Horizon Scanning report No. 9

Implantable device for patients with gastro-oesophageal reflux disease

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Methods

Agenas is a public body. Its mission is to promote innovations and developments within the Italian national healthcare service and develop a Horizon Scanning (HS) function in the field of healthcare technologies. A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology/procedure: **Implantable device for patients with gastro-oesophageal reflux disease**

Target population

The new technology is indicated for those subjects (adults) diagnosed with pathologic gastro-oesophageal reflux disease (GORD), defined by abnormal pH testing, and who continue to have chronic GORD symptoms despite anti-reflux drug therapy.

Description of the procedure and technology

Laparoscopic oesophagogastric fundoplication (by Nissen's, Toupet's or Dor's procedure) [Pessaux P, 2005] is considered the gold standard for the surgical management of GORD whether pharmacological therapy is not effective [Bergman S, 2008]. However potential complications as dysphagia, bloating, nausea, vomiting and other symptoms related to vagal nerve injury have been reported post-operatively [Beldi G, 2002; Waring J, 1999]. In addition it has been shown that such procedure is strongly linked to the setting and surgeon's experience: poor results were registered within low speciality facilities [Richter J, 2008; Vakil N, 2003]. Several techniques have been proposed in the past years for the lower oesophageal sphincter augmentation: endoscopic suture or plication, and polymer injection either failed to provide a safe or effective treatment, or were unable to establish a sustainable business model [Smith CD, 2010]. The endoscopic esophago-gastric plication (performed by the Esophyx device from EndoGastric Solutions, Inc.) remains the only new technique currently approved by the FDA; it allows performing fundoplication transorally, without any laparoscopic access. Results in terms of health-related quality of life and other effectiveness measures appear favourable but comparative studies versus standard treatment are lacking [ANZHSN, 2010].

Recently a new device has been proposed to perform the laparoscopic sphincter augmentation; such procedure is proposed as an option for those patients that are not satisfied by the pharmacological therapy and don't want to face the surgical-related side effects. The sphincter augmentation device is implanted by a standard laparoscopic procedure, under general anaesthesia, is wrapped and secured around the oesophagus, and does not involve any anatomical alteration of the stomach not requiring a specific post-operative diet. In the present HS report we will assess such implantable device for sphincter augmentation.

Clinical importance and burden of disease

Gastro-oesophageal reflux disease (GORD) is defined as a retrograde movement of gastric contents, including pepsin, bile, and pancreatic enzymes, into the oesophagus due to the abnormal relaxation of the lower oesophageal sphincter. The classic symptoms for GORD include heartburn, regurgitation, and dyspepsia. The atypical symptoms are angina-like pain, chronic cough, asthma, hoarseness, protracted hiccups, globus sensation, dental erosion, ear pain, night sweats and sleep apnoea, and water brash. Besides GORD can lead to more serious diseases; Barrett's oesophagus and oesophageal adenocarcinoma are known as complications of GORD [Vassiliou MC, 2010]. The diagnostic tests generally used when

GORD is suspected are 24-hour pH-metry and upper gastrointestinal endoscopy [ANZHSN, 2010]. Standard therapy in treating symptoms of GORD is pharmacological, by proton pump inhibitors (PPIs); interventional therapies (open surgery, laparoscopic or endoscopic) are also available. Although PPIs therapy is largely effective in controlling common reflux symptoms in great part of patients, they are often required indefinitely and may be associated with intolerable side effects and persistence of non-acid regurgitation as they do not address the mechanical causes of the condition [Vassiliou MC, 2010].
Symptoms of GORD affect up to 20% of the population in the western world [Dent J, 2005] and the prevalence seems to be increasing [Delaney BC, 2004; Fujimoto K, 2004; Goh K, 2004; Graham DY, 2003; Shaheen N, 2003]; such increase represents a significant financial burden for the healthcare systems [Dent J, 2005]. No data on the incidence and prevalence of GORD in Italy are available. According to the SDO database held by the Italian Ministry of Health, the number of admissions (ordinary and day-hospital) for gastro-oesophageal reflux (ICD-9-CM code 530.81) was 20,549 in 2009 (last year available) considering primary and secondary diagnosis. However 32% of admissions refer to patients younger than 15 years.

Products, manufacturers, distributors and approval

The new technology assessed in the present HS report is the LINX™ Reflux Management System, manufactured by Torax Medical Inc. The LINX™ gained the CE mark on April 2010; the device is not yet approved by the FDA (the PMA application has been submitted by the Manufacturer to the FDA). At time of writing there is no distributor for the Italian market and the devices are supplied directly by the manufacturer Torax Medical Inc. from the US. According to the Manufacturer's indications *"The LINX™ Reflux Management System is intended for use in the treatment of symptoms associated with GORD; It is designed to augment a weak lower oesophageal sphincter and minimize or eliminate GORD-related symptoms"* [Torax Medical Inc.]. The LINX™ consists of a series of titanium beads with magnetic cores hermetically sealed inside. The beads are interlinked together with independent titanium wires to form a flexible ring that rests around the lower oesophageal sphincter in a circular fashion. The magnetic force that the core beads apply to each other augments the ability of the sphincter to resist opening from gastric pressures. On the other hand such magnetic bonds are broken when a bolus is swallowed. This allows the free passage of the bolus and the closure of the sphincter after that. For a proper implantation procedure, the device needs to be sized specifically to the circumference of the patient's oesophagus. Different sizes are available (from 11 to 17 beads) and a special measuring tool (LINX™ Esophagus Sizing Tool) is needed to select the right size of the implantable device [Bonavina L, 2010; Torax Medical Inc.].

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
LINX™ Reflux Management System [Torax Medical Inc.]	None for Italy	☑	☑	☐

Setting

The implantation procedure has to be performed in an operating room equipped for laparoscopic upper gastro-intestinal (GI) procedures.

☐ Home	☑ Hospital	☐ Outpatients
☐ Accident and Emergency	☑ Other: Day-surgery	

Roll out in Italy

The manufacturer stated that, at time of writing, sixty-eight LINX™ devices have been implanted in Italy. All these implants have been performed in the same hospital in Milan; a further 120 devices have been implanted in other countries.

☐ Pre-marketing	☐ On the market for 1-6 months	☑ On the market for 7-12 months
☐ On the market for more than 12 months	☐ Not identified	

Comparators

The LINX™ device is proposed as an additional treatment option within the clinical pathway of GORD patients, i.e. when drug therapies (i.e. H2RA and PPIs) are not effective to reduce symptoms or the patient is not satisfied with his/her symptoms control. In the latter case the GORD may not be considered serious enough for traditional anti-reflux surgery.

Effectiveness and safety

We carried out searches on EuroScan and CRD (DARE & HTA) databases (10th March 2011) looking for documents published in Italian and English on the use of implantable devices for treatment of GORD. Eight reports on GORD treatment were found, but none of them was considered as they assessed surgical treatments, drugs or other kinds of devices (not implantable or no longer available on the market).
We looked for evidence on effectiveness and safety by searching for studies published in English and Italian from January 2005 in the major databases: Medline, EMBASE and the Cochrane Library (16th March 2011).
We found 10 citations. After reading title and abstract, only 2 citations were considered eligible for full text analysis [Bonavina L, 2008; Bonavina L, 2010]. These were clinical studies on patients (humans) which underwent management of GORD by LINX™ implantation. Both papers reported on the same multicentre prospective clinical study performed to evaluate the safety and efficacy of the LINX™ in a cohort of patients with GORD. The short-term results have been shown in the study by Bonavina et al. 2008.
The study by Bonavina et al. 2010 reported the last updated evidence. A total of 44 patients had laparoscopic implantation of the LINX™ between February 2007 and October 2008. The mean age was 42.3 years (range: 19–72) and the body mass index ranged from 19.0 to 38.4 kg/m^2 (mean: 25.7). At baseline, all patients had abnormal oesophageal acid exposure on 24-hour pH monitoring and improved, but persistent, typical GORD symptoms while on acid suppression therapy with PPIs. From the initial cohort, two patients were explanted because of persistent dysphagia and one because of the need for a magnetic resonance

imaging (MRI) study; other two patients withdrew consent and one subject was lost to follow-up. Results at 2 years of follow-up are available for 28 of the 44 patients.
Outcomes considered were: GORD Health-Related Quality of Life symptom (HRQL) score; PPIs usage; 24 hours oesophageal pH monitoring; and patient satisfaction. The total mean GORD HRQL scores improved from a mean baseline value of 25.7 to 3.8 and 2.4 at 1- and 2-year follow-up, representing an 85% and 90% reduction, respectively ($P < 0.0001$). Complete cessation of PPIs use was reported by 90% of patients at 1 year and by 86% of patients at 2 years. The mean percentage time pH < 4 decreased from a baseline of 11.9% to 3.1% ($P < 0.0001$) at 1 year and to 2.4% ($P < 0.0001$) at 2 years; 77% and 90% of patients had a normal oesophageal acid exposure at 1 and 2 years respectively. Patient satisfaction was 87% at 1 year and 86% at 2 years.
Early dysphagia occurred in 43% of the patients and self-resolved by 90 days. One device was laparoscopically explanted for persistent dysphagia without other complications. There were no device migrations, erosions, or induced mucosal injuries. Authors concluded that by LINX™ implantation the relief from GORD symptoms was excellent and a significantly reduced oesophageal acid exposure has been reached without relevant side effects [Bonavina L, 2010].
We also searched in the *clinicaltrial.gov* database (16th March 2011): three clinical trials were found (Table 1). All these trials assess the LINX™ device; they are non comparative, phase I - phase II, and they are all active not recruiting. These trials are the same for which results have been reported by Bonavina et al. 2008 and 2010.
Another study (the LINX™ Reflux Management System Clinical Study), sponsored by Torax Medical Inc. has been conducting at 13 sites in the USA and 1 site in Europe; this is a multicentre, prospective, single-arm study. The study implanted the device in 100 subjects enrolled between January 2009 and September 2009. The primary outcome is reduction in distal oesophageal acid exposure time while reduction in GORD-HRQL score and PPIs use are secondary outcomes. Outcomes assessment was performed at 12 months and continued follow-up is planned for up to five years. The expected date of publication is unknown.
The Manufacturer (Torax Medical Inc.) is running a prospective multicentre registry (called the Anti-Reflux Surgical Registry) that will be conducted primarily in Europe at up to 50 sites. The observational database will track patients over a 3 years period and will enrol approximately 500 LINX™ patients and 300 Nissen patients. The registry is currently enrolling subjects and the anticipated date of full patient accrual is 2012. No data for interim analysis or publication are available at the time of writing.

Potential benefits to patients

The new technology aims to reduce GORD symptoms and PPI usage allowing also to maintain the ability to blench or vomit after surgery and reducing the dysphagia associated to the standard surgical treatments.

☐ Mortality reduction or increased survival	☑ Reduction of the morbidity	☑ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology / procedure

For a single implantation procedure two devices are needed: the implantable LINX™ device and the single-use sizing tool. We contacted the manufacturer (Torax Medical, Inc.) to gain the following price list (all

prices are exclusive of VAT):

- LINX™ Reflux Management System: € 3.000;
- LINX™ Esophagus Sizing Tool: € 100.

Cost per treatment is the cost of both devices plus the costs for the implantation procedure via laparoscopy. The Manufacturer stated that costs can be similar to the current surgical approach (Nissen's fundoplication) with the additional cost of the LINX™ devices. It is also possible to implant the LINX™ device as part of a day-care protocol (day-surgery). It is expected that LINX™ implantation should be around 15 minutes faster to perform than a Nissen's fundoplication, saving surgical and theatre time. However, at the time of writing no economic evaluations have been performed on the LINX™. The cost per procedure for a laparoscopic Nissen's fundoplication can be estimated in € 1.527 [Morino M, 2006]. There is not a specific DRG fee for Nissen's fundoplication procedure that is currently linked to the ICD-9-CM code 44.67 *"Laparoscopic procedures for creation of esophagogastric sphincteric competence"*.

☑ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☑ New costs	☐ Other: Variations not identified	☐ Not identified

Potential structural and organisational impact

Structural impact

There are no relevant issues from a structural point of view. The implantation procedure of the LINX™ is performed in an operating room equipped for laparoscopic upper GI procedures. No further equipment in addition to standard laparoscopy is needed.

☐ Increase in requirement of instruments	☐ Always be used	☑ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

The staff required for the LINX™ implantation procedure is the same as for any laparoscopic upper GI procedure (surgeon, one or two assistants, scrub nurse, anaesthetist, circulators). According to the manufacturer indications, an experienced upper GI laparoscopic surgeon, who has been trained, can safely perform the procedure. The training is mandatory for all surgeons wishing to perform the procedure. Such training is managed by the manufacturer and is free of charge. At the time of writing the manufacturer states that effects of the learning curve have not been formally studied. However, the procedure is performed using basic laparoscopic techniques and is not complex as a Nissen's fundoplication since it requires minimal dissections and leaves intact the gastric anatomy.

☐ Increase in the number of procedures	☐ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

The magnetic oesophageal sphincter device is an innovative technology targeted to GORD patients (adult) that had no symptoms relief from drug therapy. The LINX™ device, currently the only on the market with these characteristics, is implanted by a minimally invasive approach (laparoscopy) and can be removed without relevant complications. The advantages of this new technology (e.g. reduction of GORD symptoms, reduction in PPIs usage, patient satisfaction) have been shown in a small cohort of patients within a multicentre non-comparative study. Although results at 1 and 2 years of follow-up are very good, further evidence is needed before giving guidance on the use of the technology. The number of treated patients is still limited, follow-up period is short, and comparative data are not available yet.

The manufacturer Torax Medical Inc. is making an effort to produce and collect an evidence base to expand its market: clinical trials have been registered, results are published periodically and a registry is going to be instituted. More robust data should be published in the coming years. However patient selection should be considered as a crucial issue in registers and clinical trials design to perform comparative analyses with data from the two arms (LINX™ and Nissen's patients). The cost of the device is significant, considering that the cost of the PPI therapies is decreasing due to patent expiry. GORD is often caused by obesity, excessive smoke, alcohol and coffee consumption, wrong dietary regimens and drugs that tend to relax the lower oesophagus sphincter; for this reason careful attention should be given to the misuse of the technology (i.e. in patients that actually don't need it). The indication for use of the device must be defined by careful choice on the target population.

The effectiveness of minimally invasive antireflux surgery and drug therapy has been proved so far [Wileman SM, 2010] and new approaches should be recommended for routine clinical use just after comparative analyses. However these new technologies could improve patients' outcomes as well as quality of life. As a good general approach, the introduction of such kind of devices (i.e. implantable device) must be undertaken after planning institutional review board-approved clinical trials and linked to a central registry to collect procedure and outcome data.

Future prospects

No future developments of the LINX™ system can be forecasted. As manufacturers and clinicians are working together to develop endoscopic devices for transluminal and natural orifice endoscopic surgery for GORD treatment, we can expect that some further treatment options will be proposed in the next years.

Table 1: Summary of the clinical studies identified in the *clinicaltrial.gov* database

Trial number and official title	Intervention model	Purpose	Primary outcome measures	Phase	Enrolment [patients]	Start and Completion
NCT01058564: "A Prospective Evaluation of the Torax Medical Inc. Magnetic Esophageal Sphincter"	Single group assignment	"To evaluate a novel method of augmenting a weak LES with a magnetic esophageal sphincter device"	Prospective performance evaluation of the magnetic esophageal sphincter.	I - II	4	May 2008 Oct 2011
NCT01058070: "An Observational Clinical Feasibility Study of the Magnetic Esophageal Sphincter"	Single group assignment	"To collect preliminary performance and safety information and develop procedural optimization for the Torax Medical Inc. MES device in reinforcement of Esophageal Sphincter function to treat GERD. The information from this study will be used to support the design and conduct of an expanded clinical trial"	To evaluate the incidence of all adverse events at various time points.	I - II	14	Feb 2007 Feb 2012
NCT01057992: "A Prospective Evaluation of the Torax Medical Inc. Magnetic Esophageal Sphincter"	Single group assignment	"To evaluate a novel method of augmenting a weak LES with a magnetic esophageal sphincter device"	Prospective performance evaluation of the magnetic esophageal sphincter	I - II	31	Mar 2007 Feb 2012

Key: LES = Lower Esophageal Sphincter; MES = Magnetic Esophageal Sphincter; GERD = Gastroesophageal Reflux Disease.

Evidence searches

Searches of the databases were carried out between 10th March 2011 and 16th March 2011, using the following key words to indicate:

- ***the technology of interest:*** *magnetic sphincter augmentation device, lower esophageal sphincter augmentation, magnetic augmentation LES, magnetic augmentation lower esophageal sphincter, magnetic enhancement LES, magnetic enhancement lower esophageal sphincter, LINX, Torax Medical LINX™ Reflux Management System, LINX® Anti-Reflux treatment*.
- ***the pathology of reference:*** *Gastro esophageal reflux disease, Gastro-oesophagel reflux disease, GERD, Gastroesophageal reflux*.

Bibliography

ANZHSN - Horizon Scanning Technology Prioritising Summary: EsophyX™ System. February 2009 (Updated April 2010); Electronic copies can be obtained from http://www.horizonscanning.gov.au

Beldi G, Glattli A. Long-term gastrointestinal symptoms after laparoscopic Nissen fundoplication. Surg Endosc Percutan Tech 2002 Oct;12(5):316-319.

Bergman S, Mikami D, Hazey J et al. Endoluminal fundoplication with EsophyX: The initial North American experience. Surgical Innovation 2008; 15(3): 166 – 170.

Bonavina L, DeMeester T, Fockens P, Dunn D, Saino GI, Bona D, Lipham J, Bemelman W, Ganz RA. Laparoscopic sphincter augmentation device eliminates reflux symptoms and normalizes esophageal acid exposure: one- and 2-year results of a feasibility trial. Ann Surg. 2010 Nov; 252(5):857-62.

Bonavina L, Saino GI, Bona D, Lipham J, Ganz RA, Dunn D, DeMeester T. Magnetic augmentation of the lower esophageal sphincter: results of a feasibility clinical trial. J Gastrointest Surg. 2008 Dec; 12(12):2133-40.

Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2004;20(Suppl 8):2– 4.

Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005 May;54(5):710-7.

Fujimoto K. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease in Japan. Aliment Pharmacol Ther2004;20(Suppl 8):5– 8.

Goh K. Changing epidemiology of gastroesophageal reflux disease in the Asian-Pacific region: an overview. J Gastroenterol Hepatol 2004;19:S22–S25.

Graham DY. The changing epidemiology of GERD: geography and Helicobacter pylori. Am J Gastroenterol 2003;98:1462–1470.

Istat - Istituto nazionale di statistica, Indagine multiscopo “Condizioni di salute e ricorso ai servizi sanitari”, 2005. Available at http://www.istat.it/dati/dataset/20080131_00/

Morino M, Pellegrino L, Giaccone C, Garrone C, Rebecchi F. Randomized clinical trial of robot-assisted versus laparoscopic Nissen fundoplication. British Journal of Surgery 2006 93:5 (553-558).

Pessaux P, Arnaud JP, Delattre JF, et al. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. Arch Surg. 2005;140(10):946-51.

Richter J, Dempsey D. Laparoscopic antireflux surgery: Keys to success in the community setting. Am J Gastroenterol 2008; 103:289-291.

Shaheen N, Provenzale D. The epidemiology of gastroesophageal reflux disease. Am J Med Sci 2003;326:264–273.

The Merck Manuals; www.merck.com/mmhe/index.html

Torax Medical Inc. LINX Reflux Management System – Instructions for use.

Vakil N, Shaw M, Kirby R. Clinical effectiveness of laparoscopic fundoplication in a US community. Am J Med. 2003;114:1–5.

Vassiliou MC, von Renteln D, Rothstein RI. Recent advances in endoscopic antireflux techniques.

Gastrointest Endosc Clin N Am. 2010;20(1):89-101.

Waring J. Postfundoplication complications. Prevention and management. Gastroenterology Clinics of North America 1999; 28(4): 1007 – 1019.

WHO, World Health Organization; http://www.who.int/topics/cataract/en/

Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD003243. DOI:10.1002/14651858.CD003243.pub2.

Glossary

CRD: Centre for Reviews and Dissemination.

DRG: Diagnosis-Related Groups.

Dysphagia: symptom of difficulty in swallowing.

FDA: Food and Drug Administration.

GORD: Gastro-oesophageal reflux disease.

H2RA: H2-receptor antagonist, a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells.

ISS: Istituto Superiore di Sanità (Italian National Health Institute).

Istat: Italian National Institute of Statistics.

Nissen's fundoplication: a surgical procedure to treat gastro-oesophageal reflux disease (GORD) and hiatus hernia. In GORD it is usually performed when medical therapy has failed. The Nissen's fundoplication is total (360º), but partial fundoplications known as Belsey fundoplication (270º anterior transthoracic), Dor fundoplication (anterior 180-200º) or Toupet fundoplication (posterior 270º) are also alternative procedures with somewhat different indications.

PMA: Premarket approval from the Food and Drug administration.

PPI: Proton pump inhibitor, a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production.

RDM: Medical device Repertory (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

Sphincter augmentation: Reconstructive surgery to increase the strength of the sphincter.

SDO: Hospital discharge record.