement of 34 at 1 year and RELAX-OAB reported an average improvement of 29 at 2 years. Absolute before and after quality-of-life scores were not reported.

It is likely the battery life of Axonics SNM system will last at least 15 years

3.5 Because there was no long-term clinical evidence, the evidence assessment centre (EAC) assessed the company's technical data supporting the claimed 15-year life span for the battery and the device's compatibility with a full body MRI. The EAC concluded that, if moderate or typical stimulus is maintained for the lifetime of the battery, it is likely that

the battery will exceed its claimed life span of 15 years. No evidence was submitted to explore the potential effect of lead migration (that is, when the lead moves from where it was inserted) or if the lead breaks. Minor lead migrations can be compensated for by increasing the stimulus, but major lead migration and breakage need to be corrected by surgery.

Cost evidence

The company's de novo cost model shows that Axonics SNM system is cost saving in people with symptoms of overactive bladder

3.6 The de novo cost analysis used a Markov model adapted from a previously published model (Noblett 2017) to compare the rechargeable Axonics SNM system with the non-rechargeable system in people with overactive bladder. Most clinical parameters in Noblett 2017 are derived from the 12-month Insite trial (Noblett 2016). The de novo model involved a quarterly progression between 3 health states (on SNM therapy, discontinuation of therapy and death). The model assumed equivalent clinical effectiveness, discontinuation rates and rate of adverse events for both the rechargeable and non-rechargeable systems, so the same inputs were used for both arms. Results showed that over a 15-year time horizon, using Axonics SNM system in this population is cost saving by £6,038 per person.

The EAC's revised model includes more appropriate clinical and resource use parameters

3.7 The EAC considered that the study central to the company's model (Noblett 2017) had potentially serious limitations in reporting data sources and that it was difficult to identify data stated in the model from the referenced papers. This limitation was partly addressed by an updated reference list submitted by the company. In the EAC's base case, clinical equivalence was not assumed so data on therapy discontinuation rate and lead migration were taken from Axonics SNM studies for the rechargeable SNM arm of the model. The company model assumed that all adverse events happen in the same cycle as the implant procedure. This was

revised because lead migration, lead breakage and pain may not be related to the procedure and may continue throughout the life of the model. The assumption that the implant procedure would need an inpatient admission was changed to a day-case surgery, based on expert advice. The committee concluded that the EAC's changes to the model were appropriate.

Axonics SNM remains cost saving after the EAC's revision of the model

3.8 In the EAC's preferred base case, Axonics SNM system was associated with a cost saving of £6,273 per person over 15 years. A one-way sensitivity analysis showed that the timing of device replacement is a key driver of the cost savings. Threshold analysis showed that Axonics SNM system remains cost saving when the minimum life span of the technology is 6 years.

4 Committee discussion

Clinical-effectiveness overview

Axonics SNM system is clinically effective

4.1 The committee noted the non-comparative evidence from 2 studies (ARTISAN-SNM and RELAX-OAB) and testimony from a patient survey. Some patients described the technology as 'completely life changing', others felt in control of their condition. The clinical experts said that, in their opinion, Axonics SNM system improves symptoms and quality of life compared with the standard non-rechargeable system. The clinical experts noted that the test phase programming for both devices was different. Axonics SNM system has 1 program that can be optimised while the standard non-rechargeable SNM system has 4 default programs that a patient can switch across remotely. The permanent implantation procedure is similar for both devices. The committee concluded that Axonics improves symptoms of overactive bladder and quality of life.

The 15-year battery life of the Axonics SNM system is plausible

4.2 The committee noted that there was a lack of long-term follow-up data from the existing studies that validated the company's claim of extended battery life in real-world use. The technical expert explained that battery longevity depends on the recharge interval, charging regime and discharge profile. The EAC carried out an assessment of accelerated battery bench testing data submitted by the company. Based on this and expert advice, the committee concluded that it is plausible that the Axonics SNM battery will last 15 years for a person who needs typical stimulus (2.1 mA) to manage their symptoms. No data on battery failure were submitted and the committee was also advised that the recharge interval depended on stimulation parameters. Also, some devices may fail within the 15-year life span if stimulus current of up to 4 mA is needed to manage symptoms. Mild cases of lead migration were noted as a possible cause of changes in stimulus current. The committee further considered that although evidence from RELAX-OAB showed that stimulation amplitude increased up to 3 months after the device was implanted, in the longer term, once the lead settles in the body, amplitude may stabilise or decrease. The committee concluded that even though evidence on battery life was limited, it was plausible that the battery would last at least 6 years and possibly beyond 15 years.

Dropout rates and desensitisation occurring with Axonics SNM system are unpredictable

4.3 The clinical experts explained that it was difficult to predict what proportion of people had symptoms that would stop responding over the 15-year life span of the Axonics SNM system. The experts stated that all treatments for overactive bladder are associated with some level of decline in response. This could be as a result of the person's lifestyle, loss of efficacy, break in circuit and anticipated changes in stimulation delivered. Clinical experts advised that a therapy break may be recommended to assess if people should continue to use SNM therapy (rechargeable or non-rechargeable). The committee noted that long-term therapy breaks

(for desensitisation or pregnancy) may reduce the rechargeable battery life although evidence of this was not available. The committee concluded that although desensitisation may occur, this was unlikely to be different with Axonics SNM system than with the non-rechargeable system.

Axonics SNM may benefit people with protected characteristics under the Equality Act 2010

4.4 Overactive bladder is common in women who have been pregnant or who are postmenopausal. It is more common in older people, people with obesity and may be common in disabled people. Axonics SNM system should not be used by people who may be unable to use the device, for example, some disabled people or people with a learning disability. The clinical experts explained that the device can be recharged by a carer. The committee noted that when a carer was not available to help with recharging Axonics SNM system, the option of a non-rechargeable SNM system would still be available.

Axonics SNM system has advantages for people with low body mass index or who are likely to need an MRI scan

4.5 The clinical experts said that the smaller size of the Axonics SNM system compared with the non-rechargeable device makes it more suitable for people with low body mass index. The full body MRI compatibility of the device means that people with overactive bladder who may need future MRI scanning do not need to have their device removed, avoiding replacement surgery. This consideration was also relevant to people with chronic conditions such as multiple sclerosis, who are likely to need regular MRI scans.

Side effects and adverse events

Axonics SNM system has no serious adverse effects

4.6 No serious adverse events have been reported with Axonics SNM system. There was no evidence on adverse events beyond 2 years. The most common minor device-related adverse events related to discomfort

associated with stimulation. Clinical experts agreed that discomfort with stimulation can usually be corrected with reprogramming.

NHS considerations overview

Axonics SNM system should be used on its own

4.7 The clinical experts explained that Axonics SNM system is usually used in their practice as a third-line therapy after conservative treatment and drug therapy have failed, which is in line with NICE's guidelines on urinary incontinence and pelvic organ prolapse and lower urinary tract symptoms. They explained that sacral neuromodulation is normally expected to be the only therapy needed to improve symptoms of overactive bladder, but that occasionally drugs might also be used. This may mean that SNM stimulation is becoming less effective. The committee concluded that Axonics SNM system should be the only treatment for overactive bladder until symptoms are no longer adequately controlled.

Patient choice is key to deciding whether to use a rechargeable SNM system

4.8 The clinical experts explained that people are told about the advantages and disadvantages of the rechargeable and non-rechargeable systems before a device is implanted. These include uncertainty about device longevity and possible causes for device failure. The longer battery life of Axonics SNM system may appeal to a person using the device. The committee concluded that this is ultimately the person's decision.

Axonics SNM system is easy to use

4.9 Clinical experts stated that Axonics SNM system is easy to use, for the person and the healthcare professional, and needs little in the way of additional training. They also explained that the implant procedure for the Axonics SNM system is minimally invasive and no more complex than for the non-rechargeable device. A clinical expert explained that people with memory problems may prefer the non-rechargeable device but that people with mild cognitive impairment may be able to have a Axonics SNM system if support is available. The committee concluded that

Axonics SNM system could be used by most people, particularly if a carer can help.

Cost modelling overview

The EAC's revised cost model is more plausible

4.10 The committee accepted the EAC's preferred cost model, which showed that Axonics SNM system becomes cost saving at 6 years after implant. The committee acknowledged the uncertainties in extrapolating data collected over 2 years to a 15-year time horizon but considered this approach to be suitable for decision making. The committee acknowledged that failure to include the cost of battery disposal in the cost modelling was a limitation.

The risk of device failure after 1 year should be shared with the company

4.11 The company explained that the device warranty lasts for 12 months. The clinical experts explained that people are advised to include their device in insurance policies to cover loss of, or damage to, the remote or charger. The committee considered that, based on the company's confidence in the longevity of the device and the results of the cost modelling, the warranty should be extended by the company to at least 6 years.

Main cost drivers

Time to device replacement is key

4.12 The EAC's sensitivity analyses identified time to device replacement as a key driver of cost savings. The committee concluded that Axonics is cost saving only if it lasts longer than the non-rechargeable device.

Cost savings

Axonics SNM system is cost saving compared with standard care

4.13 The EAC's revised cost modelling showed that over 15 years, using Axonics SNM system for managing refractory overactive bladder is associated with an estimated cost saving of £6,273 per person in the base

case. Also, the amount of cost savings increases progressively from 6 years after implant.

Further research

Further research would help address uncertainties

4.14 Further evidence on the long-term clinical benefits and device longevity of Axonics SNM in people with refractory overactive bladder would be welcomed.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technology advisory committee which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technology advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more technical analysts (who act as technical leads for the topic), a technical adviser and a project manager.

Tosin Oladapo

Technical analyst

Lizzy Latimer

Technical adviser

Elizabeth Islam

Project manager

ISBN: [to be added at publication]

