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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

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

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Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in conjunction with the Royal Australasian College of Surgeons has undertaken a Horizon Scanning Report to provide advice on the state of play of the introduction and use of injectable silicone biomaterial implants in the treatment of vesicoureteric reflux, faecal incontinence, periprosthetical leakage of voice prostheses, unilateral vocal fold paralysis, laryngeal cleft type I, and stomal leakage in continent diversion.

Treatment with silicone-based products for this series of indications is at various stages of development in Australia. Uroplasty Ltd. (http://www.uroplasty.com) currently produces a range of silicone products specifically for the treatment of these indications, including Macroplastique®, Bioplastique® (or PTP®), PTQ® and VOX™ implants. Each of these products consists of textured polydimethylsiloxane (PDMS) particles suspended in a bioexcretable carrier hydrogel of polyvinylpyrrolidone (PVP) (Malouf *et al.* 2001). Both Bioplastique® and Macroplastique® are listed in Australia by the Therapeutic Goods Administration (http://www.tga.gov.au/).

This Horizon Scanning report provides an assessment of the current state of development of injectable silicone biomaterial, its present use, the potential future application of the technology, and the likely impact on the Australian health care system. This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with injectable silicone biomaterial implants.

Background

Background to the Conditions

The injection of silicone-based biomaterial implants (polydimethylsiloxane, or PDMS) is a minimally invasive treatment option for vesicoureteric reflux, faecal incontinence, periprosthetical leakage of voice prostheses, unilateral vocal fold paralysis, laryngeal cleft type I, and stomal leakage in continent diversion.

Vesicoureteric reflux (VUR)

Vesicoureteric reflux, or kidney reflux, is the chronic reflux of urine from the bladder to the kidneys due to abnormal or absent vesicoureteric valves (Choe et al. 2004). These valves are located between the bladder and the ureters, and they serve to prevent the reflux of urine.

Congenital or inherited VUR cases are defined as 'primary' (Division of General Practice 2002). Secondary causes of VUR include bladder outlet obstruction, paraureteric (Hutch) diverticulum, cystitis or urinary tract infections, bladder outlet obstruction, neurogenic bladder, detrusor instability and duplicated collecting systems (Choe et al. 2004). The severity of VUR is assessed by a grading system. Grade I VUR is considered the least severe and grade V the most severe. Untreated, undetected or poorly managed VUR can result in chronic urinary tract infection, kidney scarring, hypertension, glomerulonephritis and kidney failure.

Conservative treatment of VUR focuses on the early detection and monitoring of children and close relatives of those with VUR; long-term antibiotic therapy to treat and/or prevent urinary tract infections (UTI), and behavioural therapies (high fluid intake and proper bladder control and emptying behaviours) which aim to limit and prevent kidney scarring and UTI (Choe et al. 2004; Division of General Practice 2002). Conservative treatments rely on spontaneous recovery from VUR, which requires long-term patient compliance. Up to a third of patients undergoing conservative treatment are lost to long-term follow-up and subsequently go without medical treatment (Oswald et al. 2002). There is also a risk of patients developing antibiotic resistance in cases where compliance with antibiotic therapy is difficult to monitor (Oswald et al. 2002). Because untreated or poorly managed VUR can result in serious renal damage and hypertension, conservative treatment may not be sufficient.

Surgical intervention is usually considered in severe cases of the condition. Ureteral reimplantation remains the gold standard in the surgical treatment of primary VUR. This procedure, which creates a valve at the ureterovesical junction, has achieved about a 95% cure rate in children with primary VUR (Choe et al. 2004). It is also more effective in preventing kidney damage than conservative antibiotic treatment (Choe et al. 2004).

Endoscopic treatment of VUR offers a less invasive alternative to standard surgical treatment. The aim of such treatment is to prevent reflux by adding bulk to the ureteral wall. This is achieved by injecting soft tissue bulking agents such as silicone (polydimethylsiloxane (PDMS)), chondrocytes, collagen, Teflon and more recently, Deflux (starch strands), beneath the ureteral orifice (Choe et al. 2004). Although endoscopic injections have been performed overseas for more than ten years, the optimum bulking agent for the treatment of VUR remains to be established (Division of General Practice 2002; Uroplasty 2005). For this reason, the procedure is still considered relatively experimental (Choe et al. 2004; Oswald et al. 2002).

Faecal incontinence

Faecal incontinence is a condition in which patients lose control over the passage of stool or gas, most commonly as a result of damage to the pelvic floor from childbirth (in women), anorectal surgery, or age-related nerve slowdown and muscle weakness (Fecal Incontinence 2004).

For a majority of patients, faecal incontinence is managed through conservative treatments such as diet management, pharmaceutical therapy (for example, with the drug loperamide), fibre supplements or biofeedback (Kamm 2003). However, conservative treatment may only be modestly effective, if at all, in cases of severe faecal incontinence (Fecal Incontinence 2004; Parkridge Medical Center 2004). In these cases, surgery has been another treatment option. While age-onset incontinence is less responsive to surgical treatment, surgical correction which involves sphincter repair with an overlapping sphincteroplasty can be performed in some instances, especially if the underlying cause of the incontinence is anal sphincter abnormality (Fecal Incontinence 2004). Other surgical treatments for severe faecal incontinence include graciloplasty (adjustment of the gracilis muscle to act as a neo-sphincter) and the formation of artificial anal sphincters or stomas (Kamm 2003). Radiofrequency ablation targeting the anorectal sphincter is currently being investigated as a possible technique for blocking nerve-directed sphincter relaxation (Kamm 2003).

Minimally invasive procedures have more recently been used in the minority of patients refractory to conservative treatment as an alternative to these invasive surgical techniques (Kamm 2003). The injection of PDMS, microspheres and ethylene vinyl alcohol (EVOH) copolymer resins into or around the internal anal sphincter (IAS) for the treatment of faecal incontinence are new minimally invasive procedures that attempts to restore functional continuity of the muscle by acting as a soft tissue bulking agent. The bulking effect of the silicone implants enhances the action of naturally occurring anal cushions (Kenefick *et al.* 2002).

Periprosthetical Leakage (Voice Prosthesis)

The voice prosthesis is widely used as a voice rehabilitation device following total laryngectomy and pharyngolaryngectomy (Lorincz et al. 2005). Leakage of fluids around the implanted valve continues to be a major complication. Periprosthetical leakage commonly leads to prosthesis removal or reimplantation with a larger prosthesis (Lorincz et al. 2005). While collagen implants have been used to seal leaking prostheses, the material is resorbed by the body and has a tendency to migrate (Lorincz et al. 2005). The injection of PDMS is a more recent development, which aims to prevent leakage by permanently augmenting the tissues surrounding leaking prostheses (Lorincz et al. 2005).

Unilateral Vocal Fold Paralysis (UVFP)

Unilateral vocal fold paralysis (UVFP) is a neurogenic condition involving damage or dysfunction of the recurrent laryngeal or vagus nerves which innervate the larynx. UVFP causes glottal incompetence, producing a hoarse or breathy dysphonia (Rosen 2003). It can also result in feelings of shortness of breath (due to impaired positive and expiratory pressure (PEEP)), and severe dysphagia with the risk of aspiration pneumonia, requiring more urgent treatment (Rosen 2003). The most common causes of UVFP are surgical or other medical injuries to the recurrent laryngeal or vagus nerves (Rosen 2003). Damage to the nerves can also result from malignancies, viral and upper respiratory infections and idiopathic causes (Rosen 2003). UVFP may spontaneously resolve in some cases.

Conservative treatment of the condition involves voice therapy techniques. These aim to assist patients in modifying their voice, utilising the voice use environment, and making use of proper respiratory support (Rosen 2003). Voice therapy is employed as both a stand-alone treatment and in conjunction with surgery in more severe cases (Rosen 2003).

Surgical intervention is usually only indicated where there is a serious aetiology (for example, malignancy), or where the condition has persisted for more than several months (Lowe & Hoare 2005). One surgical option in the treatment of UVFP is temporary vocal fold injection with Gelfoam, or permanent injection with Teflon, lipids or PDMS. The aim of injection is to medialise the paralysed vocal fold (Rosen 2003). Medialisation laryngoplasty is another surgical alternative. This procedure is a form of laryngeal framework surgery which involves the implantation of a silastic block through a small incised window in the thyroid cartilage (Rosen 2003). More recent laryngeal framework techniques aim to facilitate vocal fold rehabilitation by either repositioning the arytenoid cartilage, or rotating the thyroid cartilage on the cricoid cartilage (Rosen 2003).

Laryngeal Cleft Type I

Typically presenting in the neonatal period, laryngeal clefts are rare congenital malformations of the posterior cricoid lamina and the tracheo-oesophageal septum (Kubba et al. 2005). Type I laryngeal clefts are defined as supraglottic interarytenoid clefts under the classification system developed by Benjamin and Inglis (1989), which groups laryngeal clefts into four specific types according to caudal extent (Kubba et al. 2005; Ahluwalia et al. 2004). Generally, the more inferior the extent of the cleft, the more severe the condition will be (Ahluwalia et al. 2004).

In utero and neonatal gastro-oesophageal reflux, tracheomalacia, laryngomalacia and developmental delay are thought to be major causes of cleft formation (Kubba et al. 2005; Ahluwalia et al. 2004). Abnormalities during early embryonic development may also cause laryngeal clefts, and some patients may present with the condition as part of an

Opitz-Frias (G) or Pallister-Hall syndrome complex (Kubba et al. 2005; Ahluwalia et al. 2004). There is some evidence that the defect may be associated with prematurity and maternal drug and alcohol use during pregnancy (Ahluwalia et al. 2004).

Laryngeal clefts can be a life-threatening disorder. Because the trachea is not protected by the supraglottic sphincter, chronic aspiration pneumonia can occur, with the risk of progressive pulmonary compromise (Kubba et al. 2005; Ahluwalia et al. 2004). The disorder can also result in episodes of cyanosis and apnoea and a general failure to thrive (Ahluwalia et al. 2004).

Conservative treatment by close observation and the management of expectorant (with proper positioning and thickened food) is used in some cases (Ahluwalia et al. 2004). However, surgical correction of the defect is often needed when the condition is more severe. Temporary Gelfoam injections have been used to preoperatively assess the clinical severity of type I clefts (Ahluwalia et al. 2004). Tissue augmentation with a permanent soft tissue bulking agent such as PDMS is a new and largely experimental procedure in the treatment of this condition. The more traditional surgical options are endoscopic layered repair and open repair techniques (Ahluwalia et al. 2004).

Stomal Leakage in Continent Diversion for Patients with a Neurogenic Bladder

Neurogenic bladder is a disorder of bladder functioning and coordination due to the effects of neurological disorder or trauma (Costa et al. 2004). In this regard, spinal cord injury and diseases of the central nervous system (such as multiple sclerosis and spina bifida) are major causes of neurogenic bladder (Jamison et al. 2005).

The condition can result in a bladder which is either underactive (impaired contraction and emptying) or overactive (excessively fast contractions and emptying) (American Urological Association 2002). Overactive bladders can lead to urinary incontinence, while urinary retention from an underactive bladder can result in urinary tract infections and vesico-ureteric reflux, with the potential of kidney damage (American Urological Association 2002).

Continent diversion is a surgical procedure involving the use of bowel segments to create a conduit (or urinary diversion) which allows urine to bypass the bladder and empty through a catheterisable stoma in the abdominal wall (Costa et al. 2004; Guys et al. 2002). It is indicated in the treatment of neurogenic bladders where conservative treatment has failed (Costa et al. 2004). Urinary leakage from the catheterised stoma is one complication facing patients with continent diversion, often requiring additional surgical intervention to amend (Guys et al. 2002). The injection of PDMS is a new technique which aims to restore stomal continence and prevent the need for invasive corrective surgery (Guys et al. 2002).

Description of the Technology

The Procedure

Bioplastique®, Macroplastique®, PTQ®, and VOX™ PDMS implants (Uroplasty Ltd.) are permanent, non-biological soft tissue bulking agents, consisting of textured PDMS microspheres and a bioexcretable carrier gel (polyvinylpyrolidone (PVP)). While the carrier gel is excreted from the body, the silicone microspheres encourage the deposition of collagen around the implant mass, encapsulating and localising the implant and forming a permanent cartilage-like structure which augments soft tissue (Enhancement Media 2005; Shah *et al.* 2001). PDMS implant injections are typically performed as an outpatient procedure under general or local anaesthesia. The exact procedure involved in PDMS injections depends on the indication.

VUR

PDMS implants are injected into the detrusor backing beneath the ureteral orifice (Division of General Practice 2002). The aim is to create a well-defined mound of PDMS and a crescent or slit-like ureteral orifice which prevents the reflux of urine from the bladder (Aboutaleb et al. 2003a; Shah et al. 2001). For paediatric patients, a flexible 5F paediatric endoscopic needle and the Macroplastique Administration Gun are generally used (Oswald et al. 2002). The volume of PDMS injected ranges from 0.5 to 1.3 mL (Aboutaleb et al. 2003a).

Faecal Incontinence

Silicone is injected within the intersphincteric space at the location of the internal anal sphincter (IAS) defect (Tjandra *et al.* 2004). An 18 gauge, 2.5 inch needle is typically used for the procedure (Tjandra *et al.* 2004; Kenefick *et al.* 2002). The goal is to prevent incontinence by augmenting the natural anal cushions of the IAS (Kenefick *et al.* 2002).

Periprosthetical Leakage

Using a 20 gauge needle, the perivalvular tissues surrounding the voice prosthesis are injected with PDMS, augmenting and sealing the leaking fistula (Lorincz et al. 2005).

Unilateral Vocal Fold Paralysis

The injection is performed during suspension microlaryngoscopy, using a 20 gauge needle and the VOX™ delivery system (Sittel et al. 2000). The application site for PDMS injection is deeply lateral to the thyroarytenoid muscle, allowing for vocal fold augmentation and voice restoration (Sittel et al. 2000). A volume of 0.5 to 0.7 cc PDMS over the course of two to three injections is generally considered sufficient for vocal fold augmentation (Sittel et al. 2000).

Laryngeal Cleft

PDMS is injected into the anteromedial surfaces of the hypoplastic arytenoid cartilages and the anterior surface of the interarytenoid space, obliterating the cleft (Ahluwalia et al. 2004).

Stomal Leakage

The submucosa of the urinary conduit is injected with PDMS, preventing the leakage of urine from the catheterisable stoma (Guys et al. 2002).

Intended Purpose

PDMS implants were developed with the aim of providing permanent, non-resorbable soft tissue augmentation for a wide array of indications.

Indications

Macroplastique® implants (Uroplasty Ltd.) are widely used in the treatment of urinary incontinence. They are also indicated in the treatment of vesicoureteric reflux in children (Uroplasty 2005). Bioplastique® (or PTP®) implants are primarily used in the treatment of soft tissue defects (Uroplasty 2005). PTQ® implants are indicated for faecal incontinence, and VOX™ implants for the treatment of vocal fold paralysis (Uroplasty 2005).

Clinical Need and Burden of Disease

VUR

Vesicoureteric reflux mostly affects children and adolescents, although cases of adult VUR do also occur. The condition accounts for as much as 20% of renal failure cases in Australian paediatric patients, and is thought to be the cause of around 25% of all recurrent urinary tract infections in children (Department of Human Services, Victoria 2005). Approximately 80% of patients spontaneously recover from VUR within about five years, as the vesicoureteric valves tend to mature with age (Department of Human Services, Victoria 2005). There is potentially a high clinical need for bladder augmentation in severe or medically intractable cases of VUR, where PDMS injections may offer a minimally invasive alternative to the more radical ureteral reimplantation surgery. However, there are indications that Deflux® (starch beads), rather than PDMS, has become the new material of choice for such procedures in Australia (personal communication, July 2005).

Faecal Incontinence

The embarrassment of faecal incontinence sees many patients reluctant to seek medical attention, leading to an underestimation of the problem within the community (Johanson *et al.* 1996). Current estimates suggest that as many as 1 million Australian community-dwelling adults have some degree of faecal incontinence (Chiarelli *et al.* 2004). The prevalence of faecal incontinence increases with age, with an approximate 7-8 fold increase in the over 80-year age group compared with the under 30-year age group for both genders. The absolute values appear to be slightly higher in men than in women (Johanson *et al.* 1996, Chiarelli *et al.* 2004).

Although PDMS injections for faecal incontinence are becoming more accepted in clinical practice, only a small proportion of patients with faecal incontinence will need this procedure. Conservative treatments remain the primary means of treating most cases, except where the incontinence is severe and unresponsive to such treatments (Kamm 2003).

Voice prostheses

No direct information could be found regarding the extent of usage of voice prostheses in Australia, or the prevalence of leaking prostheses. Laryngeal cancer, one of the conditions which may lead to the implantation of voice prostheses, has an incidence of about 500 cases in Australia each year (Laryngectomee Association of New Sout Wales 2005). According to the Laryngectomee Association of NSW (2005), there are approximately 2000 Australians who have undergone a laryngectomy. At least some of these patients may require voice prostheses as part of their rehabilitation.

UVFP

Voice disorders (including vocal fold paralysis) presently affect 3% to 9% of the United States population (Ernest George White Society 2005). While there are no specific figures on the prevalence of UVFP in Australia, the condition tends to be more common than bilateral vocal fold paralysis. Given that vocal fold augmentation can offer more rapid recovery from UVFP, this procedure has particular application in restoring voice to terminally ill patients who would not otherwise have the opportunity to regain vocal competence (Alves et al. 2002).

Laryngeal Cleft

Of all patients with laryngeal abnormalities, the incidence of cleft larynx is about 0.4% (Porter 1994). Estimated to affect just 0.1% of the total population, laryngeal cleft is an extremely rare condition, although most patients with the condition could potentially

benefit from treatment with PDMS implants (Porter 1994). It is unlikely that there will be much clinical need for this procedure, except in the small percentage of cleft larynx cases which require surgical intervention.

Neurogenic Bladder, Continent Diversion Surgery and Stomal Leakage

The exact prevalence of neurogenic bladder is unknown. Spinal cord injury, a major cause of neurogenic bladder dysfunction, is estimated to affect about 10 000 Australians, with a yearly incidence of 300-400 cases (Cripps 2004). Multiple sclerosis, another cause of neurogenic bladder, has a prevalence of 2.5 million worldwide, while spina bifida affects approximately 1 in 1000 pregnancies (Jamison et al. 2005; Department of Human Service, Victoria 2005).

Continent diversion and urinary reservoir implantation are relatively uncommon procedures in Australia. According to the Health Insurance Commission, a total of fifty intestinal urinary conduit or ureterostomy procedures were performed in Australia from July 2004 to June 2005 (Health Insurance Commission 2005). Intestinal urinary reservoir formation (including the formation of nonreturn valves and ureteral implantation) was performed in just 29 cases over this same period (Health Insurance Commission 2005). This may suggest that the prevalence or severity of neurogenic bladder in Australia is relatively low, or that other treatments for the condition are more commonly pursued.

Stomal leakage following continent diversion is a major long-term complication of the procedure. While the exact incidence and prevalence of this complication is unclear, the overall long-term complication rate of continent diversion surgery is 33-37% (Husain et al. 2004).

Stage of Development

Uroplasty Ltd. PDMS implants have been in existence since 1989, although they are yet to be commercially available in the United States (Sittel et al. 2000). The U.S. Federal Drug Administration (FDA) has advised that further trials and testing are required before it will grant marketing approval for Uroplasty Ltd. PDMS products (Uroplasty 2005). Premarket approval may be gained by late 2007, if these trials are carried out (Uroplasty 2005). It remains unclear what indications have been submitted to the FDA for evaluation, although the Uroplasty Ltd. website does mention at least one premarket approval submission for Macroplastique® in the treatment of VUR (Uroplasty 2005).

While Uroplasty Ltd. silicone products are not yet approved in the U.S., they have been widely available since 1991 for facial tissue augmentation and urinary incontinence treatment in Europe, Canada, Australia, Latin America and the Pacific (Uroplasty 2005;

Haylen 2004). In Australia, Macroplastique® and Bioplastique® implants (including PTQ® and VOX™) are both listed by the Therapeutic Goods Administration (TGA) as 'tissue reconstructive materials' under the Australian Register of Therapeutic Goods (ARTG) numbers 53283 and 69960, respectively (TGA 2005).

Macroplastique® injections for the treatment of VUR have been practiced at an experimental level since about 1993 in Canada, Europe and the U.K.. One systematic review was published in Canada by Leonard (2002), examining endoscopic injection treatments for VUR, including an analysis of the use of Macroplastique®. A randomised controlled trial comparing Macroplastique® injections to Deflux injections was conducted in Austria by Oswald et al. (2002). Two Canadian comparative reports have been published, both carried out by Aboutaleb et al. (2003a&b). Prospective and retrospective case series publications from France (Dodat et al. 1998,2004; Kouame et al. 2003), Turkey (Muslumanoglu et al. 2003) and the U.K. (Shah et al. 2001; Van Capelle et al. 2004) have appeared in the literature. No trials of the procedure have appeared in the Australian literature. However, one safety-related report documenting a case of implant migration was published by Australian authors in 2000 (Dewan et al. 2000). There are indications that silicone is no longer widely used by Australian surgeons for the treatment of VUR, and that it may have been superseded by the starch-derivative Deflux® (personal communication, August 2005).

The use of Bioplastique® for the treatment of faecal incontinence has been reported in a number of studies in Australia and the U.K. Tjandra et al. (2004) reported the results of an Australian randomised controlled trial comparing Bioplastique injection through ultrasound guidance with injection by palpation. The procedure has also reportedly been performed on a few cases in South Australia (P. Hewett (surgeon), SA: personal communication, March 2004). In the U.K., two case series studies were conducted from St Mark's Hospital, London. Malouf et al. (2001) published a case series report on ten patients who received silicone-based injections for the treatment of faecal incontinence. Kenefick et al. (2001) subsequently published a case series report on six patients who received the same treatment in 2002. With an estimated 1 million people within the Australian population suffering from faecal incontinence (Chiarelli et al. 2004), and the simplicity of the procedure in comparison with its surgical comparators, the procedure could potentially be widely and rapidly diffusible within the Australian health system.

Augmentation of voice prostheses with Bioplastique® was first performed by Lichtenberger (2001) in the mid- to late-1990s as an ad-hoc measure. From 2002 to 2004, the procedure was subsequently trialled in a case series of seven patients (Lorincz et al. 2005). The study was conducted at the same Hungarian centre, by a team of surgeons including Lichtenberger (Lorincz et al. 2005). A separate case series from Italy (Bertino et al. 2002) and a case report from the U.K. (Rokade et al. 2003) also reported the use of Bioplastique® in patients with periprosthetical leakage. The procedure still appears to be in a relatively experimental stage overseas, and is not reported in Australian literature.

Given that voice prostheses are not a widely used technology in Australia, this procedure might not have a high potential for uptake. In the Australian clinical setting, PDMS also tends not to be considered primary therapeutic material. This is largely due to the slight risk of granulation, implant migration and extrusion which may worsen, rather than seal, tracheoesophageal fistulas (G Rees, personal communication, 2005).

Endoscopic vocal fold augmentation was first advanced in 1911 by otolaryngologist Brünings, who attempted to treat vocal fold paralysis with paraffin oil injections (Sittel et al. 2000). The use of PDMS injections in laryngology was first documented in the literature in 1993. Long-term results on the use of Bioplastique® in vocal fold augmentation were not reported until recently, following the publication of two case series in Germany and the U.K. (Sittel et al. 2000; Alves et al. 2002). No Australian studies have been published as yet. Bioplastique® injections appear to be at an experimental stage overseas, and may remain so while the optimum materials for vocal fold augmentation are still in question. There is some thought among the medical community that the vibratory qualities of silicone implants may make it a more useful substance than hard plastics (such as those used in medialisation thyroplasty), although there is no clinical evidence to support this (G Rees, personal communication, 2005). While the procedure has potential for wide diffusion in Australia (given its minimally invasive nature and its rapid recovery outcomes compared to conservative treatment) PDMS is not presently considered an ideal material in the treatment of UVFP, due to both the small risk of granuloma formation and implant migration, and the general lack of high quality evidence of its safety and effectiveness in treating this indication (Rees, personal communication, 2005).

The only documented report of Bioplastique® in the treatment of laryngeal cleft type I was published in the U.K. in a case report by Ahluwalia *et al.* (2004). Given that cleft larynx is an extremely rare condition, it is unlikely that this indication will contribute much to the diffusion of PDMS technology in Australia.

There are similarly few studies on the use of PDMS injections for the treatment of stomal leakage. Only one study exists in the literature, published in France by Guys et al. (2002). Again, like prosthesis augmentation, the risk of granuloma formation worsening the state of a fistula has prevented silicone implants from becoming ideal treatment materials for this indication in Australian clinical practice (G Rees, personal communication, 2005). Moreover, because continent diversion surgery is not a popular procedure in Australia, future utilisation of this technology is unlikely to be high.

International Utilisation of PDMS Implants for Indications Covered in this Report

COUNTRY	LEVEL OF USE		
	Trials underway	**Limited use**	**Widely diffused**
U.K/Europe	Voice prostheses; UVFP; laryngeal cleft; stomal leaks	VUR; faecal incontinence	
Canada		VUR	

Treatment Alternatives

Existing Comparators

VUR

- **Behavioural modifications** (voiding regimen, monitored fluid intake, biofeedback)
- **Pharmaceutical therapy** (antibiotic prophylaxis; anticholinergic medications)
- **Surgery** (ureteral reimplantation)
- **Endoscopic injections** (Deflux® (beads of starch), bovine collagen, Teflon, chondrocyte injections)
- **Alternative surgery** (intravesical reimplantation; extravesical (Lich-Gregoir) reimplantation; extravesical detrusorrhaphy (Hodgson-Zaontz))

Faecal Incontinence

- **Surgery** (sphincteroplasty, direct repair of anal sphincter, graciloplasty, artificial anal sphincter and stomas)
- Delivery of **radiofrequency energy (ablation)** to the anal sphincter
- **Endoscopic injections** (microspheres and EVOH)

Periprosthetical Leakage

- **Replacement or removal** of prostheses
- **Endoscopic injections** (collagen)

UVFP

- **Voice therapy**
- **Surgery** (medialisation laryngoplasty or thyroplasty)

- **Endoscopic injections** (Teflon, collagen, gelfoam, autologous fat, fascia)

Laryngeal Cleft Type I

- **Conservative** (observation and management of expectant)
- **Surgery** (endoscopic and open repair)

Stomal Leakage

- **Surgical revision** of continent diversion

Clinical Outcomes

Effectiveness

VUR

Long and short-term evidence for the efficacy of Macroplastique® in treating VUR comes from, one RCT (Oswald *et al.* 2002), two comparative non-randomised studies (Aboutaleb 2003a and b), one basic systematic review of six case series studies (Leonard 2002), six case series (Dodat *et al.* 1998; Dodat *et al.* 2004; Kouame *et al.* 2003; Muslumanoglu *et al.* 2003; Shah *et al.* 2001; Van Capelle *et al.* 2004) and one case report (Dewan *et al.* 2000).

Needle size was not widely specified in the studies, with the exception of Oswald *et al.* (2002), who reported the use of a 5F paediatric endoscopic needle in administering Macroplastique® injections. The volume of Macroplastique® used for each patient varied. Oswald *et al.* (2002) administered a mean of 0.8 ml (range 0.6 to 1 ml); Aboutaleb *et al.* (2003a and b) 0.5 to 1.3 ml; Dodat *et al.* (1998) 0.25 ml; Kouame *et al.* (2003) 0.1 to 0.5 ml; Muslumanoglu *et al.* (2003) a mean of 1.26 cc (range 0.5 to 2.6 cc), and Van Capelle *et al.* (2004) a mean of 0.6 ml (range 0.2 to 2.0 ml).

'Cure' or 'success' was defined in most studies as either no reflux or grade I reflux, with no *de novo* hydronephrosis. The postoperative presence of persistent reflux, an increase in reflux grade, contralateral reflux, UTIs, voiding dysfunction and other complications (such as implant migration) requiring repeat injections or conversions to extravesical reimplantation surgery negatively affected the cure or success rates.

Cure and success rates

Oswald *et al.* (2002) compared patients who received a single Macroplastique® injection with those who received a single injection of Deflux® in their RCT study. All patients

underwent the procedure in a day surgery setting as had been planned. Reflux was cured in 50/58 (86%) ureteral units in the Deflux® group, and in 40/56 (71%) ureteral units in the Macroplastique® group at three months follow-up. There was no statistically significant difference between the groups (p=0.0536). The response rate following injection decreased to 76% in Deflux® patients and 63% in Macroplastique® patients.

In their comparative non-randomised study, Aboutaleb *et al.* (2003a) compared patients who received a single injection of Macroplastique® with patients who underwent extravesical reimplantation surgery. An overall cure rate of 81% (p=<0.0001) at three months follow-up and 92% (p=0.008) at last follow-up (an average of 12 months) was reported in the Macroplastique® group. Reimplantation was required in 1/180 (6%) patient who had been treated with Macroplastique®, due to the patient's decision not to undergo a repeat injection. The overall cure rate for patients who underwent extravesical reimplantation was higher than that achieved in Macroplastique® patients, with 96% (p=<0.0001) of surgical patients cured at three months, and 99% (p=0.008) at last follow-up. The cure rate for grades I and II VUR in the Macroplastique® group was 83% at three months, improving to 93% at last follow-up. In the surgical group, the cure rate for grades I and II improved from 96% to 100% at last follow-up. Grade III VUR cure rates improved from 78% in Macroplastique® patients and 95% in surgical patients at three months follow-up, to 88% in Macroplastique® patients and 98% in surgical patients at last follow-up.

Some patient overlap with Aboutaleb *et al.* (2003a) may have been present in Aboutaleb *et al.* (2003b). In this retrospective comparative study, 15/22 (68%) patients who received a single Macroplastique® injection were cured at three months follow-up, compared to 42/44 (96%) patients who underwent extravesical common sheath reimplantation (ECSR). At last follow-up, 16/22 (82%) Macroplastique® patients and 43/44 (98%) ECSR patients were cured. A second injection was required in 2/15 (13%) Macroplastique® patients, which cured reflux in 1/15 (7%) patient. The overall cure rate for ECSR patients was significantly higher than that achieved in the Macroplastique® group (p=<0.04).

Leonard (2002) reviewed two initial European case series studies (Buckley 1993; Dodat 1994) which reported an 80-90% success rate after a single Macroplastique® injection. One Canadian case sereis (Hafez *et al.* 2001) reviewed by Leonard (2002) reported a successful cure in 76% of patients (81% of ureters) following one injection. The cure rate improved to 84% of patients (90% of renal units) after a second injection, at a follow-up of twenty four months. The author noted that there was a general lack of long-term efficacy follow-up data in the literature; although there was mention of two case series (Harriss *et al.* 1997; Sheriff *et al.* 1997) which had reported 'successful treatment' of VUR at up to three years follow-up.

In their case series study, Dodat *et al.* (1998) reported the successful resolution of VUR in a total of 452/454 (99.6%) ureteral units treated with Macroplastique® injections. At six weeks follow-up, 84% of all ureteral units had been cured after a single injection, 271/297 (98%) were cured after one or two injections, and 223/239 (93%) children with primary VUR were cured (195/239 (82%) after one injection and 28/239 (12%) after two injections). Dodat *et al.* (1998) noted that in comparison to the cure rate for unilateral reflux and primary reflux, the cure rate for secondary VUR was lower: just 51% of ureteral units were cured after one injection, and 61% after two injections (18/24 (75%) children were cured, 15/18 (83%) after one injection and 3/18 (17%) after two injections). Of this sub-group of patients, 6/24 required a conversion to secondary surgery. The authors hypothesised that these poorer results may have been attributable to the large opening of the refluxing ureters in these patients, and the narrow width of the submucosal layer. When reflux only affected the lower renal pelvis, the results were worse, with only 52% of cases cured after a single injection, and 58% after two injections.

Out of a subset of 11 patients in the Dodat *et al.* (1998) case series who had initially presented with persistent reflux caused by Teflon injections, 90% were cured after one injection and 100% after two injections. Similar results were observed in eight patients who had developed persistent reflux following surgical reimplantation, with a 79% cure rate following a single Macroplastique® injection and 100% of patients cured following two injections. All patients with a comorbid neurogenic bladder were cured following one or two Macroplastique® injections. However, in three patients who had developed VUR following a valve resection, only two (67%) were cured after receiving Macroplastique® injections.

The Dodat *et al.* (2004) retrospective case series reported similar results on a long term follow-up basis, possibly with some patient overlap from the Dodat *et al.* (1998) study. Administering plain or bilateral injections of Macroplastique®, complete cures were achieved in a total of 309/389 (79%) cases at a minimum of five to seven years follow-up. Of these, 286/389 (74%) were cured after a single injection of Macroplastique®, 21/389 (5%) after two injections, and 2/389 (0.5%) after three injections. Surgical reimplantation was used to treat persistent or reappearing VUR in 80/389 (21%) patients, with endoscopic treatment failing in 32% of grade I cases and 12% of grade II. The long-term cure rate (between five and seven years) was reported as 78%, with 461/590 ureteral units not requiring a conversion to surgery following treatment with Macroplastique®. Unlike the earlier case series by Dodat *et al.* (1998), there was no reported difference in cure rates between primary and secondary reflux. The authors commented that at a follow-up of five to seven years, the cure rate of high grade reflux cases (III, IV and V) was higher with the use of Macroplastique® injections than other (presumably surgical) treatments. However, it could not be established whether the cure rate of low VUR grades (I or II) using Macroplastique® was higher than the rate of spontaneously resolving cases of low grade VUR.

Of 477 children treated with Macroplastique® injections in the Kouame *et al.* (2003) retrospective case series, 354 (74%) were cured, including 167 cases of bilateral reflux and 180 cases of unilateral reflux. The authors observed a significant difference between the cure rate of bilateral (88%) and unilateral (63%) reflux (p=<0.05). Treatment failed in 123/477 (26%) patients. Of these cases, 58 (47%) were converted to surgery (technique of Cohen), 36/58 (62%) with unilateral VUR and 22/58 (38%) with bilateral VUR. In the patients followed up (follow-up period not specified by the authors), two required a second injection, one of which was successful, and one of which failed, requiring surgical correction.

In the Muslumanoglu *et al.* (2003) retrospective case series, reflux was cured in 25 ureters (69.4%) following the first injection, and in a further six ureters after a second injection. A total of 31/36 (86%) ureters were cured after one to two injections.

The case series study by Shah *et al.* (2001) reported the successful cure of VUR in 16/22 (73%) ureters after a single injection, and in 1/22 ureters (5%) after a second injection. VUR could not be cured with Macroplastique® injections in 3/22 (14%) ureters.

In their multicentre retrospective case series, Van Capelle *et al.* (2004) reported an overall success rate of 84% in their Glasgow subset (n=71) and 77% (n=94) in their Zwolle subset. The overall cure rate for both groups was 82% of patients, with 71/311 (23%) ureters requiring re-treatment and 31/311 (10%) ureters and 7/195 (7%) patients requiring ureteric reimplantation. Contralateral reflux was reported in 7/311 (2%) ureters. Of these patients, three grade I patients had no further surgical treatment, two grade II patients were cured, and two grade III patients were cured after further endoscopic treatment. For the Glasgow subset, the cure rate at three months was 58% after the first injection, which improved to 80% at a mean follow-up of 6 (1 to 9) years. It should be noted that the Glasgow patients received additional treatments, resulting in a higher rate of cure at 12 months follow-up compared with three months follow-up. The overall success rate for this group was 86%. The authors noted that it was only in the Glasgow group that third (11 ureteral units) and fourth (3 units) implantations were required. In the Zwolle subset, the cure rate at three months was 80% after the first injection and 73% at twelve months follow-up. The cure rate was 68% and the success rate 79% after a mean follow-up of 4.1 (range 0.25 to 9.2) years.

Changes in reflux grade

In Oswald *et al.* (2002), two patients (one in each group) who initially had grade III reflux decreased to grade II following the procedure. Conversely, there was an increase from grade I reflux at three months follow-up (n=7) to grade II reflux at twelve months follow-up in one Macroplastique® patient (14%) and two Deflux® patients (29%). Aboutaleb *et al.* (2003b) reported an improvement in VUR from grade III to I after the

first Macroplastique® injection in 1/15 (7%) patient. Reflux was downgraded after one or two injections in 2/22 (9%) ureters in Shah *et al.* (2001).

Contralateral and persistent reflux, voiding dysfunction and UTIs

A repeated bilateral injection was required for the treatment of persistent reflux in 3/34 (9%) Macroplastique® patients and 2/38 (5%) Deflux® patients in the Oswald *et al* (2002) RCT.

In the Aboutaleb *et al.* (2003a) study, persistent reflux was reported in 21/108 (19%) ureteral units after a single Macroplastique® injection. At last follow-up (range 6 to 24 months), this had resolved in 11 units and was downgraded to grade I in three units. No cases of contralateral reflux were reported at follow-up in Macroplastique® patients. In the surgical group, persistent reflux was seen in 7/166 (19%) ureteral units at three months, resolving spontaneously at last follow-up in all except three cases (two ipsilateral, one contralateral). Contralateral reflux was noted in 11% (p=0.06) of surgical patients at three months and in 2% (p=1.0) at last follow-up.

Preoperative voiding dysfunction was seen in 18/108 (24%) Macroplastique® patients in Aboutaleb *et al.* (2003a). Persistent reflux was noted in 9 of these 18 patients postoperatively. Voiding was returned to normal and reflux was resolved in 4/9 (44%) patients following behavioural modification treatment. No postoperative cases of *de novo* voiding dysfunction were observed in this group. In the surgical group, preoperative voiding dysfunction was recorded in 20 patients (19%). All of these patients were provided with bladder retraining and anticholinergic drug treatment prior to surgery, and they continued to participate in behavioural modification treatment at last follow-up. Postoperatively, none of these patients developed persistent reflux, although *de novo* voiding dysfunction was seen in 6/86 (7%) patients, none of whom had UTI or persistent reflux. Urethral catheterisation was required less than two weeks after bilateral reimplantation in two female patients (3%) who had experienced transient urinary retention. One of these patients (50%) had a preoperative medical history of voiding dysfunction.

Postoperative contralateral grade II reflux was observed in 1/15 (7%) group one patient (one moiety), but had resolved by last follow-up in Aboutaleb *et al.* (2003b). Persistent low grade reflux was also observed in two group two ureteral units, resolving after six months in one unit, while continuing to persist in the other. Contralateral reflux appeared postoperatively in four group two ureteral units (17%), resolving spontaneously by last follow-up.

There were 22/297 (7%) cases of persistent reflux following one or two Macroplastique® injections in the Dodat *et al.* (1998) case series. Depending on the severity of reflux grade, these cases were either treated surgically or supervised for signs of infection. At last follow-up, three grade I and one grade II patients remained under medical supervision, while two grade I and three grade II patients had successfully undergone surgical reimplantation.

At medium-term follow-up (approximately twelve months), VUR had returned in 14/161 (9%) children (23/253 (9%) ureteral units) in the Dodat *et al.* (1998) case series study. Macroplastique® was re-administered in ten patients one year following initial treatment, and six patients had undergone surgical reimplantation. At two years follow-up, sixty children were re-examined with renal echography. All of these patients showed signs of normal bladders.

Contralateral VUR was seen in 7/96 (7%) patients who received a bilateral injection of Macroplastique®, and in 17/189 (9%) patients who received a unilateral injection in Kouame *et al.* (2003). The authors noted no statistical relationship between *de novo* contralateral reflux and the use of either bilateral or unilateral injections in the treatment of unilateral VUR.

Twelve months following the first injection in Shah *et al.* (2001), 1/15 (7%) patient developed bilateral VUR, which was successfully treated with a second injection. Persistent bilateral reflux developed in 1/15 (7%) patient four years after the first injection, which was also successfully resolved with a second injection. Preoperative renal function deterioration was noted in 3/15 (20%) patients. Renal function did not improve in these patients following treatment with Macroplastique®. A clam ileocystoplasty with reimplantation of the right ureter was required in 1/15 (7%) patient with poorly controlled high intravesical pressures and persisting low grade reflux post treatment with Macroplastique®. This treatment successfully cured the persistent reflux. The authors also noted that the ureteric orifice was difficult to identify in three patients with grossly trabeculated, thick-walled bladders, making the procedure problematic to perform in these cases. At last follow-up, two of these patients were awaiting a second injection after failing to respond to the initial injection. A history of bladder stone formation was noted in one of these problematic patients.

Implant migration

Dewan *et al.* (2000) reported on the single case of a patient treated for bilateral grade III VUR with a 0.7 ml injection of Bioplastique®, to be followed two months later with surgical reimplantation. When the patient presented for surgery, an enlarged pelvic lymph node was discovered. An excision was performed on the lymph node, and a biopsy of the PDMS implant was taken from the ureteric orifice. The excised node revealed the presence of migrated silicone particles. Most of the particles were <50 μm, despite the

normal size of Bioplastique® particles being reported as 100-400 μm. It was concluded that the smaller particle size may have facilitated particle migration, but that the exact mechanism of migration was unknown.

Faecal Incontinence

Short and long-term efficacy data on the use of injectable silicone biomaterial for the treatment of faecal incontinence exist from one randomised controlled trial (RCT) (Tjandra *et al.* 2004) and two cases series studies (Kenefick *et al.* 2002, Malouf *et al.* 2001).

Needle size and injected volume varied, depending on the study. Tjandra *et al.* (2004) administered four 2.5 ml injections of Bioplastique® at the affected IAS site, using an 18 gauge 2.5-inch needle. Kenefick *et al.* (2002) used an 18-gauge 2.5-inch needle to administer three 2 ml injections of Bioplastique, corresponding to the positions of the anal sphincter. The needle size used in the case series by Malouf *et al.* (2001) varied from 18-gauge 2.5-inch to 18-gauge 1.0-inch.

Efficacy outcome measures included Wexner's continence scores[1], visual analog quality of life scores, patient diaries and SF-12 or SF-36 health survey questionnaire results; maximum anal resting pressure and maximum squeeze pressure, pudenal nerve terminal motor latency (PNTML) and endoanal ultrasound results.

Continence scores

The Tjandra *et al.* (2004) RCT compared Bioplastique® injections using endoanal ultrasound guidance (n=42) with injections using palpation (n=40) for the treatment of faecal incontinence caused by internal anal sphincter (IAS) dysfunction. Although Tjandra *et al.* (2005) reported a significant improvement in faecal incontinence outcomes for both groups following Bioplastique® injections, a significantly greater improvement was seen in patients with endanal ultrasound guidance. At three months follow-up, the proportion of ultrasound patients with >50% improvement in Wexner's continence scores was significantly greater (p=0.014) than in the palpation group (69% compared to 40%, respectively).

In Kenefick *et al.* (2002), faecal incontinence scores improved significantly from a median of 14 (range 11 to 20) before the procedure to 8 (range 6 to 15) after the procedure. Migration of the implant away from the anal canal was identified in the one patient who showed no improvement in continence scores.

[1] Wexner's score: 0= perfect continence; 20= complete incontinence

Malouf *et al.* (2001) reported a marked improvement in anal sphincter function at six-week follow-up in 6/10 (60%) patients in their case series. Three of ten (30%) patients did not improve after one or two injections and were found to have had a leakage of product from the injection site. One of the 10 (10%) patients improved after a second injection.

Quality of life assessments

Quality of life visual analog scores[2] (VAS) also showed a significant improvement at follow-up in Tjandra *et al.* (2004), but with the ultrasound patients demonstrating a more significant change (p=<0.001) than the palpation group (p=0.07). The proportion of patients with >50% improvement in VAS scores was 93% in ultrasound patients and 92% in palpation patients (p= <0.001). Significant improvements in SF-12 physical and mental health scores were seen at a median of six months follow up in the ultrasound group (*P*=0.003; p=0.004 respectively), but no significant improvements were found in the palpation patients at six months (p=>0.05*)*.

The Kenefick *et al.* (2002) case series reported a marked improvement in symptoms and patient satisfaction in 5/6 (83.3%) patients. Quality of life scores showed significant improvement, with physical function improving from a median of 26 (range 5 to 33) to 79 (range 25 to 100) (p=0.02) and social function improving from 10 (range 5 to 37) to 100 (range 50 to 100) (p=0.02).

In Malouf *et al.* (2001), 7/10 (70%) patients reported no relief of symptoms and 3/10 (30%) reported an improvement of symptoms at six-months follow-up.

Maximum anal resting pressure and squeeze pressure

In Tjandra *et al.* (2004), maximum anal resting pressure increased by 89% in ultrasound patients, improving significantly from a median of 23 (range 10 to 51) mmHg at baseline to 38 (range 21 to 62) mmHg at a median of six months follow-up (p=<0.01). Improvements in maximum anal resting pressure were less significant in palpation patients, with a 42% increase in maximum anal resting pressure (p=<0.01), increasing from a median of 27 (range 10 to 47) mmHg at baseline to 35 (range 25 to 55) mmHg at a median of six months follow-up. Both groups experienced a minor (10%) improvement in maximum squeeze pressure at six months.

Median resting anal pressure in Kenefick *et al.* (2002) improved from 46 cm H_2O to 75 cm H_2O (p=0.03) and squeeze pressure also had significantly improved from 98 cm H_2O to 142 cm H_2O (p=0.01).

[2] Visual analog scale: 1-10, 10 being best

Pudenal nerve terminal motor latency

Tjandra *et al.* (2004) reported unilaterally or bilaterally prolonged pudenal nerve terminal motor latency (PNTML) in 26/42 (62%)ultrasound patients, and 22/40 (55%) palpation patients. For both groups, improvements in continence and quality of life scores appeared to be independent of PNTML.

Endoanal ultrasound results

Endoanal ultrasound at one month follow-up in Tjandra *et al.* (2004) confirmed that all implants remained at the injection sites. By six months follow-up, endoanal ultrasound in 66 patients showed that the IAS and intersphincteric space had become more hyperechoic and the PDMS implants were less globular in form.

Periprosthetical Leakage

Short and long-term efficacy data on the use of PDMS injections for the treatment of periprosthetical leakage come from one case series study (Lorincz *et al.* 2005) and two case reports (Rokade *et al.* 2003; Bertino *et al.* 2002).

The needle gauges and volumes injected were not specified by the authors. Successful prevention of leakage was regarded as the primary outcome measure.

In their case series study, Lorincz *et al.* (2005) performed voice prosthesis augmentation with Bioplastique® injections in seven patients who had undergone total laryngectomy. At two-year follow-up, all procedures were deemed successful in either stopping leakage or reducing it to a minimum level. Four out of seven (57%) patients only required a single injection to achieve these results, while 2/7 (29%) required a repeat injection four to six months later, due to further enlargement of the leaking fistula. In 1/7 cases (14%), more than three consecutive injections were needed. The reasons for this were not stated. It was noted that the tissue-adhesive effect of Bioplastique® appeared to improve irradiated tissue in patients who had received radiotherapy in the past.

Rokade *et al.* (2003) published a case report documenting the treatment of two patients with chronic leakage surrounding Provox 2 voice prostheses. Fistula leakage in these patients could not be resolved by either inserting valves of different sizes, or by inserting a feeding tube through the fistula. Injection of Bioplastique® was considered as a 'last resort'. Using a 20 gauge needle, 0.4 ml of Bioplastique® was injected at the two, six and ten o'clock positions surrounding the fistula. In addition to PDMS injections, the valves were removed and replaced with Provox valves of a different size. No further leakage was found in patient one at 11 months follow-up, and no leakage was reported for more than eight months in the second patient.

In the case report by Bertino *et al.* (2002), three patients with Provox 2 voice prostheses were treated with Bioplastique® injections after enduring fistula leakage for about four months. Fluid-tightness and fistula size remained stable at approximately five months follow-up, and the augmentation was well-tolerated by the patients.

Unilateral Vocal Fold Paralysis (UVFP)

Data on the effectiveness of injectable silicone in the treatment of UVFP are available from one prospective case series (Alves *et al.* 2002) and one retrospective case series study (Sittel *et al.* 2000).

Needle size and injectable volume were not reported by the authors, with the exception of the Sittel *et al.* (2000) retrospective case series, which assessed ten patients with UVFP who had been treated with two to three injections of 0.5 to 0.7 cc Bioplastique®. Of these ten patients, seven were available for laryngeal evaluation at a mean follow-up of 88.4 months (range 69 to 102).

Outcome measures of the studies included voice scores[3] and the voice handicap index, mean maximum phonation time (MPT), quality of life and degree of glottic closure.

Voice score and voice handicap index

Alves *et al.* (2002) reported the use of Bioplastique® injections in 16 patients with UVFP resulting from terminal cancer. Outcomes were assessed by two independent observers (an otolaryngologist and a speech therapist) blind to patient treatment. It should be noted that statistical significance was not reached for three and six months follow-up, given that only five patients were available for follow-up at three months and one patient at six months. No significant difference was found between the two observer assessments of voice score. Prior to treatment, the mean voice scores were 3.8 (observer one) and 3.7 (observer two). At one month follow-up, voice scores had significantly improved to 1.9 and 2.2 (observer one and two, respectively) ($p=<0.001$). Voice scores continued to improve to a mean of 2 and 1.75 at three months, and to a score of 2 at six months follow-up. The mean total voice handicap index (VHI) decreased from a baseline of 74.4 to 20.9 at one month ($p=<0.001$). At three and six months, VHI was 21.8 and 4 respectively.

Maximum phonation time

[3] Voice score: 1=normal voice with no 'breathiness'; 5=no voice or whisper only

MPT in Alves *et al.* (2002) significantly improved (p=<0.0001 compared to baseline) from a baseline of 3.2 seconds to 7.8 seconds at one month, remaining constant at three months. In the one patient studied at six months follow-up, the reported MPT was five seconds.

Sittel *et al.* (2000) reported a mean maximum phonation time of 16.1 seconds at follow-up. All seven patients reported that their voice had improved after injection laryngoplasty, and that the improvement remained at the time of follow-up evaluation.

Quality of life

Of the eight sub-groups comprising the SF-36 quality of life questionnaire, significant improvements were seen at one month follow-up in social functioning (p=<0.01), mental health (p=<0.05) and emotional functioning (p=<0.001) in Alves *et al.* (2002)

Glottic closure

Five out of seven (71%) patients in the Sittel *et al.* (2000) study had complete glottic closure, while one patient (14%) had a significant glottic gap. The authors hypothesised that under-correction was the underlying cause of the persisting gap. In one patient (14%), the surface of the augmented vocal fold was irregular, which was thought to be due to the superficial placement of the implant and inadvertent injection of PDMS particles in the lamina propria of the vocal fold. Patients with complete glottic closure were assessed as having fair to near-normal voices at follow-up. Voice quality was poor, although usable, in the patient with persistent glottic insufficiency. The outcome was better than expected in the patient with an irregular vocal fold surface, who was assessed at follow-up as having a 'fair' quality of voice.

Laryngeal Cleft Type I

Evidence for the efficacy of injectable PDMS in the treatment of laryngeal cleft type I comes from one case report by Ahluwalia *et al.* (2004). The case report documented a 17 year old woman who had received two separate injections of Bioplastique® following initial endoscopic repair of a type I laryngeal cleft at seven years of age, and a trial endoscopic injection of Pentastarch at 17 years. The patient made a rapid recovery after the first Bioplastique® injection, speaking with an audibly louder voice. However, the first injection failed to completely correct the laryngeal defect. Further defect closure and voice improvement were attained after the second injection of Bioplastique®, with no signs of odynophagia or dysphagia. At twelve months follow-up, the patient had maintained a strong voice. Near complete closure of the posterior glottic chink was confirmed by videostroboscopy.

Stomal Leakage

Efficacy data on the use of Macroplastique® for the treatment of stomal leaks come from a single case series published by Guys *et al.* (2002). Six patients with stomal leakage after continent diversion received injections of Macroplastique®. All patients were able to resume intermittent catheterisation without delay following the procedure. In one patient (17%), a second injection was required three months after the initial injection. Restored stomal continence was achieved in four out of six (67%) patients at a mean of eleven months (range 8 to 18) follow-up.

Safety

VUR

Leonard (2002) documented local inflammatory reaction in a French study (Bertschy *et al.* 2001) comparing Teflon and Macroplastique® injections. It was noted that a more 'intense' reaction was observed in patients receiving Macroplastique®. The authors hypothesised that this may have been due to the break down of Macroplastique® implants into small 6 μm particles by the action of macrophages, allowing for implant migration.

No intraoperative complications, adverse reactions or toxicity were reported by Oswald *et al.* (2002). A mild, temporary dilation of the collecting system was observed in twenty three (40%) ureterorenal units following Macroplastique® injection, and in twelve (21%) ureterorenal units following Deflux injection. One patient developed contralateral *de novo* grade I reflux which did not need treatment. Afebrile postoperative urinary tract infection was seen in 6/38 (16%) patients who received Macroplastique® injections, and in 4/34 (12%) patients who received Deflux injections.

Aboutaleb *et al.* (2003a) reported mild *de novo* hydronephrosis in three renal units (3%) in patients receiving Macroplastique® injections, and in 17 (11%) renal units in patients receiving ureteral reimplantation. Of these group two patients, 12 cases of hydronephrosis were mild and five were considered moderate. The condition had resolved by follow-up in all Macroplastique® patients, and in seven ureteral reimplantation patients. All remaining cases of hydronephrosis were stable at follow-up, requiring no further treatment. There was a significant difference in the incidence of hydronephrosis between the two groups ($p<0.02$).

No urinary tract infections (UTIs) were observed in Macroplastique® patients in Aboutaleb *et al.* (2003a), however two male and ten female (11%; $p=0.0002$) reimplantation patients experienced UTI following ureteral reimplantation. Four of the

twelve infections (33%) were febrile, and nine infections (75%) were accompanied by voiding dysfunction. None of the patients with infection were on clean intermittent catheterisation. No further complications were reported in the Macroplastique® group, although suprapubic fluid collection was found in two reimplantation patients, and a wound seroma in another reimplantation patient.

Aboutaleb *et al.* (2003b) found no complications, and no cases of *de novo* hydronephrosis or UTI in patients who received Macroplastique® injections (group one). *De novo* hydronephrosis was found in two ureteral units following ECSR surgery (group two). The cases were mild and resolved by one year follow-up. Postoperative UTIs were seen in 4/34 (12%) group two patients. No cases of haematuria, postoperative urinary retention or bladder spasms were reported in group two. There was no association between post-ECSR complications and VUR grade.

In Dodat *et al.* (1998), two urinary infections and one case of pyelonephritis were reported in patients who received Macroplastique® injections. Unilateral blockage was noted in two out of 454 (4%) treated refluxing ureters. One case (50%) was likely caused by a megaloureter obstruction which had not previously been diagnosed. Ureteral reimplantation was subsequently performed three and six months after the endoscopic injections in these two patients. A case of lumbar pain stemming from hypotonia of the ureter was also documented in one patient. The condition resolved following treatment with non-steroidal anti-inflammatory drugs (NSAIDs).

Dodat *et al.* (2004) reported 19 immediate complications out of 464 patients (4%). Notably, there was one case of delayed micturition resumption, two cases of pyelonephritis which required medical treatment, and two transitory haematurias which were thought to have resulted from haemorrhage at the puncture sites. Complications such as stenosis, ureteric stricture and anuria were not encountered.

No complications or safety issues were reported by Kouame *et al.* 2003.

Muslumanoglu *et al.* (2003) reported persisting VUR in one patient who had been administered two injections of Macroplastique®. The child developed pyelonephritis and was treated surgically. Extravasation of the Macroplastique® implant occurred in one patient. No complications resulted and the incident was corrected with a second injection. There were no reports of obstruction or implant migration. One case of postoperative grade two *de novo* contralateral VUR was noted in one patient (4%), who remained under close observation at the conclusion of the study.

Shah *et al.* (2001) reported no cases of postoperative UTI or obstruction. In 13/15 (87%) patients, laboratory proven urinary tract infections were 'reduced' following endoscopic treatment. The extent of reduction and the statistical significance of this finding were not reported by the authors.

Erosion of Macroplastique® implants was seen in 2/195 (1%) patients in the Van Capelle *et al.* (2004) study. Postoperative UTIs were reported in 14/94 (15%) patients from the Zwolle subset (11 with persistent VUR), and in 18/101 (18%) patients from the Glasgow subset (six with persistent VUR). Ureteric obstruction was noted in a total of 4/311 (2%) ureters.

In Dewan *et al.* (2000), migration of silicone particles to a pelvic lymph node was observed in one paediatric patient. While some of the particles were 5-15 μm, others ranged up to 100 μm in size. The exact mechanism of the migration was unknown.

Faecal Incontinence

Tjandra *et al.* (2005) reported no cases of implant migration, erosion, fistula formation or infection. No constipation was reported, however 2/42 (5%) ultrasound patients and 4/40 (10%) palpation patients required simple oral analgesic treatment after experiencing minor discomfort at injection sites. In 1/40 (3%) ultrasound patients, anal discomfort persisted for six weeks post-procedure. Digital rectal examination and endoanal ultrasound revealed that the implant was located more superficially than intended.

No episodes of infection or leakages were reported by Kenefick *et al.* (2002). Reportedly no patient experienced severe pain or constipation and erosion of the implants was not encountered. Malouf *et al.* (2001) reported leakage and infection resulting in ulceration and pain in five out of the first six patients (83%) who received the procedure using the 1-inch needle. Pain and infection resolved in all patients. No complications or adverse events were seen with the use of the 2.5-inch needles.

Periprosthetical Leakage

Lorincz *et al.* (2005) recorded no complications in previously irradiated tissue augmented with Bioplastique®, although it was recommended that a minimum of 12 months is maintained between total laryngectomies and the implantation of PDMS (Lorincz *et al.* 2005). Rokade *et al.* (2003) similarly reported no complications. No sign of granuloma formation, inflammation or other pathology was noted by Bertino *et al.* (2002).

UVFP

No safety issues were reported by Alves *et al.* (2002). Sittel *et al.* (2000) reported no complications related to Bioplastique® and no cases of granuloma formation, infection or other pathology.

Laryngeal Cleft Type I

Ahluwalia *et al.* (2004) reported no laryngeal discomfort, dysphagia or odynophagia following either the first or second injections of Bioplastique®.

Stomal Leakage

Guys *et al.* (2002) reported no complications during or subsequent to treatment.

Potential Cost Impact

Cost Analysis

There are no studies available in the literature which might shed light on the cost-effectiveness of PDMS implants as an endoscopic treatment. There is some, albeit limited, evidence to suggest that endoscopic treatment with PDMS injections might be cheaper than the more invasive surgical alternatives which are currently used to treat a majority of the indications covered in this report. However, it should be noted that the present cost of PDMS per procedure has been prohibitive enough to limit capacity for independent, non-company funded research into the safety and efficacy of this material (N Rieger, personal communication, 2005). Another issue to consider is the general lack of evidence on the long-term efficacy of PDMS implants.

Although the costs associated with the use of PDMS products in Australia are not currently listed on the Medicare Benefits Schedule (MBS), Brennan (2004) and Rieger (personal communication 2005) cite the injection of PDMS in the treatment of stress urinary incontinence and faecal incontinence as presently costing around $2000 per 2 ml injection in Australia. This gives an indication of the cost of performing PDMS augmentation in cases of VUR and stomal leakage. The reimbursement fee for the injection of vocal cords with Teflon®, collagen or fat is listed by the MBS (Medicare Benefits Schedule item number 41870) at $385.95 (Australian Department of Health and Ageing 2005). Similarly, the MBS reimbursement fee (schedule item number 52321) for inserting a non-biological implant in the oral or maxillofacial region for contour reconstruction is listed by the MBS at $402 (Australian Department of Health and Ageing 2005). These fees may be an indication of the possible reimbursement cost of using Macroplastique or Bioplastique® implants in the treatment of UVFP and laryngeal cleft. By comparison, laryngoplasty - the prevailing surgical treatment option for severe cases of UVFP - is listed by the MBS (schedule item number 41879) at a reimbursement fee of $807.85 (Australian Department of Health and Ageing 2005).

By raw figures alone, a single PDMS treatment session would amount to an approximate saving of between $385.95 and $421.90 in reimbursement fees per patient. However, given the limited clinical need and burden of disease profile of UVFP and laryngeal cleft, it is questionable whether such savings would have much of an overall impact.

Based on current MBS figures, there is also some evidence to suggest that PDMS injections are a cheaper alternative to ureteral reimplantation in the treatment of VUR. Currently, the MBS reimbursement fee for periurethral or transurethral injection of 'materials' in the treatment of urinary incontinence is listed at $203.55 per injection (MBS schedule item number 37339). This gives a good indication of the likely cost of using PDMS implants in the treatment of VUR. By comparison, ureteral reimplantation is currently listed by the MBS at a reimbursement schedule fee of $784.55 per procedure (item number 36588). If a single PDMS injection was used instead of ureteral reimplantation, this would amount to a raw saving of $581 per person.

There is insufficient evidence in the available literature to attempt an analysis of cost impact for the other indications examined in this report. However, for all indications, it should be stressed that existing surgical and medical treatment alternatives may in fact be cheaper (or equal to) the endoscopic alternative if repeat injections or conversions to surgery are required to ensure long-term effectiveness.

Ethical Considerations

Informed Consent

Although PDMS implants have been approved for sale within Australia, the use of the implants is essentially experimental for the indications examined in this report and should be subject to written informed consent by patients

Access Issues

No significant access issues are anticipated. Considering the endoscopic procedure is performed on an outpatient basis, PDMS implants may in fact facilitate better access and patient compliance than traditional medical and surgical approaches. The non-biological nature of PDMS may also offer an alternative to bovine-derived tissue bulking materials for patients with religious, cultural or ethical concerns.

Training and Accreditation

Training

No information could be found in regard to the training required.

Clinical Guidelines

No clinical guidelines were found for the use of PDMS injections in the treatment of the indications covered in this report.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy Used for Report

Database	Platform	Searched/edition
MEDLINE	Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Medline	searched 12 July 2005
EMBASE	Ovid	searched 12 July 2005
Current Contents	Web of Science	searched 15 July 2005
The Cochrane Library	http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME	Searched 12 July 2005
NHS Centre for Research and Dissemination (UK)	http://144.32.228.3/scripts/WEBC.EXE/nhscrd/newsearch	searched 15 July 2005
NHS Health Technology Assessment (UK)	http://www.ncchta.org/	searched 15 July 2005
National Research Register (UK)	http://www.doh.gov.uk/research/nrr.htm	searched 21 July 2005
Google	http://www.google	searched 23 July 2005

INAHTA	http://www.inahta.org/publication.html	searched 16 July 2005
Meta-Register of Controlled Trials	www.controlled-trials.com	searched 16 July 2005

Abbreviations: NHS, National Health Service; UK, United Kingdom

Search terms used included: bioplastique; macroplastique; uroplasty + soft tissue*; injectable silicone biomaterial; injectable silicone; ptp injection*; perianal injection; polydimethylsiloxane; faecal incontinence; vesicoureteral reflux; vesicoureteric reflux; neurogenic bladder; periprosthetic* + leakage; provox; unilateral vocal fold paralysis; laryngeal cleft; cleft larynx; stomal leak*; continent diversion.

Availability and Level of Evidence

Vesicoureteral reflux

Total number of studies: 11

Review of case series	1
RCTs	1
Non-randomised comparative studies	2 (possible overlap)
Case series	6 (possible overlap in 2 studies)
Case reports	1

High level evidence (II) was derived from a small RCT (Oswald *et al.* 2002). It should be noted that the Oswald *et al.* (2002) RCT used only a small to moderate sample size (n=72) and a somewhat short-term follow-up period of twelve months. Patient overlap was a possibility in two non-randomised comparative studies (Aboutaleb *et al.* 2003a & b) and two case series (Dodat *et al.* 1998; Dodat *et al.* 2004). It should be noted that the Van Capelle *et al.* (2004) case series received partial funding from Uroplasty Ltd.

Faecal incontinence

Total number of studies: 3

Systematic reviews	0
RCTs	1
Non-randomised comparative studies	0
Case series	2
Case reports	0

High level evidence (level II) came from one RCT (Tjandra *et al.* 2004) with a small to moderate sample size (n=82) and a relatively short mean follow-up period of six months. However, it compared two methods of silicone injection, rather than silicone injections versus a standard or placebo treatment. In addition, the Kenefick *et al.* (2002) case series was insufficiently powered, due to the small patient sample (n=6).

Periprosthetical leakage

Total number of studies: 3

Systematic reviews	0
RCTs	0
Non-randomised comparative studies	0
Case series	1
Case reports	2

No high level evidence could be found in the literature. Sample size was extremely small in all of the studies, limiting the statistical power and significance of the findings. While the Lorincz *et al.* (2005) case series provided long-term (two year) follow-up results, it was difficult to interpret patient course. This was primarily due to the poor presentation of tabular results.

Unilateral vocal fold paralysis

Total number of studies: 2

Systematic reviews	0
RCTs	0
Non-randomised comparative studies	0
Case series	2
Case reports	0

Only level IV evidence could be found in the literature. Both studies (Sittel *et al.* 2000; Alves *et al.* 2002) used relatively small sample sizes. Subjective symptom outcome measures in Sittel *et al.* (2000) may have been a potential source of participant bias. A visual analog scale may have been a more objective, validated measure when assessing voice quality. Nevertheless, the study did provide long-term results, with a mean follow-up of 88.4 months (range 69 to 102 months). By contrast, the small case series by Alves *et al.* (2002), while implementing blinding measures and objective scoring, only provided short term results (a maximum of six months follow-up).

Laryngeal cleft type I

Total number of studies: 1

Systematic reviews	0
RCTs	0
Non-randomised comparative studies	0
Case series	0
Case reports	1

The evidence level was extremely low, with one case report (Ahluwalia *et al.* 2004), providing only anecdotal/professional assessment.

Stomal leakage

Total number of studies: 1

Systematic reviews	0
RCTs	0
Non-randomised comparative studies	0
Case series	1
Case reports	0

One case series (level IV) could be found (Guys *et al.* 2002), with a small sample size of six patients and a relatively short follow-up (11 months).

Sources of Further Information

In the U.S., the FDA has indicated that further trials of Uroplasty Ltd. PDMS products are required before they can be assessed for premarket approval. As yet, the nature and date of these trials have not been indicated by Uroplasty Ltd. For up-to-date information on this issue, see the Uroplasty Ltd. website at http://www.uroplasty.com/ .

For the first reported use of Bioplastique® as an adjunct to voice prosthesis insertion, see Lichtenberger G. Advances and refinements in surgical voice rehabilitation after laryngectomy. *European Archives of Otorhinolaryngology* 2001; **258**: 281-284.

Impact Summary

The likely impact which injectable silicone biomaterial may have in Australia varies widely, depending on the condition for which it is indicated. In the treatment of VUR, the minimally invasive nature of PDMS injections may have the potential to benefit the 20% of paediatric VUR patients with protracted or medically intractable reflux (Department of Human Services, Victoria 2005). However, Deflux® appears to have overtaken PDMS as the material of choice in treating VUR. This is presumably due to the biodegradable nature of Deflux®, allowing for a more temporary augmentation which takes into account the 80% of VUR patients whose condition resolves spontaneously (Department of Human Services, Victoria 2005). Moreover, while the evidence outlined in this report suggests that PDMS carries slightly fewer risks of complications or safety issues relative to extravesical reimplantation surgery and Deflux® and Teflon® injections, PDMS does appear to have the trade-off of a slightly lower overall success rate than these same comparators. Together, these factors suggest that

PDMS may not be the optimum material for the endoscopic treatment of VUR in Australia.

By contrast, PDMS injections have the potential for greatly impacting the treatment of faecal incontinence in Australia. As many as one million Australians are thought to suffer from this condition and in cases of severe incontinence, current treatment alternatives are only moderately effective in relieving the symptoms – much less the structural causes – of the incontinence (Chiarelli *et al.* 2004). While the procedure may be more costly than existing medical treatments (such as diet and lifestyle modifications), its minimally invasive nature will likely offset the cost impact of performing more invasive sphincteroplasty in patients with severe anal sphincter dysfunction. Although there are currently no studies in the literature comparing PDMS treatment with existing treatments, the favourable treatment outcomes revealed by existing evidence suggests that this procedure may greatly benefit patients with severe, medically refractory faecal incontinence, should the treatment become more established.

It is difficult to gauge what impact voice prosthesis augmentation with PDMS might have in Australia. There is a general lack of information on the extent of prosthesis leakage and clinical need in this country, much less comparative information on the cost of replacing prostheses relative to PDMS augmentation. There are also concerns about the slight risk of granuloma formation, extrusion and implant migration associated with PDMS augmentation of voice prostheses (Rees, personal communication 2005). Given these issues, it is possible to assume that the impact on the health system will be minimal in the foreseeable future.

Although the exact extent of clinical need remains unidentified in the literature, it could probably be assumed – based on figures from the U.S. – that the 3% to 9% of the Australian population affected by UVFP will benefit to some degree from vocal fold augmentation with PDMS implants (Ernest George White Society 2005). However, this procedure is most likely to have the greatest impact for terminally ill patients suffering from UVFP. Given the rapid recovery outcomes of this procedure relative to existing treatments, terminally ill patients stand to gain the greatest quality of life benefits. Figures from the MBS also suggest that PDMS injections will be cheaper – at least in the short-term - than other surgical treatment options such as laryngoplasty. Despite this, the evidence base remains limited and safety concerns about granulation and extrusion are deterrents in clinical practice (G Rees, personal communication, 2005). With only two case series studies published in the literature, the procedure is likely to remain at a relatively experimental stage into the near future, particularly while scientific uncertainty surrounds the ideal material for vocal fold augmentation.

Treating laryngeal cleft with PDMS injections is not likely to have a noticeable impact on the Australian health system, given the extremely rare nature of this disorder. Also, with a current evidence base of just one overseas case report, PDMS injections are unlikely to

become a new treatment option for laryngeal cleft in the near future. However, the potentially life-threatening nature of severe laryngeal cleft and its tendency to affect young children and infants does create an added imperative to develop procedures like PDMS augmentation beyond the experimental stage.

The impact on the Australian health system of treating stomal leakage with PDMS implants is difficult to assess. There is no precise data on the clinical need for continent diversions stemming from neurogenic bladder conditions, much less the extent of stomal leakage complications. Continent diversions do not appear to be a highly demanded procedure in the Australian health care system, which tends to suggest that treating stomal leaks will not have much of an impact. For those patients who may have undergone continent diversions, however, the use of PDMS implants to seal leaking stomas would have the obvious benefit of preventing the need for invasive, costly corrective surgery, provided the risk of granuloma formation or extrusion does not outweigh the benefits. Whatever the potential gains, treating stomal leakage with PDMS implants remains at a highly experimental stage, with an evidence base of just one small case series.

Conclusions

Polydimethylsiloxane injections are a minimally-invasive option in the treatment of VUR, faecal incontinence, periprosthetical leakage, UVFP, laryngeal cleft type I, and stomal leakage in continent diversion. All studies covered in this report have generally demonstrated the safety and efficacy of PDMS implants in treating these indications, although long-term and high level evidence is conspicuously lacking for most indications.

The results of fifteen studies (including one systematic review, one RCT, and two comparative non-RCTs) indicated that PDMS implants are relatively safe in the treatment of VUR, with few serious complications or side-effects. While non-comparative studies showed a favourable cure rate, comparative and RCT studies indicated that PDMS injection generally yielded a roughly equal or slightly lower cure rate in comparison to treatment with Deflux® or extravesical reimplantation.

In the treatment of faecal incontinence, three studies (including one RCT) demonstrated that PDMS implants were relatively safe, with complications generally resolved through proper positioning of injections or adjustments to needle gauge. Overall, marked or significant improvements in all outcome measures were reported, although no studies sought to compare PDMS treatment with other forms of treatment.

Three studies demonstrated the safety and effectiveness of PDMS injections in the treatment of periprosthetical leakage. Although the level of evidence was relatively low

and no comparisons were sought, the studies did suggest that PDMS implants were generally effective in sealing prosthesis leakage, with no complications or side-effects in the small patient samples used.

Low level evidence for the efficacy and safety of PDMS implants in treating UVFP came from two studies. Both studies reported significant short-term improvements in outcome measures, with no safety issues.

The results of a single case report suggested that PDMS injections were effective in treating one young patient with laryngeal cleft type I, carrying no complications or safety issues.

Similarly, one case series indicated the effectiveness of PDMS injections in sealing stomal leakage in six patients. No complications or safety issues were reported.

Overall, with the exception of PDMS implants in the treatment of VUR - which may have been superseded by Deflux® injections - more long-term, higher quality evidence is required to determine the value of PDMS injections in treating the indications outlined in this report.

HealthPACT Advisory

This technology is well established for vesico-ureteric reflux and is widely used. Use of the technology for other indications, such as laryngeal injections, is less well established. Data are needed to establish its effectiveness as a treatment for faecal incontinence, however this will be supplied at a later date by the MSAC review (Application 1100).

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Appendix A: Table of Key Efficacy and Safety Findings (Vesicoureteral reflux (VUR))

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Systematic review			
Leonard 2002 46 studies of different endoscopic treatments for VUR were selected for review *Selection criteria:* review articles, original reports and abstracts pertaining to endoscopic injection therapy from 1981-2001. Four studies were selected to support basic concepts in the management of VUR, and the remainder (42) pertained specifically to endoscopic injection therapy for VUR. Therapies included were: polytetrafluoroethylene (Teflon or polytef) paste, glutaraldehyde cross-linked bovine dermal collagen (Zyplast or Contigen), polydimethylsiloxane (Macroplastique), dextranomer in sodium hyaluronan (Deflux), and fat (autologous material)..	Initial European reports (Buckley 1993, Dodat 1994) claimed 80-90% success after one injection of Macroplastique. Canadian report (Hafez *et al.* 2001): 74 children (111 renal units) were treated. 76% of the children (81% of renal units) were cured after one injection. Repeat injection increased cure rate to 84% of children (90% of ureters). Follow-up at 24 months. Paucity of long-term follow-up data, although Harriss *et al.* 1997 and Sheriff *et al.* 1997 reported cures for up to three years post-injection.	French study (Bertschy *et al.* 2001) found that Macroplastique caused a more intense local inflammatory reaction than Teflon, and was fragmented into 6 μm particles by macrophage action. These particles are small enough to allow for distant migration.	*Brand used:* Macroplastique.

Data extraction: reports were analysed with focus on the physical properties of the biomaterial injected, results of treatment in regard to the cure of VUR, duration of cure, and possible adverse effects and clinical benefits engendered by the use of injectable materials.			

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Randomised Controlled Trial			
Oswald *et al*. 2002 72 paediatric patients (16 boys; 56 girls; total of 114 ureters). Mean age: 34.5 months **Group 1**: Single Macroplastique injection (34 children; 56 ureters/ureteral units) **Group 2**: single Deflux injection (38 children; 58 ureters/ureteral units) *Follow-up*: 3 and 12 months *Lost to follow-up:* at 12 months follow-up, voiding cystourethrography (VCUG) was available for only 24 patients (41 ureters) in the Macroplastique group and only 22 (32 ureters) in the Deflux group. Additional follow-up VCUGs of the remaining patients were in progress at last follow-up. *Comparison:* single injection Macroplastique PDMS vs. single injection Deflux (dextranomer/hyaluronic acid copolymer) in the treatment of VUR in children. *Randomisation method:* not specified *Selection criteria:* Children with VUR. Exclusion criteria: Duplicated refluxing ureters, Hutch diverticulum, failed surgical reimplantation, neurogenic bladder , and voiding dysfunction	All procedures were performed as planned on an outpatient setting under general anaesthesia At 3 months follow-up: reflux was corrected in 50/58 (86.21%) ureteral units in the Macroplastique group, and in 40/56 (71.43%) ureteral units in the Deflux group. At 95% confidence interval, no statistically significant difference was observed (p=0.0536). Defining the success rate as no evidence of reflux, the response rate after Macroplastique injection decreased to 75.8% and response after Deflux decreased to 62.5%. On follow-up VCUG, initial grade III reflux in 2 patients (1 patient in either group) had decreased to grade II reflux. Of a total 7 patients who had grade I reflux at 3 months follow-up (4 with 6 ureters in group 1, and 3 with 5 ureters in group 2), 1 (14.29%) patient with two ureterorenal units in group 1, and 2 patients (28.57%) with 4 ureterorenal units in group 2 developed grade II	No intraoperative complications. No significant dilation of the upper urinary tract was observed in either group. However, a temporary mild dilation of the collecting system was found in 23 ureterorenal units (40%) after Macroplastique injection and 12 (21%) after Deflux injection. Contralateral *de novo* grade I reflux developed in 1 patient in both groups but did not require additional treatment. Neither adverse reactions nor any signs of toxicity in either group were observed. 6/38 (15.79%) patients in group 1 and 4/34 (11.76%) patients in group 2 had postoperative afebrile urinary tract infection after injection with Macroplastique/Deflux.	*Brand used:* Macroplastique *Potential for bias:* Method of allocation not specified. Blinding not specified. Previous treatments could be potential confounding factor. *Outcome measures and their validity:* Successful reflux correction was defined as absent or grade I reflux on follow-up VCUG and no *de novo* hydroureteronephrosis on renal ultrasonography. International classification of reflux grades used. *Other comments:* Differences in the injected volumes between the two groups were not statistically significant (p>0.05). Bilateral reflux was present in 24 children in the Macroplastique group and in 18 children in the Deflux group.

Procedure details: antibiotic prophylaxis using either trimethoprim (1 to 2 mg/kg daily) or co-trimoxazole (sulfamethoxazole 5 to 10 mg/kg daily) was administered to all patients. Treatment was performed as outpatient procedure. A flexible 5F paediatric endoscopic needle prepared with the Macroplastique Administration Gun, and a 3.5F polytetrafluoroethylene-coated needle was used to inject Deflux. A single endoscopic subuteral Macroplastique or Deflux injection was performed in 58 and 56 ureters with grade II to IV VUR, respectively. Antibiotic prophylaxis was stopped if VUR was absent or grade I. If reflux persisted, repeated treatment with the previous bulking agent was offered to the parents. *Parameters assessed:* One week after the injection, control renal ultrasonography was performed to recognise urinary obstruction. Voiding cystourethrography (VCUG), ultrasonography, and urine culture were done in all patients 3 months after discharge. Routine parameters, including medical history, physical condition, and adverse events, were recorded at 3 and 12 months follow-up.	reflux after 12 months 3/34 (8.82%) patients in group 1 and 2/38 (5.26%) patients in group 2 underwent bilateral repeated injection for persisting reflux.		

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Comparative non-RCT</td></tr>
<tr>
<td>Aboutaleb et al. 2003a

180 paediatric patients (40 boys, 140 girls)
Mean age at surgery:
60 months (group 1)
77 months (group 2)

Group 1: single polydimethylsiloxane injection (74, 108 ureters)
Group 2: extravesical reimplantation (106, 166 ureters)

Mean follow-up:
12 months (group 1)
15 months (group 2)

Comparison: single polydimethylsiloxane injection vs. extravesical ureteral reimplantation

Selection criteria: children with low-grade primary VUR refractory to medical management. Patients with concomitant unilateral high grade reflux (grades IV and V) were excluded from the study.

Procedure details: observational therapy with prophylactic antibiotics was used initially in all</td>
<td>Group 1 overall success rate:
80.6% of the ureters in group 1 were cured of VUR at 3 months and 91.6% were cured at last follow-up (average 12 months).

Group 2 overall success rate:
Success rate was 95.8% of ureters at 3 months which improved to 98.8% one year later.

<table>
<tr><th></th><th>% group 1</th><th>% group 2</th><th>p value</th></tr>
<tr><td>Success rates:
3 mos.
Last f/u</td><td>
80.6
91.6</td><td>
95.8
98.8</td><td>
<0.0001
0.008</td></tr>
<tr><td>Contral. Reflux:
3 mos.
Last f/u</td><td>
0
0</td><td>
10.9
2.2</td><td>
0.06
1.0</td></tr>
<tr><td>Urinary retention</td><td>(0)</td><td>(3.3)</td><td>0.53</td></tr>
<tr><td>Urinary tract infect.</td><td>0</td><td>11.4</td><td><0.002</td></tr>
<tr><td>De novo hydroneph.
3 mos.
Last f/u</td><td>
3
0</td><td>
11.3
6.7</td><td>
<0.02
<0.01</td></tr>
<tr><td>De novo voiding dys. (no./total no.)</td><td>(0/56)</td><td>7 (6/86)</td><td>0.08</td></tr>
</table>
</td>
<td>De novo hydronephrosis:
In group 1, de novo mild hydronephrosis developed in 3 renal units (3%), which resolved with follow-up. In group 2, hydronephrosis developed in 17 (11.3%) renal units (mild 12 and moderate 5) and resolved with follow-up in 7 (mild 5 and moderate 2).
Remaining cases are stable and none have required diuretic renography or further treatment.
Incidence of de novo hydronephrosis was significantly different between the 2 groups (p<0.02).

Urinary tract infections (UTIs)::
None were observed in group 1 following PDMS injection.
UTIs were documented in 10 female and 2 male patients (11.3%; p=0.0002) in group 2, following extravesical ureteral reimplantation. 4/12 (33.33%) infections were febrile and 9/12 (75%) had associated voiding dysfunction but none were on clean intermittent catherisation.
No patients had UTIs in the first month after surgery. 4 patients had concomitant</td>
<td>Brand used: Macroplastique

Potential for bias:
To account for the learning curve in mastering polydimethylsiloxane technique, which was already acquired for the open surgery, authors elected to exclude the first 6 months of their experience with the new injectable material.

No difference in the distribution of grade of VUR between the two treatment groups

Outcome measures and their validity:
Success rates, de novo hydronephrosis, voiding efficiency, urinary tract infections, and complications. Ultrasound at 6 weeks and voiding cystography at 12 weeks. If reflux persisted the voiding cystogram was repeated after 1 year. International classification of reflux grades</td>
</tr>
</table>

patients. Extravesical reimplantation was performed as described by Zaontz *et al.* (1987). PDMS injection was performed with the patient under general anaesthesia as an outpatient procedure. The material was injected subuteral at the 6 o'clock position inferomedially. Injected volume was 0.5 to 1.3 ml, with the aim of obtaining a well-formed mound of PDMS and a slit-like appearance of the ureteral orifice. Patients were discharged home the same day of surgery with postoperative analgesia. *Parameters assessed:* initially, all children were assessed for dysfunctional voiding. Flow rate and post-void residual urinary volume assessment were obtained in select patients. To normalise bladder dynamics and decrease severity of voiding dysfunction, this evaluation was repeated semiannually in each case.	Short-term success rate was significantly different between group 1 and 2 at 3 and 15 months ($p<0.0001$ and $p=0.008$, for the first and last follow-up, respectively). *Success rates by grade (group 1& 2):* Success rates for grades I and II reflux were 83% in group 1 and 95.9% in group 2, which improved to 93.2% and 100%, respectively. Success rates for grade III reflux at 3 months was 77.6% in group 1 and 94.6% in group 2, which improved to 87.8% and 97.8%, respectively, at the last follow-up. Reimplantation was necessary in 1/180 (5.56%) patient after failure of PDMS injection because the parents preferred reflux over repeat injection. *Persistent reflux:* In group 1, VUR persisted after a single PDMS injection in 21/108 (19.44%) ureter units at 3 months, which resolved in 11 units and was down graded to grade I in 3 units at last follow-up (range 6-24 months) No contralateral reflux was noted in group 1. In group 2 , VUR persisted in 7 /166 (4.22%) units and new reflux developed in 5 contralateral units (10.9%) at 3 months. All except 3 cases (2 ipsilateral, 1 contralateral)	hydronephrosis (mild 2 and moderate 2). *Other complications:* No complications were found in group 1. In group two, 2 patients had suprapubic fluid collections requiring drainage; 1 had a wound seroma, which resolved with conservative management.	used.

	had resolved spontaneously at 15-month follow-up. *Voiding dysfunction:* 18 patients (24%) in group 1 still had elements of voiding dysfunction prior to surgery. Of these 18 patients 9 (50%) had persistent reflux postoperatively. With continued behavioural modification, voiding pattern returned to normal and reflux resolved in 4 patients. No *de novo* voiding dysfunction occurred in this group postoperatively. 20 patients (18.9%) in group 2 had symptoms of voiding dysfunction preoperatively. All underwent bladder retraining and were given anticholinergic drugs when indicated. Postoperatively, none of these patients had persistent reflux. They remain on a behavioural modification to date. *De novo* voiding dysfunction occurredin 6/86 (7%) patients. None of these 6 patients had UTI or persistent reflux. 2 female patients (3.3%) had transient urinary retention requiring urethral catheterisation <2 weeks after bilateral reimplantation. 1/2 (50%) of these patients had a history of voiding dysfunction preoperatively		

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Retrospective comparative non-RCT</td></tr>
<tr>
<td>Aboutaleb et al. 2003b

49 patients (15 females; 34 children)
(may be overlap with
Aboutaleb et al 2003a)

Follow-up: All patients were assessed postoperatively at 6 weeks and 3 months. Further follow-up yearly for surgery group, and at 6-9 months for injection group.

Comparison:
Group 1: PDMS injection (15 females)
Group 2: extravesical common sheath reimplantation (ECSR) surgery (34 children).

Selection criteria: patients with varying degrees of VUR. Indications for surgery were persistent VUR for more than 4 years, breakthrough urinary infections, upper tract deterioration (increase in reflux grade associated with increase in hydronephrosis grade, or thinning of parenchyma, with or without a decrease in renal function on renal scans) and non-compliance with medical management. Patients with incomplete ureteral duplications and other pathological conditions (e.g. ureterocele) were excluded from the study.</td>
<td>
<table>
<tr><th>No. success total no. (%):</th><th>Group 1</th><th>Group 2</th></tr>
<tr><td>3 mos.</td><td>15/22 (68)</td><td>42/44 (95.5)</td></tr>
<tr><td>Last Follow-up</td><td>16/22 (81.8)</td><td>43/44 (97.7)</td></tr>
</table>
Group 1:
Success rate per moiety after single injection was 68% (10/15 (66.67%) patients) at 3 months, which increased to 81.8% (12/15 (80%) patients) at 12 months.
Reflux improved in 1 moiety after the first injection from grade III to grade I, which persists to date.
2/15 (13.33%) patients received a second injection (3 moieties) which corrected reflux in 1/15 (6.67%) patients (1 moiety). 1/15 (6.67%) (1 unit) had postoperative contralateral grade II VUR, which had resolved by the last follow-up.
</td>
<td>Group 1:
0/15 patients had urinary tract infection, de novo hydronephrosis or complications.

Group 2:
De novo hydronephrosis was noted after ECSR in 2 units, which was mild and resolved after 1 year of follow-up. 0/34 patients had postoperative urinary retention, haematuria or bladder spasms.
4/34 (11.76%) patients had postoperative urinary tract infections. No post-ECSR complications correlated with VUR grade.</td>
<td>Brand used: Macroplastique

Potential bias: previous treatments could be potential confounding factor.

Outcome measures and their validity: Success rate, contralateral reflux, de novo hydronephrosis, urinary tract infections and complications. VCUG and ultrasound were performed at follow-up. International classification of reflux grades used.</td>
</tr>
</table>

Procedure details: Medical treatment initiated with continuous low dose prophylactic antibiotics. Endoscopic PDMS injection was done as outpatient procedure. Puncture site was made at the 6 o'clock position on the inferomedial aspect of the orifice of the refluxing moiety. Injected volume varied from 0.5 to 1.3 ml per refluxing ureter. Postoperative analgesia consisted of acetaminophen and codeine, and the patients were discharged after 4 hours. ECSR was performed as described by Zaontz *et al* (1987). *Postoperative care:* all patients were assessed postoperatively by ultrasound and voiding cystourethrography (VCUG). Patients with persistent reflux were kept on antibiotics, and a repeat ultrasound and VCUG were performed at follow-up. All children were maintained on prophylactic antibiotics until resolution of reflux had been documented on VCUG.	**Group 2:** Success rate was 95.5% (32/34 (94.11%) patients) at 3 months, which improved to 97.7% (33/34 (97.03%) patients) at an average of 15 months postoperatively (range 6 to 32). Persistent low grade reflux was noted after ECSR in 2 units, which resolved after 6 months in 1 and persistent in the other resulting in a 97% success rate. New contralateral reflux was detected in 4 renal units (16.7%) after ECSR but resolved spontaneously at follow-up. The success rate for low grade reflux in this group was statistically significantly higher than that of group 1 ($p<0.04$).		

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case series			
Dodat *et al*. 1998 297 paediatric patients (40 boys (13.5%); 257 girls (86.5%)). Total of 454 vesico-renal refluxes. *Follow-up*: 6 weeks and 12 months. *Comparison:* Treatment efficacy compared for various aetiologies (all aetiologies; primitive vesico-renal reflux; residual reflux after Teflon; secondary or associated malformation) *Patient details:* children presenting with vesico-renal reflux were given endoscopic treatment with Macroplastique.	Reflux successfully resolved in 452/454 (99.56%) patients. *Disappearance of reflux at 6 weeks follow-up with Macroplastique:* Resolved in 83.6% of all ureters after 1 injection, and 93.3% after two injections. 271/297 (97.98%) were cured after 1 or 2 injections. 223/239 (93.33%) children with primitive? reflux were cured: 195/239 (81.59%) after 1 injection, and 28/239 (11.72%) after 2nd injection. 22 residual reflux cases persisted after 1 or 2 injections of Macroplastique. Reflux of higher rank (III and IV) were treated with surgery. Reflux cases of low rank (I or II) were either supervised in the absence of infectious episode, or surgically reimplanted in the event of new infection. 3 rank I and 1 rank II cases were still under medical supervision at time of writing. 2 rank I and 3 rank II cases were operated on successfully. *Efficacy of Macroplastique in secondary or associated malformation cases of reflux* Whereas figures obtained for reflux on partial duplicity are very similar to results of treatment for primitive reflux cases (80% of disappearance of reflux after 1 injection; 90% after 2 establishments, i.e. 87.5% cured children), success rate for Macroplastique treatment of total duplicity reflux is lower: only 51.1% disappearance of reflux after 1 injections and 60.9% after 2 injections. Thus, 18 children were cured	*Complications with Macroplastique:* A painful lumbar episode related to pyelo-ureter hypotonia. Resolved spontaneously after treatment with NSAIDs. 2 low urinary infections. 1 episode of pyelonephritis. Unilateral blockage of ureter in 2/454 (4.41%) treated reflux cases. These two ureters were surgically reimplanted 3 and 6 months after the endoscopic treatment before the absence of regression of this moderate dilation (not exceeding 10 mm). 1 of the 2 (50%) obstructions probably related to a megaloureter obstruction and reflux which had not been diagnosed.	*Brand used:* Macroplastique *Outcome measures and their validity:* Success rates. International classification of reflux grades used. *Other comments:* 11 reflux cases were treated with Macroplastique after Teflon failure. 10 post-operative cases in 8 children were also the subject of complementary treatment? with Macroplastique. Authors comment that advantages of Macroplastique compared to Teflon can be explained by less liquid consistency, the absence of retraction of the product and by the presence of larger microparticles without any local/remote inflammation.

	(75%); 15 (83.33%) after 1 injection and 3 (16.67%) after 2 injections. 6 patients (25%) required a secondary surgical procedure. These poorer results are explained by the large gaping of the refluxing orifice, corresponding to the lower pyelo (renal pelvis) and the thin or narrow width of the submucosal layer. When the reflux was only in the lower pyelo, the results were even worse. Only 52.25% of patients were cured after 1 injection, and 57.5% after 2 injections. *Treatment with Macroplastique after persistent reflux caused by injection of Teflon or surgical reimplantation:* Macroplastique successfully treated all cases: 11 children presented with residual reflux after Teflon: 90% cure after 1 injection, and 100% after 2 injections. 8 children had persistent reflux in spite of surgical reimplantation: all 8 were cured, 79% after 1 injection, 100% after 2 injections. Reflux also cured when it occurred with a neurological bladder. However, in the even of reflux after valve resection, reflux successfully treated in only 2/3 (66.67%) patients. *Results in medium term follow-up:* 14 children (23 ureters) experienced reappearance of reflux (8.7% of the children, 9.1% of ureters). 16 reflux cases profited from a complementary treatment because of infection: for 10 ureters, Macroplastique re-administered 1 year later?; 6 ureters were reimplanted according the process of Cohen? 60 children were re-examined 2 years later with a new renal echography which was always normal.		

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Case series</td></tr>
<tr><td>Shah et al. 2001

15 patients (12 male, 3 female, 22 ureters)
Age range: 19-80 years (median age 38)

Follow-up: 9-68 months. Mean follow-up 28.5 months

Procedure details: Macroplastique (0.5 – 1.5 ml) was injected submucosally under each ureteric orifice to convert the opening to a slit like shape. Procedures usually performed as a day case. Patients were treated under general anaesthesia.</td><td>Identification of ureteric orifice was difficult in 3 patients who had grossly trabeculated, thick walled bladders. Hence, the procedure was more difficult to perform in these patients.

Overall results of Macroplastique injection in 22 ureters:

<table><tr><th>Result</th><th>Ureters (%)</th></tr><tr><td>Cessation of VUR after 1st injection</td><td>16 (72.7)</td></tr><tr><td>Cessation of VUR after 2nd injection</td><td>1 (4.5)</td></tr><tr><td>Downgrading of reflux after one or two injections</td><td>2 (9.1)</td></tr><tr><td>Failure to correct VUR</td><td>3 (13.7)</td></tr></table>
1/15 (6.67%) patient developed bilateral VUR 12 months following the first injection and this was cured following a further injection.

1/15 (6.67%) patient developed recurrent bilateral reflux 4 years following the first injection and this too resolved following a further injection.

3/15 (20%) patients had had pre-operative deterioration in renal function. No</td><td>No patients developed postoperative UTI or ureteric obstruction as a result of the procedure.

13/15 (86.67%) patients experienced a reduction in the frequency of laboratory proven infections post-operatively.</td><td>Brand used: Macroplastique.

Potential for bias:
Previous treatments could be potential confounding factors.

Outcome measures and their validity:
Frequency of laboratory proven urinary tract infections requiring treatment was recorded at each follow-up from infection diaries. Videourodynamics (VCMG) and an upper urinary tract ultrasound scan were routinely performed post-operatively. Results were graded as Cured, Improved (downgrading of reflux) and Failed. Repeat injections were given in cases of failure and recurrence. Open surgical intervention was reserved for those who failed to show any improvement. International classification of reflux grades used.</td></tr>
</table>

	improvement in renal function was noted post Macroplastique injection. 2/15 (13.3%) patients failed to respond to the first injection and are currently awaiting further injection. Both of these patients had small capacity (< 150 ml), grossly trabeculated, thick walled bladders. One of these patients had recurrent problems of bladder stone formation. Due to poorly controlled high intravesical pressures in one patient (6.67%), a clam-ileocystoplasty was performed with reimplantation of the right ureter in which there was persisting low grade reflux post Macroplastique injection. This cured the residual reflux.		

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Retrospective case series (multicentre)			
Dodat *et al*. 2004 464 paediatric patients. 389/464 (83.8%) girls. 75/464 (16.2%) girls. *Follow-up:* Minimum of 5-7 years. 151/464 patients only treated with Macroplastique had been re-examined in 2002 at the time of analysis of the files. In order to locate all of the patients and their evolution, surveys were sent out to the other 313 patients, their families, attending physicians and to case workers. 75 patients (16.2%) could not be reached. Consequently, long term results were evaluated for 389 patients (590 ureters). *Selection criteria:* Collection of data was carried out on hospital files. Files of patients with refluxing ureters having had a cystography between an average of 5 to 7 years after being treated with Macroplastique were used. Files were obtained from eight different	Reflux was cured and did not recur in 309/389 (79.43%) cases at follow-up: 286/389 (73.52%) cases after one injection; 21/389 (5.40%) cases after two injections, and 2/389 (0.51%) after 3 injections. 80/389 (20.57%) patients benefited from a surgical procedure for treatment of persistent or reappearing reflux. Long-term success rate of treatment was 78.1% (461/590 refluxing ureters treated with Macroplastique injections did not require surgery) The success rate at 5 to 7 years was identical between primitive and secondary reflux. On a follow-up of 5 to 7 years, % of disappearance of reflux ranks III, IV and V is higher with the endoscopic treatment by injection of Macroplastique, whereas it is difficult to affirm that it is higher than the percentage of spontaneous cure for reflux of low rank (I or II). 32.4% of rank I and 12.2% of rank II reflux cases required a surgical intervention after the failure? of the endoscopic treatment	19/464 (4.09%)patients injected presented an immediate complication: 1 late resumption of the micturition per 24th hour 2 transitory haematurias related to a haemorrhage at the point of puncture 2 pyelonephritis cases treated medically. No cases of stenosis or anuria were observed. No cases of ureteric stricture were observed. Benign complications (may have been related to anaesthesia): momentary vomiting or transitory abdominal pains yielding quickly with paracetamol	*Brand used:* Macroplastique *Potential for bias:* Previous treatments may be confounding factors. Authors note that figures for low grade reflux results appear high, and they are higher than other series in the literature coming from only one operator. However, because this is a multi-centre study, the character of operator dependent results of the endoscopic treatment perhaps explains this difference. *Outcome measures and their validity:* Criterion of success of endoscopic treatment was the observation of total absence of reflux on cystography (whereas certain teams included an

centres.

Procedure details: injections of Macroplastique were plain or bilateral. They were carried out under caudal, loco-regional anaesthesia (58% of cases) or under general anaesthesia (42%). Average period of hospitalisation was 1.7 days (± 0.8 standard deviation?).

Results according to the aetiology of reflux:

	Primitive reflux success	Secondary reflux success	Primitive and secondary reflux success	Total success
No unilateral reinjection	253 73.5%	29 74.4%	4 66.7%	286 73.5%
1 unilateral reinjection	19 5.5%	2 5.1%	0 0%	21 5.4%
2 unilateral reinjections	2 0.6%	0 0%	0 0%	2 0.5%
Surgery	70 20.3%	8 20.5%	2 33.3%	80 20.6%
Total	344 88.4%	39 10.0%	80 20.6%	389 100%

Distribution of the results by patient according to reflux rank:

	Grade I success	Grade II success	Grade III success	Grade IV success	Grade V success	Total success
No unilateral reinjection	40 65.6%	171 78.1%	49 67.1%	23 71.9%	3 75.0%	286 73.5%
1 unilateral reinjection	2 3.3%	17 7.8%	2 2.7%	0 0%	0 0%	21 5.4%
2 unilateral reinjections	0 0%	2 0.9%	0 0%	0 0%	0 0%	2 0.5%
Surgery	19 31.1%	29 13.2%	22 30.1%	9 28.1%	1 25.0%	80 20.6%
Total	61 15.7%	219 56.3%	73 18.8%	32 8.2%	4 1.0%	389 100%

improvement in reflux rank as a criterion of success). International classification of reflux grades used.

Distribution of results by ureteral units according to reflux rank:

	Grade I success	Grade II success	Grade III success	Grade IV success	Grade V success	Total success
No unilateral reinjection	47 66.2%	248 78.5%	86 65.2%	45 70.3%	5 71.4%	431 73.1%
1 unilateral reinjection	1 1.4%	20 6.3%	4 3.0%	1 1.6%	1 14.3%	27 4.6%
2 unilateral reinjections	0 0%	3 0.9%	0 0%	0 0%	0 0%	3 0.5%
Surgery	23 32.4%	45 14.2%	42 31.8%	18 28.1%	1 14.3%	129 21.9%
Total	71 12.0%	316 53.6%	132 22.4%	64 10.8%	7 1.2%	590 100%

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Retrospective case series</td></tr>
<tr><td>Kouame et al. 2003

477 paediatric patients (699 ureters). Follow-up:

Selection criteria: Patients with reflux grades I-IV treated with injection of Macroplastique were included. Patients with reflux grade V were excluded. Males <2 years old were also excluded, due to technical impossibility of procedure in this population.

Patient characteristics: vesico-ureteric reflux (VUR) was bilateral in 192 children (40%) and unilateral in 285 children (60%).

Procedure details: all patients were operated on by the same surgeon, on an outpatient basis. 0.1 to 0.5 ml (0.3 ml average) of Macroplastique injected. Intravenous prophylactic antibiotics (Cefuroxime 50 mg/kg) and oral antibiotics (sulfamethoxazole-trimethoprime) 5 mg/kg/j prescribed over period of 15</td><td>354/477 (74%) children and 514/669 (77%) of refluxing ureters, including 167 cases of bilateral reflux and 180 cases of unilateral reflux were cured.

A difference was observed between the cure rate for bilateral reflux (88%) and unilateral reflux (63%) (p <0.05).

Total results: percentages of cure of the treated children and ureters
<table><tr><td></td><td>Number of children</td><td>Refluxing ureters</td><td>Total ureters injected</td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>Total</td><td>477</td><td>669</td><td>765</td></tr><tr><td>Cure</td><td>354 (74%)</td><td>514 (77%)</td><td>603 (79%)</td></tr><tr><td>Failure</td><td>123 (26%)</td><td>155 (23%)</td><td>162 (21%)</td></tr></table>
Failure rate in cases of grade I and II reflux was significantly higher than in grade III and IV (p <0.05).

Distribution of failure according to the rank of reflux after the first injection
<table><tr><td>Failure by grade</td><td>N=155/669</td><td>Percentage (%)</td></tr><tr><td>I</td><td>31/96</td><td>32</td></tr><tr><td>II</td><td>106/435</td><td>24</td></tr><tr><td>III</td><td>18/125</td><td>14</td></tr><tr><td>IV</td><td>0/13</td><td>0</td></tr></table>
Distribution of failure after first injection (by age):
17% (0-2 years), 25% (2-3 years), 23% (3-5 years), 42% (5-10 years), 1% (10-15 years).
Of the 123 (26%) children who weren't cured, 58 (47%) had surgical</td><td></td><td>Brand used: Macroplastique

Potential for bias:
The authors believe that the failure rate for grade I and II reflux could be explained by the concomitant presence of detrusor-sphincter dyssynergy that was not systematically investigated preoperatively and by the fact that endoscopic correction of anatomical lesions gives better results in the case of more serious grade III and IV reflux malformations.

Outcome measures and their validity:
Criteria of effectiveness of treatment were absence of the clinical and bacteriological urinary infection and the disappearance of reflux as assessed by cystography. Failures assessed by clinical and bacteriological monitoring when the children</td></tr>
</table>

<table>
<tr>
<td>days.</td>
<td>correction of reflux (technique of Cohen) of which 36 (62%) had unilateral reflux and 22 (38%) had bilateral reflux.

Among patients surveyed, two had a second injection (1/2 (50%) successful, 1/2 (50%) failure on duplicity, corrected surgically).

Appearance of contralateral reflux according to the unilateral or bilateral treatment of unilateral VUR.
<table>
<tr><th></th><th></th><th>Appearance of contralateral reflux</th><th>Absence of contralateral reflux</th></tr>
<tr><td>Bilateral injection</td><td>n=96</td><td>7</td><td>89</td></tr>
<tr><td>Unilateral injection</td><td>n=189</td><td>17</td><td>172</td></tr>
</table>
The development of de novo contralateral reflux was not statistically related to unilateral or bilateral injection for the treatment of unilateral reflux.</td>
<td></td>
<td>were asymptomatic without prophylactic antibiotics, requiring either a re-injection or a reimplantation. Results for unilateral and bilateral reflux patients were compared by a chi square test. Failures were studied according to the age of the children and the grade of reflux. International classification of reflux grades used.</td>
</tr>
</table>

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Retrospective case series			
Muslumanoglu *et al*. 2003 24 paediatric patients (36 renoureteral units). *Mean follow up:* 13.2 ±8.4 (standard deviation) months (range 6-30 months) *Selection criteria:* patients with primary VUR who were treated with endoscopic injection of Macroplastique into the ureterovesical junction of the refluxing ureters. Grade III: 25 ureters Grade II: 8 ureters Grade I: 3 ureters *Procedure details:* mean volume of PDMS injected was 1.26 cc (0.5-2.6 cc).	Initial injection resolved reflux in 36 ureters (69.4%). Second injection was successful in an additional 9 reno-ureteral units. Overall success rate was 86.1% (31/36 reno-ureteral units).	Of one case with persisting VUR after two injections, one child, who experienced pylonephritis (4.1%) underwent open surgery. Extravasation of injection material in 1 case (4.1%). Did not result in any complications. A second injection successfully corrected reflux in this case. *De novo* contralateral VUR (grade 2) developed in 1 child (4.1%), and she was under close follow-up at time of writing. Evidence of PDMS migration was not observed in any case.	*Brand used:* Macroplastique. *Outcome measures and their validity:* Voiding cysto-urethrography at 6 months.

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Retrospective case series (multicentre)</td></tr>
<tr>
<td>Van Capelle et al. 2004

195 paediatric patients (94 patients in Zwolle (152 ureters, 72 girls, 22 boys); 101 patients in Glasgow (161 ureters, 63 girls, 38 boys).

Follow-up: 3 months, 12 months. Patients considered cured at 1 year follow-up were discharged from further follow-up visits. Patients, or parents/guardians were interviewed after several years (mean of 4.1 and 6 years after last treatment in Zwolle and Glasgow, respectively).

Lost to follow-up: data for 26 ureteral units was missing before treatment; 3 missing after treatment.

Selection criteria: inclusion criteria were informed consent, persisting reflux after treating the underlying condition and grade I-V reflux. Exclusion criteria were secondary reflux, UTI at the time of treatment, malignancies of the bladder or ureters, previous injection therapy and a ‘golf-hole’ ostium.</td>
<td>
<table>
<tr><td>N ureters (%)</td><td colspan="2">Zwolle, 3-mo.</td><td colspan="2">Glasgow, 3-month</td><td>Zwolle, final</td><td>Glasgow, final</td></tr>
<tr><td>Grade</td><td>units</td><td>cured</td><td>units</td><td>cured</td><td>cured</td><td>cured</td></tr>
<tr><td>I</td><td>10</td><td>7</td><td>6</td><td>5</td><td>7</td><td>4</td></tr>
<tr><td>II</td><td>52</td><td>45 (87)</td><td>23</td><td>16 (70)</td><td>37 (71)</td><td>23 (100)</td></tr>
<tr><td>III</td><td>61</td><td>45 (74)</td><td>73</td><td>41 (56)</td><td>44 (72)</td><td>54 (74)</td></tr>
<tr><td>IV</td><td>27</td><td>19 (70)</td><td>44</td><td>31 (71)</td><td>14 (52)</td><td>38 (86)</td></tr>
<tr><td>V</td><td>2</td><td>2</td><td>4</td><td>1</td><td>2</td><td>2</td></tr>
<tr><td>Missing</td><td>0</td><td>0</td><td>11</td><td>7</td><td>3</td><td>8</td></tr>
<tr><td>Total</td><td>152</td><td>118 (80)</td><td>161</td><td>94 (58)</td><td>104 (68)</td><td>129 (80)</td></tr>
<tr><td>Downgraded to I</td><td></td><td></td><td></td><td></td><td>16</td><td>9</td></tr>
<tr><td>Final success rate</td><td></td><td></td><td></td><td></td><td>120 (79)</td><td>138 (86)</td></tr>
<tr><td>Total</td><td></td><td></td><td></td><td></td><td>107</td><td>129</td></tr>
</table>
Overall results:
84% and 77% of the patients were successfully treated in Glasgow and Zwolle, respectively. Overall success rate was 82.3% of patients.
71/311 (23%) ureters were re-treated.
Ureteric re-implantation was necessary in 31/311 (9.97%) refluxing ureters.
Contralateral reflux occurred in 7/311 (2.25%) ureters. Three grade I patients had no further surgical treatment, 2 grade II patients</td>
<td>Ureteric obstruction in 4/311 (1.29%) ureters.

Erosion of PDMS implant in 2/195 (1.03%) patients. Did not compromise further treatment.

UTI recurred after treatment in 14/94 (14.89%) Zwolle patients (11 with persistent VUR), and in 18/101(17.82%) Glasgow patients (6 with VUR).</td>
<td>Brand used: Macroplastique.

Potential for bias:
High re-treatment levels may be attributable to early inexperience of operators.
Not all patients received the same treatment. Glasgow patients received additional treatments, resulting in a higher rate of cure at 12 months compared to 3 months.

Outcome measures and their validity:
Clinical cure was defined as reduction to grade 0, while the success rate was defined as grade 0 or reduction to grade I VUR. All patients were investigated for renal function with ultrasonography and a reflux study, DMSA scan and VCUG; if the VCUG indicated no reflux the prophylactic antibiotics were discontinued. If reflux was persistent the patient was re-treated at 3-6 months after initial injection. If patients were cured on the basis of the</td>
</tr>
</table>

Procedure details: Outpatient procedure under general anaesthesia. Patients maintained on prophylactic antibiotic cover until their 3-month follow-up.	were cured, and 2 grade III patients were cured after endoscopic treatment. *Zwolle results:* Cure rate at 3 months after one injection was 80%. Screening at 1 year after the last treatment showed a 73% cure rate. After a mean (range) follow-up of 4.1 (0.25-9.2) years, the cure rate was 68%, while the success rate was 79% *Glasgow results:* Cure rate at 3 months after one injection was 58%, which was improved by additional treatments to 80% at a mean (range) follow-up of 6 (1-9) years. The success rate was 86%. Only in Glasgow were third (11 units) and fourth (3 units) implantations required.		VCUG and DMSA scan after 1 year, and free of symptoms, they were considered cured. If re-treatment failed, patients were scheduled for open surgical correction. If there had been no signs or other symptoms related to VUR at interview follow-up, patients were considered clinically cured. Failure to correct the reflux was defined as the persistence of VUR after endoscopic injection that was also documented on VCUG. Contralateral reflux was defined as the appearance of reflux on the contralateral side of the refluxing ureter after endoscopic injection. All patients were graded according to the international classification system. Grades of VUR weren't documented in 11 patients. *Other comments:* Some support from Uroplasty received.

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case report			
Dewan *et al*. 2000 1 paediatric patient (10 months old) *Follow- up:* complication found 2 months after initial injection. *Patient details:* underwent injection of 0.7 mL of Bioplastique for treatment of bilateral grade III VUR., followed 2 months later by extravesical ureteric reimplantation. Enlarged pelvic lymph node was discovered at this time. Lymph node was excised and biopsy of silicone implant taken at the ureteric orifice.	Large proportion of excised silicone particles and particles in the lymph node were <50 μm, while the usual particle size of Bioplastique is reported as 100-400 μm. Smaller particle size increases risk of migration.	Silicone particles migrated to pelvic lymph node. Several particles measured 5-15 μm, but particles of up to 100 μm were also found. Exact mechanism of migration is unknown.	*Brand used:* Bioplastique

Appendix B: Table of Key Efficacy and Safety Findings (Faecal Incontinence)

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Randomised Controlled Trial</td></tr>
<tr>
<td>Tjandra et al. 2004

82 patients (64 female, 18 male, median age 66, range 34-89).

Group A: Bioplastique injection with endoanal ultrasound guidance (n=42).
Group B: Bioplastique injection by palpation (feel) (n=40).

Median follow-up: 6 months (range 1-12 months).

Comparison: Bioplastique injection into the intersphincteric space and internal anal sphincter with or without endoanal ultrasound.

Selection criteria: Patients with faecal incontinence caused by internal sphincter dysfunction. All patients had previously failed treatment with bulking or constipating agents</td>
<td>Bioplastique implants significantly improved faecal incontinence in both groups, although the improvement was significantly greater in group A. Global quality of life scores also improved significantly in both groups.

Continence score and visual analog scale before and after injection in Group A (guided by endoanal ultrasound)
<table>
<tr><td></td><td>Baseline</td><td colspan="5">After injection</td></tr>
<tr><td></td><td></td><td>5 weeks</td><td>3 months</td><td>6 months</td><td>9 months</td><td>12 months</td></tr>
<tr><td>Patients</td><td>42</td><td>42</td><td>38</td><td>30</td><td>22</td><td>(10)</td></tr>
<tr><td>Wexner's continence score[a]</td><td>14.5 (10-20)</td><td>10 (3-18)</td><td>7 (1-12)</td><td>5 (2-13)</td><td>4 (2-13)</td><td>3 (1-12)</td></tr>
<tr><td>Visual analog quality of life score[b]</td><td>4 (1-8)</td><td>7 (4-9)</td><td>9 (6-10)</td><td>9 (6-10)</td><td>9.5 (8-10)</td><td>10 (9-10)</td></tr>
</table>
Median (range) for Wexner's continence score and VAS. P <0.01 was considered statistically significant. P value for all values of Wexner's continence score and VAS during follow-up was <0.001.
[a] Wexner's score: 0, perfect continence; 20, complete incontinence
[b] Visual analog scale: 1-10, 10 being best</td>
<td>Skin testing for silicone was performed and allergy was not a problem in any of the patients.

No infections, erosion of implants, or fistulation.

No constipation.

2/42 (4.76%) patients in group A and 4/40 (10%) patients in group B noted minor discomfort at anal injection sites that required simple oral analgesia.

1/40 (2.5%) patients in group B had persistent anal discomfort for six weeks after the procedure. When evaluated by digital rectal examination and by endoanal ultrasound, the</td>
<td>Brand used: Bioplastique.

Potential for bias:
Both groups were similar with regard to age, gender, past anorectal surgery, duration of follow-up and baseline continence score. During follow-up, the use of bulking agents or anti-diarrhoeal medications was not monitored or controlled, because excessive need for these agents would be indicated by worsened continence scores.

Outcome measures and their validity:
Clinical assessment, endoanal ultrasound, anorectal physiologic testing including pudenal nerve terminal motor latency (PNTML), Wexner continence score (0-20; 0, perfect continence; 20, complete</td>
</tr>
</table>

and dedicated pelvic floor physiotherapy. Exclusion criteria included pregnancy, active perianal sepsis, unresected anorectal cancer, and immunosuppression.

Procedure details:
All patients received an enema or, if performed in conjunction with a colonoscopy, a full mechanical bowel preparation. A single dose of prophylactic antibiotics was given, followed by a five-day course of augmentin duo forte tablets. Procedure was performed on outpatient basis under mild sedation with local anaesthesia. Patients were randomised to have injection of Bioplastique either by feel or guided by endoanal ultrasound. A total of three doses of 2.5 ml of Bioplastique implants were injected into the area of defect of internal anal sphincter (IAS), and a fourth dose in the intersphincteric space contralateral to the IAS defect to provide symmetry. Four doses of 2.5 ml implants were injected at 2, 4, 8 and 10 o'clock positions in patients with a structurally intact but

Continence score and visual analog scale before and after injection in Group B (guided by palpation)

	Baseline	After injection				
		5 weeks	3 months	6 months	9 months	12 months
Patients	40	40	32	21	11	5
Wexner's continence score	14.5 (11-20)	11 (5-17)	9.5 (3-14)	8 (2-12)	10 (2-13)	11 (2-12)[a]
Visual analog quality of life score	4 (1-7)	8 (1-9)	9 (2-10)	9 (1-10)	8 (2-10)	4 (2-10)[b]

[a] $P = 0.05$
[b] $P = 0.07$

At 3 months follow-up, significantly more group A patients than group B patients had >50% improvement in Wexner's score (69% vs. 40%; $P = 0.014$). There was a significant trend toward improved faecal continence at 1-month review, and the continence continued to improve significantly until the 12-month review in group A and up to the 6-month review in group B.

Wexner's continence score improved from a median of 14.5 (range 10-20) at baseline to 10 (range 3-18) at 1 month and 5 (range 2-13) at 6 months after the procedure in group A; 93% of group A and 92% of group B patients had >50% improvement in VAS (P <0.001).

VAS improved from a median of 4 at baseline to 9 at three months follow-up for both groups. At six months median follow-up, there was significant improvement in all four domains (lifestyle, coping/behaviour,

injected material was more superficial than intended, located in the submucosal plane.

incontinence), visual analog scale (1-10; 10 being best) for global quality of life, faecal incontinence quality of life scales, and the Short Form-12 (SF-12) health survey questionnaire were undertaken before injection (baseline) and at one-month and three-month intervals after Bioplastique injection. A patient with PNTML longer than 2.6 ms was considered to have pudenal neuropathy.

diffusely weakened IAS.	depression/self perception, and embarrassment) of the faecal incontinence quality of life scale for both groups. At median follow-up of 6 months, both the physical health scale and mental health scale of SF-12 improved significantly in group A but not in group B. 26/42 (61.9%) patients in group A and 22/40 (55%) patients in group B had a unilaterally or bilaterally prolonged PNTML. The improvement in continence scores and VAS were similar in both group regardless of whether pudenal neuropathy was present. Changes in faecal incontinence quality of life scales and SF-12 within each group were also independent of PNTML (all values P <0.05). Thus presence of a prolonged PNTML did not appear to have an adverse impact on outcome. Maximum anal resting pressure increased significantly from 23 (range 10-51) mmHg to 38 (range 21-62) mmHg at three months after injection in group A. This increase of 89% was statistically significant (P <0.01). There was a smaller increase in the maximum resting pressure in group B (42%; P <0.01). The improvement in maximum resting pressure in group A was significantly greater than that in group B (P <0.01). There was a minor and similar improvement in maximum squeeze pressure (10%) in both groups. Endoanal ultrasound at 1 month follow-up showed that the injected implants appeared globular and remained at the site of injection around the IAS in the middle and upper anal canal, without any evidence of migration. Endoanal ultrasound was performed in 66 patients at 3 months follow-up. The IAS and intersphincteric space became more hyperechoic and the injected material became less discretely globular in all patients.		

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Case series</td></tr>
<tr>
<td>Kenefick et al. 2002

6 patients.

Follow-up: median 18 months (range 15-19).

Selection criteria: patients with severe passive faecal incontinence for solid or liquid stool due to IAS dysfunction were selected for the study. Patients with IAS muscle degeneration and those with discrete IAS defects were included. All patients had failed standard conventional treatment including anti-diarrhoeal agents and behavioural therapy (biofeedback), and were considered psychologically suitable to enter a trial. Patients with perianal sepsis, severe scarring, diabetes, immunosuppression, or those who were pregnant were excluded.

Procedure details: performed as outpatient procedure under local anaesthesia. 18 gauge 2.5 inch needle was used. Three injection of 2 ml Bioplastique were injected at the 3, 7,</td>
<td>5/6 (83.33%) patients showed improvement in symptoms and patient satisfaction. The patient who did not improve proceeded to have a colostomy.

Faecal incontinence scores (worst score=24; best score=0) improved significantly from a median of 14 (range 11-20) before the procedure to 8 (range 6-15) after the procedure (p=0.04).

Continence scores before and after injection:
<table>
<tr><td></td><td colspan="2">Continence score</td></tr>
<tr><td>Patient no.</td><td>Before</td><td>After</td></tr>
<tr><td>1</td><td>11</td><td>9</td></tr>
<tr><td>2</td><td>15</td><td>15</td></tr>
<tr><td>3</td><td>15</td><td>13</td></tr>
<tr><td>4</td><td>12</td><td>7</td></tr>
<tr><td>5</td><td>11</td><td>7</td></tr>
<tr><td>6</td><td>20</td><td>6</td></tr>
<tr><td>Median</td><td>13.5</td><td>8*</td></tr>
</table>
*p <0.05
Continence score ranges from 0=complete continence to 24= worst incontinence.

Physical function SF-36 score improved from a median of 26 (range 5-33) pre-procedure to 79 (range 25-100) post-procedure (p=0.02) and social function score from 10 (range 5-37) to 100 (range 50-100) (p=0.02).</td>
<td>Endoanal ultrasounds in the five patients who showed a marked improvement confirmed that the Bioplastique was within the upper part of the anal canal extending up to, and partly beyond, the level of the puborectalis ring. The material remained at the site of the injection with no apparent local migration, either within or around the IAS.

In the patient who showed no improvement, ultrasound revealed that the residual Bioplastique had migrated to lie above the puborectalis muscle so that there was no material remaining within the anal canal.

There were no episodes of infection or leakage in any of the patients. No patient experienced severe pain or constipation, and erosion of the implants was not encountered.</td>
<td>Brand used: Bioplastique.

Outcome measures and their validity: Maximum anal resting pressure, maximum squeeze pressure (the increment above resting pressure), rectal sensation to balloon distension with air at threshold, urge and maximum tolerated volume, and a two week bowel symptom diary, validated faecal incontinence severity score, and the SF-36 health survey questionnaire were used before injection and at follow-up. Postprocedural ultrasound was not performed until six weeks after injection to avoid possible compression or displacement of the biomaterial.</td>
</tr>
</table>

and 11 o'clock positions into the area of the internal anal sphincter. Prior to injection, patients were given intravenous prophylactic antibiotics. Patients were observed for a four hour period post-procedure to exclude early complications of pain and bleeding or any other unexpected complications. They were then discharged with post-procedural oral antibiotics, analgesia and laxatives for one week.

Quality of life scores before and after injection:

	SF-36 physical function		SF-36 social functioning	
Patient no.	Before	After	Before	After
1	28	100	10	100
2	29	90	10	100
3	24	70	5	100
4	5	87	20	100
5	15	25	3	50
6	33	70	37	62
Median	26	78.5*	10	100*

* $p<0.05$

Quality of life score ranges form 0=minimum to 100=maximum

Median anal resting pressure showed a significant increase from 46 cm H_2O (range 20-79) to 75 cm H_2O (range 57-96) ($p=0.03$) and median squeeze pressure increased from 98 cm H_2O (range 63-268) to 142 cm H_2O (range 57-300) ($p=0.1$).

Anal manometry results before and after injection:

	Max resting pressure (cm H_2O)		Max squeeze pressure (cm H_2O)	
Patient no.	Before	After	Before	After
1	79	92	268	300
2	65	85	96	132
3	52	96	167	151
4	30	60	86	290
5	40	64	63	57

	6	20	57	100	123		
	Median	46	74.5*	98	141.5		

* $p<0.05$

Maximum resting pressure was measured using a stationary pull through technique. Maximum squeeze pressure was measured as the increment above resting pressure.

<table>
<tr><th>Study Details</th><th>Key Efficacy Findings</th><th>Key Safety Findings</th><th>Appraisal/Comments</th></tr>
<tr><td colspan="4">Case series</td></tr>
<tr>
<td>Malouf et al. 2001

10 patients (6 female, 4 male; median age, 64; range, 41-80 years).

Follow-up: 6 weeks; 12 weeks; 6 months.

Selection criteria: Passive faecal incontinence to solid or liquid stool causing interference with daily living. All patients had to have failed previous treatment with antidiarrhoeal agents and had to be considered psychologically stable and suitable for intervention. Patients with diabetes, perianal sepsis, marked perianal scarring, immunosuppression, and pregnancy were excluded.

Procedure details: All injections were performed on an outpatient basis. Ultrasound was used to identify the injection site for patients with a single sphincter disruption. Local anaesthetic was</td>
<td>The first two patients (20%) were injected using an 18-gauge, 2.5-inch needle without complications or therapeutic response. These two patients were reinjected, and the next four patients (40%) were injected using an 18-gauge, 1-inch needle. Because of leakage and infection experienced with the 1-inch needle, a 2.5-inch needle was again used for the final four patients (40%).

Improvement in symptoms at follow-up:
<table>
<tr><th>Improvement at 6 weeks</th><th>Improvement at 6 months</th></tr>
<tr><td>Marked after 2nd injection</td><td>Nil</td></tr>
<tr><td>Nil</td><td>Nil</td></tr>
<tr><td>Nil</td><td>Nil</td></tr>
<tr><td>Complete</td><td>Marked</td></tr>
<tr><td>Complete</td><td>Nil</td></tr>
<tr><td>Complete</td><td>Nil</td></tr>
<tr><td>Marked</td><td>Nil</td></tr>
<tr><td>Marked</td><td>Marked</td></tr>
<tr><td>Nil</td><td>Nil</td></tr>
<tr><td>Marked</td><td>Minor</td></tr>
</table>
Complete improvement = no leakage of solid or liquid stool; marked improvement = minimal leakage of liquid stool and judged by the patient as ≥75% improvement; minor improvement = leakage of liquid stool and judged by the patient as a 20-50% improvement; nil improvement = leakage of liquid and at times solid stool and judged by the patient as <20% improvement..</td>
<td>Five out of the first six patients (83.33%) had pain or ulceration over the injection site or in the anal canal after being injected with the 1-inch needle. This pain was often severe, and the infection required up to ten weeks of antibiotic therapy. All patients ultimately healed with resolution of pain. With the altered protocol of the last four patients, there were no complications or adverse effects.

One of the patients who showed no improvement after one or two injection sessions had leakage of the product out of the injection site.</td>
<td>Brand used: Bioplastique.

Potential for bias:

Outcome measures and their validity: Clinical assessment, anal manometry, endoanal ultrasound, and completion of a two-week bowel diary documenting bowel activity and all episodes of incontinence to liquid or solid stool were undertaken before and six weeks after injection with Bioplastique. Those patients who failed to become continent to solid and liquid stool at six weeks were offered a second injection session and were assessed again six weeks later. All patients were clinically reviewed at six months follow-up. Patients were precluded from taking anti-diarrhoeal agents during the diary assessment periods.</td>
</tr>
</table>

used. Patients with a localised disruption of the internal anal sphincter received a localised single injection of 5 ml Bioplastique to the site of the disruption, whereas patients with diffuse internal sphincter weakness but a structurally intact muscle received multiple circumferential injections totalling between 5 and 11.5 ml.	At six-month follow-up, 7/10 (70%) patients reported no relief of symptoms; 2/10 (20%) patients had sustained marked improvement, and 1/10 (10%) patient had sustained slight improvement. Examination of 9 patients at six months revealed that the Bioplastique could still be palpated at the injection sites in 8 patients (88.89%). There was no significant change in either the maximum resting pressure (median and (range) of 54 (28-95) *vs.* 40 (30-86) *vs.* 60 (35-127); $P = 0.83$ at 6 weeks and $P = 0.66$ at 6 months) or the maximum squeeze pressure increment. The endoanal ultrasound scans performed at six weeks after injection showed correct placement of Bioplastique in 9/10 (90%) patients. 1/10 (10%) patient lost all the product through leakage. 5/10 (50%) patients had a repeat endosonographic examination		

Appendix C: Table of Key Efficacy and Safety Findings (Periprosthetical Leakage)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case series			
Lorincz *et al*. 2005 7 patients *Follow-up:* 2 years. *Patient characteristics:* All patients had undergone total laryngectomy with implantation of voice prosthesis. *Procedure details:* Patients with total laryngectomy underwent Bioplastique® augmentation of the tissues surrounding the periprosthetical fistula, thus reducing the gap between the implanted prosthesis and the mural structures of the fistula.	All surgeries were successful in terms of either eliminating or reducing the leakage to the minimal level. A single injection was sufficient for 4/7 (57.1%) patients. The augmentation needed to be repeated in 2/7 (28.6%) cases within 4-6 months after the initial treatment. This was due to further subsequent enlargement of the fistula. In 1/7 (14.3%) cases, the augmentation had to be performed more than three consecutive times (reason not stated). The tissue-adhesive effect of Bioplastique® improves the quality of the irradiated tissues.	A majority of patients had undergone radiotherapy after the total laryngectomy. Hence, in most patients, Bioplastique® was injected into previously irradiated tissues. This did not provoke further complications. It is best that a minimum of 1 year is maintained between the total laryngectomy and the implantation of Bioplastique®.	*Brand used:* Bioplastique® (mixture of textured poly-dimethyl-siloxane (PDMS) suspended in poly-vinyl-pyrrolidone (PVP) *Outcome measures and their validity:* Number of injections required before leakage stopped. Time taken (in months) before appearance of leakage after implant. *Other comments:* Poorly presented results. Patient course table very unclear.

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case report			
Bertino *et al*. 2002 3 patients. *Follow-up*: 5 months *Patient characteristics* : patients fitted with Provox2 tracheoesophageal voice prostheses who had been experiencing leakage for about 4 months underwent injectable silicone implant procedures.	Correction of fistula size was easy to accomplish and well-tolerated by patients. Size of fistula and its fluid-tightness remained stable in time.	No sign of inflammation, formation of granulomas or other pathological modifications	*Brand used:* Bioplastique™ (Bioplasty BV, Hofkamp 2, 1616 DC Geleen, the Netherlands)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case report			
Rokade *et al*. 2003 2 patients. *Follow-up*: Patient 1: 11 months Patient 2: >8 months *Patient characteristics:* Chronic leakage around a Provox 2 valve that could not be managed by replacement with valves of different sizes and insertion of a feeding tube through the fistula. *Procedure details:* Bioplastique® was injected around the tracheo-oesophageal fistula (TOF) to reduce the size of the TOF and treat the intractable leakage. Procedure was carried out as day surgery. 1/2 (50%) patients did not require anaesthesia, while the other patient (50%) was given general anaesthesia on his demand. The leaking valve was removed and 0.4ml of Bioplastique® was injected at three sties (2, 6 and 10 o'clock positions) around the TOF using a 20 gauge needle and a special gun with a ratchet mechanism designed to inject exact quantities. A new size 8 Provox 2 valve was re-inserted.	Patient 1: no further leakage was found at follow-up. Patient 2: No further leakage for more than eight months.		*Brand used:* Bioplastique®.

Appendix D: Table of Key Efficacy and Safety Findings (Unilateral Vocal Fold Paralysis)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case series			
Alves *et al*. 2002 16 patients (10 male, 6 female) *Follow-up*: 1, 3 and 6 months. *Lost to follow-up:* 2 patients were unable to attend voice clinic follow-up for completion of the questionnaire. 5/16 (31.25%) survived to the 3-month assessment and 1/16 (6.25%) to 6 months assessment. *Aetiology:* 14/16 (87.5%) patients had bronchogenic carcinoma (underlying cause of vocal cord paralysis). Two out of 16 patients (12.5%) had squamous carcinoma in the neck. *Selection criteria:* Patients with unilateral vocal cord palsy resuling from terminal malignant disease attending the voice	*Voice score:* There was no significant difference between the two observer scores at any of the follow-up periods. The mean voice score preoperatively was 3.8 (observer 1) and 3.7 (observer 2). This improved at 1 month to 1.9 and 2.2 ($p < 0.001$ compared with preoperative score). At 3 months, voice scores further improved to 2 and 1.75 (only 5 patients reached this stage), and at 6 months, score was 2 (but only one patient reached this stage). *Maximum phonation time:* Mean MPT was 3.2s preoperatively, 7.8s at 1 month ($p < 0.001$ compared with preoperative MPT), 7.8s at 3 months and 5s at 6 months. *Voice handicap index:* Mean total preoperative VHI was 74.4, decreasing to 20.9 at 1 month ($p < 0.0001$), 21.8 at 3 months and 4.0 at 6 months. All		*Brand used:* Bioplastique. *Outcome measures and their validity:* Patients were asked to read a standard passage (*The North Wind and the Sun*). Two independent observers (a speech and language therapist and an otolaryngologist) who were not involved in treating the patients blindly assessed these digital recordings on a scale from 1 to 5, where 1 represented a normal voice with no 'breathiness' and 5 no voice or whisper only. Maximum phonation time (MPT) was assessed (best of three attempts). Two questionnaires were used to assess quality of life (Voice Handicap Index (VHI)) assessed patients' own perceptions of their voice quality, and the Medical Outcomes Study (MOS) assessed eight areas of health.

<table>
<tr>
<td>clinic at Gartnavel General Hospital were eligible for inclusion. Those with a significant phonatory gap and poor voice quality were offered Bioplastique injection therapy.

Procedure details: injection carried out using a tubeless jet insufflation general anaesthetic. One consultant surgeon performed all surgery.</td>
<td>postoperative scores decreased but, because of losses to follow-up, statistical significance was not reached at 3 and 6 months.

<table>
<tr><th>VHI category</th><th>Preop</th><th>1 month</th><th>3 months</th><th>6 months</th></tr>
<tr><td>Total</td><td>74.4</td><td>27.2</td><td>25.3</td><td>4</td></tr>
<tr><td>Physical</td><td>20.9</td><td>11.8</td><td>7.2</td><td>3</td></tr>
<tr><td>Functional</td><td>21.8</td><td>8.8</td><td>5.3</td><td>0</td></tr>
<tr><td>Emotional</td><td>4</td><td>3</td><td>0</td><td>1</td></tr>
</table>

SF-36:
Significant improvement in social functioning at 1 month ($p < 0.01$), emotional role functioning at 1 month ($p < 0.001$) and mental health score at 1 month ($p < 0.05$).</td>
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Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Retrospective case series			
Sittel *et al*. 2000 10 patients. *Mean follow-up:* 88.4 months (range 69-102 months). *Lost to follow-up:* one patient died for reasons not associated with injection laryngoplasty. Two patients had moved without notice and were lost to follow-up. 7/10 patients were contacted and agreed to have their larynges re-evaluated. *Selection criteria:* medical records of 10 patients who were treated with PDMS were identified and retrieved. All procedures had been performed by two of the authors. *Procedure details:* application was performed during suspension microlaryngoscopy under general anaesthesia. For vocal fold augmentation, the correct application site is deeply lateral to the thyroarytaenoid muscle. Typically a	7/7 (100%) patients answered 'yes' to the question "Did your voice improve after injection laryngoplasty?" 7/7 (100%) also answered 'yes' to the question of whether the effect had been lasting (until present time). Glottic closure was complete in 5/7 patients (71.43%). Significant glottal gap observed in 1/7 patients (14.29%). Persisting glottal gap due to under-correction from the beginning was hypothesised as underlying cause. The surface of the injected vocal fold was irregular in 1/7 (14.29%) patients. Authors propose this is because the PDMS had not been injected deep enough, leading to the subepithelial placement of several particles in the lamina propria of the vocal fold. Voice quality was reflected in the endoscopic findings: those patients without a glottal gap had fair to near-normal voices. The one patient with persisting glottic insufficiency had a breathy and hoarse, though usable, voice. In the patient with irregular lining of the free vocal	0/7 (0%) patients reported any complications that could be blamed on the substance injected. No larynges showed any signs of inflammation, granuloma formation, or other pathologic changes.	*Brand used:* Bioplastique. *Potential for bias:* Subjective outcome measures. *Outcome measures and their validity:* Videostroboscopy, documentation of vocal ability in a voice profile, and measurement of maximum phonation time. Each patient was asked three standardised questions: 1. Did your voice improve after injection laryngoplasty? 2. Was the improvement lasting? 3. Were there are any complications connected in your or your attending physician's mind with injection laryngoplasty?

total volume of 0.5 – 0.7cc in 2-3 injections is sufficient to augment a paralysed vocal fold.	fold edge, voice quality was better than anticipated and rated 'fair'. Maximum phonation time was 16.1 s in the average.		

Appendix E: Table of Key Efficacy and Safety Findings (Laryngeal Cleft Type I)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case report			
Ahluwalia *et al*. 2004 1 patient (17 year old female). *Follow-up*: 12 months *Patient details:* posterior glottic chink subsequently diagnosed at microlaryngoscopy as type I laryngeal cleft. *Procedure details:* underwent injection of Bioplastique. Previous treatments included initial endoscopic repair at 7 years of age, and a trial injection with Pentastarch at 17 years, followed by two separate injections Bioplastique.	Patient made a quick recovery and had an audibly louder voice after first injection. However, a smaller, although sizeable, defect remained. After a second, similar, injection of Bioplastique, there was further closure of the defect with further improvement in voice. At 1 year follow-up, patient had maintained a strong voice (perceptually within normal limits). Videostroboscopy demonstrated almost complete closure of the posterior glottic chink.	No subsequent dysphagia or laryngeal discomfort after first injection. No dysphagia or odynophagia after second injection.	*Brand used:* Bioplastique. *Outcome measures and their validity:* Videostroboscopy.

Appendix F: Table of Key Efficacy and Safety Findings (Stomal Leaks in Continent Diversion)

Study Details	Key Efficacy Findings	Key Safety Findings	Appraisal/Comments
Case Series			
Guys *et al.* 2002 6 patients (3 male and 3 female) *Mean follow-up*: 11 months (range 8-18). *Patient details:* patients with a neurogenic bladder who had a bladder augmentation and a continent catheterisable channel (four appendix and two ileum). *Procedure details:* injections were given under general anaesthesia or slight premedication. Procedure performed on an outpatient basis. Endoscopy was performed via the conduit in all cases, or if necessary and if possible, via the urethra. PDMS was injected around the vesico-appendiceal junction and along the conduit in the submucosal plane. *Mean volume injected:* 6 mL (range 3-8 mL)	After procedure, patients were able to continue intermittent catheterisation without delay. 1/6 (16.67%) patients had a second injection 3 months after the first injection. Stomal continence was restored in 4/6 (66.67%) patients. The results were stable at follow-up.	No complications occurred during or after treatment.	*Brand used:* Macroplastique. *Outcome measures and their validity:* Stomal continence, complications, resumption of catheterisation.