MEDICAL POLICY

Medical Policy Title	**Plugs for Fistula Repair**
Policy Number	**7.01.86**
Current Effective Date	February 20, 2025
Next Review Date	February 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Biosynthetic fistula plugs, including plugs made of porcine small intestine submucosa (SIS) or of synthetic material (e.g., mesenchymal stem cells), are considered **investigational** for all indications, including, but not limited to, the repair of anal and rectal fistulas.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational

POLICY GUIDELINE(S)

Not applicable

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. Fistulas may occur singly or in multiples. Symptoms include a purulent discharge and drainage of pus and/or stool near the anus, which can irritate the outer tissues causing itching and discomfort. Pain occurs when fistulas become blocked, and abscesses recur.

The most widely used classification of anal fistulas is the Parks classification system, which defines anal fistulas by their position relative to the anal sphincter as transsphincteric, intersphincteric, suprasphincteric, or extrasphincteric. More simply, anal fistulas are described as low (present distally and not extending up to the anorectal sling) or high (extending up to or beyond the anorectal sling). The repair of high fistulas can be associated with incontinence. Diagnosis may involve a fistula probe, anoscopy, fistulography, ultrasound, or magnetic resonance imaging.

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.

Darvadstrocel is a stem cell treatment that uses 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 Crohn's disease (CD). Darvadstrocel (DVS) is designed to be administered through local injection in the fistula region.

SUPPORTIVE LITERATURE

Overall, the evidence of efficacy of anal fistula plug treatment is limited and is insufficient to determine that the technology results in an improvement in net health outcomes. Randomized controlled trials (RCTs), nonrandomized studies and systematic reviews did not demonstrate that anal plugs improved healing rates or reduced recurrence of anal fistulas. Numerous case series (e.g., Ellis 2010; Champagne 2006; McGee 2010; Gonsalves 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.

Van Koperen and colleagues (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).

In a European RCT, Ortiz and colleagues (2009) compared the use of Surgisis, a porcine submucosal anal fistula plug (AFP) with an endorectal anal flap (ERAF) procedure with 43 patients who had high anal fistula. 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.

Christoforidis and colleagues (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 and colleagues (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 Garg and colleagues to assess the efficacy of the anal fistula plug (AFP) 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.

Jayne and colleagues (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. No significant differences were seen in fecal incontinence quality of life (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 and colleagues (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.

INSPECT, a retrospective study evaluated the long-term effectiveness and safety of DVS in patient with perianal fistulizing CD treated in the ADMIRE-CD trial and evaluated whether the responses to DVS observed during the ADMIRE-CD trial were maintained beyond 104 weeks after treatment (Panes et al., 2022). Findings were limited by small patient numbers, potential for population bias, and an inherent limitation of chart reviews, preventing robust comparisons across all outcomes. 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. Serclova and colleagues (2024) published long-term follow-up findings of the ADMIRE-CD II phase 3 study, which found that the efficacy outcomes were not statistically different between DVS and placebo and the placebo response rate was higher than expected. Based on these findings the pharmaceutical company, Takeda, voluntarily removed DVS from the European market.

An and colleagues (2023) compared clinical outcomes of AFP versus endoanal advancement flap repair (EAFR) for treatment of complex anal fistula in a systematic review and meta-analysis. Twelve studies were included (5 RCTs; 7 nonrandomized trials) with a total of 847 patients. The difference between pooled healing rates of AFP 48.3% and EAFR 64.4% was statistically significant ($p = 0.03$), with EAFR having a higher healing rate. There was no significant difference between groups for recurrence rate, wound infection rate, or complication rate.

In 2024, a phase I/II, open-label, single arm clinical trial of ex-vivo expanded human bone marrow derived allogeneic mesenchymal stromal cells in adult patients with perianal fistulizing Crohn's Disease was conducted to assess the safety of local administration (Swaroop 2024). A small sample of patients (n=10) were assessed for clinical severity and biomarkers at baseline and periodically until week 104 and underwent an MRI at week 24 and 104. Self-resolving procedure-related adverse events occurred in three patients, with no follow-up adverse events. In intention to treat analysis at week 24, two patients (20%) achieved fistula remission and seven (70%) had fistula response. At week 52, two (20%) patients were in remission and seven (70%) maintained response. At 104 weeks, two (20%) patients maintained a response and one (10%) was in remission. Despite a number of study limitation, the authors report a statistically significant decrease in perianal disease activity index ($p=0.008$), Van Assche Index ($p=0.008$) and improvement in quality-of-life ($p=0.001$) were observed over time, and that allogeneic bone marrow stem cells are safe and effective for the treatment of perianal fistulizing CD with significant improvement in clinical severity and radiological healing.

PROFESSIONAL GUIDELINE(S)

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 (Gaertner 2022).

According to the guidelines, an 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 (weak recommendation, level 2B evidence.

In 2019, the National Institute for Health and Care Excellence (NICE) determined that "current evidence on the safety and efficacy of bioprosthetic plug insertion for anal fistula is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit." The issued guidance notes that the procedure should only be done by a surgeon experienced in managing anal fistulas.

In 2019, the National Institute for Health and Care Excellence (NICE) determined that "Darvadstrocel is not recommended, within its marketing authorization, for previously treated complex perianal fistulas in adults with non-active or mildly active luminal Crohn's disease".

REGULATORY STATUS

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. 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 received Section 510(k) clearance in October 2006. This porcine SIS is supplied in a tapered configuration, with a button to provide increased retention of the plug and improved blockage of the fistula.

In March 2009, the BIO-A Fistula Plug, received FDA section 510(k) clearance for intended 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.

In 2019, darvadstrocel (DVS) received a Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA for complex perianal fistulas in adult patients with Crohn's disease; however, DVS approval is currently under review. RMAT was granted based on DVS being approved in the European Union/European Economic Area, Israel, Switzerland, and the United Kingdom. In December 2024, pharmaceutical company Takeda voluntarily withdrew DVS from the European market based on the published long-term findings from the ADMIRE II phase III clinical trial. DVS did not meet the primary endpoint of combined remission at 24 weeks.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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])

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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CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

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.

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a

specific service, medical policy criteria apply to the benefit.

- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
07/19/12, 06/20/13, 05/22/14, 04/16/15, 03/17/16, 03/16/17, 03/15/18, 03/21/19, 02/20/20, 02/18/21, 02/17/22, 02/16/23, 02/22/24, 02/20/25	
Date	**Summary of Changes**
02/20/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
08/18/11	• Original effective date