MEDICAL POLICY

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MEDICAL POLICY DETAILS	
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POLICY STATEMENT

Based upon our criteria and assessment of the peer-reviewed literature, biosynthetic fistula plugs, including plugs made of porcine small intestine submucosa (SIS) or of synthetic material (e.g., mesenchymal stem cells), have not been medically proven to be effective and, therefore, are considered **investigational** for all indications, including, but not limited to, the repair of anal and rectal fistulas.

DESCRIPTION

An anal fistula is an abnormal communication between the interior of the anal canal or rectum and the skin surface. Rarer forms may communicate with the vagina or other pelvic structures, including the bowel. Most fistulas begin as anorectal abscesses. When the abscess opens spontaneously into the anal canal (or has been opened surgically), a fistula may occur. Anal fistulas are described as low (present in the lower part and not extending up to the anorectal sling) or high (extending up to or beyond the anorectal sling). High fistula can be associated with incontinence. Anal fistulas are also classified according to their relationship with the external sphincter. Inter-sphincteric fistulas are the most common and cross only the internal sphincter. Trans-sphincteric fistulas pass through the internal and external sphincters. The type of surgical treatment depends on the location and complexity of the fistula. Treatments include fistulotomy/fistulectomy, endorectal/anal sliding flaps, seton drain, and fibrin glue. Lay-open fistulotomy in high fistulas carries risk of incontinence. Draining setons can control sepsis, but few patients heal after removal of the seton, and setons are poorly tolerated long-term. Cutting setons can cause continence disturbances. Because of recurrence rates and the significant risk of incontinence with these surgical procedures, sphincter-preserving techniques such as fistula plugs have been evaluated and proposed as an alternative method in the treatment of anorectal fistulas.

Anal fistula plugs are biosynthetic devices used to promote healing and prevent recurrence of an anal fistula. In a minimally invasive procedure, the fistula tract is identified using a probe or imaging techniques and then cleaned by irrigation. The conical-shaped fistula plug is pulled into the tract until it blocks the internal opening and then is anchored

in place with sutures. The external opening is not completely sealed so that drainage of the fistula can continue. The plug reinforces the soft tissue and then acts as a scaffold into which new tissue can grow to close the fistula. The plug is usually absorbed into the body in six to eight weeks. The procedure can be repeated in case of failure.

Adipose-derived mesenchymal stem cells (ASCs) injections are emerging as a new treatment option for the management of complex perianal fistulas. Mesenchymal stem cells are being used because of their immunomodulatory action and anti-inflammatory response. ASCs are easy to harvest and can differentiate into various cell types. The delivery of stem cells directly to fistula tracts can increase cell numbers locally and aid in fistula healing (Panes et al., 2022).

Darvadstrocel (Cx601, Alofisel; TiGenix S.A.U.) is a suspension of allogeneic expanded adipose-derived mesenchymal stem cells for the treatment of complex perianal fistulas in adult patients with non-active or mildly active luminal Crohns disease (CD). Darvadstrocel (DVS) is designed to be administered through local injection in the fistula region. In 2019, darvadstrocel received a Regenerative Medicine Advanced Therapy (RMAT) designation from the U.S. FDA for complex perianal fistulas in adult patients with CD. DVS is approved in the European Union/European Economic Area, Israel, Switzerland, and the United Kingdom but still under review for the United States. The safety and efficacy of DVS was demonstrated in the ADMIRE-CD (Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease) phase 3, double-blind, randomized trial (NCT01541579), during which DVS or control group, in combination with standard of care, was administered locally after fistula curettage and closure of the internal opening (Panes et al., 2022).

RATIONALE

The SIS Fistula Plug (Cook Biotech Incorporated) received Section 510(k) clearance from the U.S. Food and Drug Administration (FDA) in March 2005, based on similarity to predicate devices, including the SURGISIS Soft Tissue Graft and the STRATASIS Urethral Sling, both manufactured by Cook Biotech Incorporated. The SIS Fistula Plug is manufactured from porcine SIS and is intended for repair of anal, rectal, and enterocutaneous fistulas. The modified SIS Fistula Plug, also manufactured from porcine SIS, is supplied in a tapered configuration with a button, to provide increased retention of the plug and improved blockage of the fistula. It received Section 510(k) clearance in October 2006. In March 2009, W.L. Gore & Associates received Section 510(k) clearance for the BIO-A Fistula Plug, intended for use in anorectal fistulas. The GORE BIO-A Fistula Plug device comprises a porous structure of synthetic, bioabsorbable PGA/TMC copolymer fiber, degraded via a combination of hydrolytic and enzymatic pathways, and the same material, technology, and three-dimensional disk with tubes mesh design as the predicate GORE Bioabsorbable Mesh hernia plug device. The indications for use and performance of the GORE BIO-A Fistula Plug are substantially equivalent to the predicate Cook SIS Fistula Plug.

In 2022, the American Society of Colon and Rectal Surgeons (ASCRS) published practice guidelines on the treatment of anorectal abscess, fistula-in-ano, and rectovaginal fistula. The guidelines indicate that anal fistula plug, and fibrin glue are relatively ineffective treatments for fistula-in-ano (strong recommendation, level 1B evidence). The guidelines support local administration of mesenchymal stem cells as a safe and effective treatment for selected patients with refractory anorectal fistulas in the setting of Crohn’s disease; however, the ASCRS notes the recommendation is weak and is based on level 2B evidence (Gaertner, 2022).

Jayne et al. (2021) conducted the FIAT randomized controlled trial (RCT) to compare the use of porcine AFPs (Biodesign Surgisis) with surgeon's preference (advancement flap, cutting seton, fistulotomy, or Ligation of the Intersphincteric Fistula Tract [LIFT] procedure) in 304 patients with transsphincteric fistulas. The primary outcome was fecal incontinence quality of life (FIQoL) at 12 months. Secondary outcome measures included fistula healing, incontinence rates, and complications. No significant differences were seen in FIQoL between groups at 12 months. Clinical fistula healing was reported in 66/122 (54%) of the AFP group and 66/119 (55%) of the surgeon's preference group at 12 months. Marginal improvement in fecal incontinence rates was observed in both groups. Frequent complications and reinterventions were observed, with significantly more complications in the AFP group at 6 weeks.

Cheung et al. (2021) completed a systematic review and meta-analysis of all the available evidence (N=28 studies) on the surgical management of adults with non-Crohn-related perianal fistulas. The primary outcomes were fistula recurrence and fecal incontinence. Since the included studies had a range of different comparison groups, pooling of data from all 28

studies was not possible. In the review, 2 RCT studies compared fistula plug with advancement flap, with an increased recurrence rate in the plug group. Pooled data analysis on recurrence revealed an odds ratio (OR) favoring the advancement flap. No difference in incontinence scores between groups was noted.

In a European trial, H. Ortiz, and colleagues (2009) compared the use of Surgisis, a porcine submucosal anal fistula plug (AFP), with an endorectal anal flap (ERAF) procedure in a randomized, controlled trial (RCT) with 43 patients who had high anal fistula. The primary endpoint was fistula healing. Recurrence was defined as the presence of an abscess in the same area or obvious evidence of fistulization. Five patients in the AFP group and six in the ERAF group did not receive the allocated intervention, leaving 32 patients. One patient in the AFP group was lost to follow-up. A large number of recurrences in the fistula plug group led to premature closure of the trial. After one year, fistula recurrence was seen in 12 of 15 patients treated with an anal fistula plug versus two of 16 patients who underwent the flap procedure (relative risk 6.40 [95% confidence interval 1.70-23.97]); p less than 0.001). Fistulas recurred in nine of 16 patients who had previously undergone fistula surgery; eight of the nine patients had an AFP. A trend for more sphincter involvement and more females in the ERAF group was noted. Complications were not reported in this paper.

P.J. van Koperen et al. (2008) conducted an RCT to compare a fistula plug (n=31) with a mucosal advancement flap (n=29) for the treatment of high trans-sphincteric fistulas. At a follow-up of 11 months, the recurrence rates were 71% (n=22) in the anal fistula plug group and 52% (n=15) in the mucosal advancement flap group, which was not significantly different (p=.126). There were no significant differences in post-operative pain, pre- and post-operative incontinence scores, soiling, or quality of life. One patient in the plug group and two in the flap group experienced post-operative complications (abscess, pain, bleeding retrospectively).

D. Christoforidis et al. (2009) performed a retrospective analysis of patients from a U.S. center with trans-sphincteric fistulas treated with ERAF (n=43) or anal plug (Surgisis) (n=37) between January 1996 and April 2007. Success was defined as closed external opening in absence of symptoms at minimal follow-up of six months. The success rate was 63% in the ERAF group and 32% in the AFP group after a mean follow-up of 56 (range, 6–136) months for ERAF and 14 (range, 6–22) months for AFP. After exclusion of patients with early AFP extrusion, which may be considered a technical failure, the ERAF advantage was not statistically significant (p=0.06). Twenty-three of 27 patients who had ERAF and seven of 12 patients who had AFP responded to a questionnaire addressing functional outcomes. In the ERAF group, 11 of 23 patients had no continence disturbance versus six of seven in the AFP group. The lack of prospectively collected incontinence scores prior to the procedure and low response rate in the AFP group preclude valid comparisons on functional outcomes. Complication rates were low in both groups; two patients in the ERAF group required reoperation for bleeding. No serious complications occurred in the AFP group. The authors concluded that “randomized trials are needed to further elucidate the efficacy and potential functional benefit of AFP in the treatment of complex anal fistulas.”

Wang et al. (2009) compared outcomes of all patients with trans-sphincteric fistulas treated with AFP from July 2005 to December 2006 (n=29) with historical controls treated with ERAF (2001–2005) (n=26). Of 26 initial flap procedures, 10 failed and 16 healed. Of 29 initial plug procedures, 19 failed and 10 healed. In total, 30 advancement flaps and 34 plug procedures were performed (including the additional treatments for failed initial procedures). Closure rates were 34% for plugs (mean follow-up 279 [range, 110–690] days) and 62% for flaps (median follow-up 819 [range, 93–1928] days; p=0.045). Complications were not reported. The authors concluded that a systematic, randomized trial with long-term follow-up comparing advancement flaps with fistula plugs is needed; they calculated that 112 patients would need to be randomized to detect a statistically significant difference in success rates for each procedure. Because the fistula plugs are costly, the authors recommended that a cost-benefit analysis be performed.

A 2009 systematic review by P. Garg and colleagues to assess the efficacy of the anal fistula plug reported a wide range of success rates. In the 12 included studies, all of which were case series, reported success rates for the AFP procedure were from 24% to 92%. Success rates in treating complex fistula-in-ano in the eight prospective studies reviewed were 35%–87%. The authors concluded that, while the anal fistula plug procedure appeared safe, further RCTs are needed.

In 2012, three reviews were published comparing AFP to conventional surgical treatment for anal fistulas. Pu and colleagues undertook a meta-analysis of five studies (two RCTs and three retrospective studies) published through April 2012. Treatment options in the conventional arm of this review included endorectal/mucosal advancement flaps, fibrin

glue, and seton drains. On combined analysis, AFP patients had a higher recurrence rate (62%) compared to those undergoing conventional treatment options (47%) after three months of follow-up (5 studies, 428 patients; p=0.004,).

Leng and Jin undertook a meta-analysis of six studies published through April 2011 (three RCTs, two retrospective studies, and one cohort study) involving 408 patients, comparing AFP with mucosal advancement flap. On combined analysis, the differences in the overall success rates (six studies) and incidence of fistula recurrence (four studies, including three RCTs) were not statistically significant between the AFP and mucosal advancement flap. The risk of continence post-operatively (three studies, including two RCTs), however, was reported to be lower with AFP. In addition to the small numbers of controlled studies and limited follow-up, the findings of this meta-analysis were further limited by significant heterogeneity across studies.

O'Riordan and colleagues undertook a systematic review of AFP for patients with Crohn's disease and non-Crohn's-related anal fistulas. The follow-up period across studies ranged from three months to 24.5 months. The pooled proportion of patients achieving fistula closure in patients with non-Crohn's anal fistula was 0.54. The proportion achieving closure in patients with Crohn's disease was similar. There were no reported cases of any significant change in continence after AFP insertion in any of the study patients (n=196). The findings of this systematic review were limited by the variability of operative technique and peri-operative care across studies, which may influence the probability of success or failure associated with the AFP.

Overall, the evidence of efficacy of anal fistula plug treatment is limited. Two RCTs and retrospective comparisons did not demonstrate that anal plugs improved healing rates or reduced recurrence of anal fistulas. Numerous case series (e.g., C.N. Ellis et al. (2010), B.J. Champagne et al. (2006), M.F. McGee et al. (2010), S. Gonsalves et al. (2009)) report a wide range of results and contribute to the inability to allow conclusions to be drawn related to the long-term efficacy of fistula plugs. RCTs with sufficient numbers of patients and with appropriate length of follow-up that report healing and recurrence rates, and sphincter function before and after procedures, are required.

INSPECT, a retrospective study to evaluate the long-term effectiveness and safety of DVS in patient with perianal fistulizing CD treated in the ADMIRE-CD trial, evaluated whether the responses to DVS observed during the ADMIRE-CD trial were maintained beyond 104 weeks after treatment (Panes et al., 2022). Finding in this retrospective review was limited by small patient numbers, potential for population bias, and an inherent limitation of chart reviews, preventing robust comparisons across all outcomes (Panes et al., 2022). Clinical remission of complex perianal fistulas, previously reported at 52 weeks after DVS treatment in patients with CD, were sustained for up to 156 weeks in more than half of patients. DVS may represent an effective minimally invasive option to achieve long-term remission of complex perianal fistulas in patients with CD.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
0748T **(E/I)**	Injections of stem cell product into perianal perifistular soft tissue, including fistula preparation (e.g., removal of setons, fistula curettage, closure of internal openings)
46707 **(E/I)**	Repair of anorectal fistula with plug (e.g., porcine small intestine mucosa [SIS])

HCPCS Codes

Code	Description
C9796 **(E/I)**	Repair of enterocutaneous fistula small intestine or colon (excluding anorectal fistula) with plug (e.g., porcine small intestine submucosa [sis]) *(effective 04/01/24)*

ICD10 Codes

Code	Description
J86.0	Pyothorax with fistula
K50.013	Crohn's disease of small intestine with fistula
K50.113	Crohn's disease of large intestine with fistula
K50.813	Crohn's disease of both small and large intestine with fistula
K50.913	Crohn's disease, unspecified, with fistula
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.213	Ulcerative (chronic) proctitis with fistula
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.413	Inflammatory polyps of colon with fistula
K51.513	Left sided colitis with fistula
K51.813	Other ulcerative colitis with fistula
K51.913	Ulcerative colitis, unspecified with fistula
K60.3 - K60.5	Anal rectal fistulas (code range)
K63.2	Fistula of intestine
N32.1	Vesicointestinal fistula
N32.2	Vesical fistula, not elsewhere classified
N82.2 - N82.4	Female intestinal-genital tract fistula (code range)

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*Key Article

KEY WORDS

Fistula plug.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based upon our review, repair of an anal fistula with a fistula plug is not addressed in National or Regional Medicare coverage determinations or policies.