Policy Number	**SUR705.039**
Policy Effective Date	**04/01/2024**
Policy End Date	**12/31/2025**

Use of i-Factor Peptide Enhanced Bone Graft During Spinal Surgery

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Use of i-Factor™ peptide enhanced bone graft product during spinal surgery **is considered experimental, investigational and/or unproven.**

Policy Guidelines

CPT code 20930 is not specific to use of i-Factor™ peptide enhanced bone graft product alone.

Description

i-Factor™ Bone Graft peptide enhanced products are intended to replace or augment the use of autologous bone commonly used in spinal fusion incorporating interbody fusion devices by providing "a bone graft substitute that is remodeled into new bone during the natural healing process," according to the company. Substitutes for autograft bone are used to avoid pain and risk of infection in the patient from whom it is harvested. i-Factor™ Bone Grafts consist of a synthetic small peptide (P-15) bound to calcium phosphate particles that are suspended in a hydrogel carrier. The P-15 peptide works by attaching to and stimulating the proliferation of osteogenic cells within bone tissue. The graft product is provided in single-use prefilled syringes and is terminally sterilized after packaging.

Regulatory Status

The U.S. Food and Drug Administration (FDA) granted premarket approval for i-Factor™ Peptide-Enhanced Bone Graft (Cerapedics, Inc., Westminster, CO, USA) in November 2015 (P140019). (1) This product is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic imaging (computerized tomography [CT], magnetic resonance imaging [MRI], x-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels, after failure of at least 6 weeks of conservative treatment. i-Factor™ Peptide Enhanced Bone Graft P-15 Putty must be used inside an allograft bone ring and with supplemental anterior plate fixation.

The approval order required that longer-term follow-up data be reported, and 218 subjects from the pivotal randomized controlled trial (RCT) were enrolled to provide long-term data in this post approval study. The schedule in the FDA approval order shows that a five-year data report was due to the FDA November 1, 2020, The FDA granted marketing approval for use of i-Factor™ Bone Grafts in only the cervical spine, not the lumbar spine.

The FDA five-year report data was designed to assess the long-tern performance of i-Factor™ compared to local autograft by continued follow-up of available subjects from the approved investigational device exemption (IDE) study. Two hundred eighteen subjects and 17 sites from the IDE were involved in the long-term follow-up. While the follow-up rates at the longer time-points were lower than those that would be excepted for ongoing follow-up during the course of an IDE and for filing a PMA, they are reasonable rates for a post-approval study collecting data out to 6 years post-op. Final study results from the FDA required five-year data report showed, "There are no new safety or efficacy findings that alter the conclusions that led to premarket approval (PMA), or would require addition to labeling. The sponsor has been instructed to submit a modified package insert containing the updated timecourse distributions of adverse events (AEs) and clinical and radiographic outcome out to 72 months post-op."

Rationale

This policy was originally created in December 2019 and has been updated regularly with searches of the PubMed database. The most recent literature updated was performed through February 20, 2023. The following is a summary of key literature to date.

The randomized controlled trials (RCTs), conducted to obtain U.S. Food and Drug Administration (FDA) marketing approval (2,3,5), reported outcomes at different time-points (one-, two- and 6-year follow-ups). The main outcomes reported were fusion, reoperation, and AEs. At all time-points, no statistically significant differences between groups were observed in the outcomes. One of these studies is an RCT (n =108) separate from the pivotal trial; the other is the ongoing pivotal RCT: 218 subjects from that RCT are being followed in an FDA-required post approval study to provide longer-term outcomes data. Six-year data of the FDA post-approval study was due to the FDA in November 2020. (4) The final 6-year data reported on 220 participants (106 i-Factor™ and 114 control).

Arnold et al. (2) conducted a prospective, randomized, controlled, parallel, single-blinded noninferiority multicenter pivotal FDA Investigational Device Exemption (IDE) trial. The objective of this study was to investigate efficacy and safety of i-Factor™ Bone Graft (i-Factor™) compared with local autograft in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy. Patients randomly received either autograft (n = 154) or i-Factor™ (n = 165) in a cortical ring allograft. Study success was defined as noninferiority in fusion, Neck Disability Index (NDI), and neurological success endpoints, and a similar adverse events profile at 12 months. At 12 months (follow-up rate 87%), both i-Factor™ and autograft subjects demonstrated a high fusion rate (88.97% and 85.82%, respectively, noninferiority $P = 0.0004$), significant improvements in NDI (28.75 and 27.40, respectively, noninferiority $P < 0.0001$), and high neurological success rate (93.71% and 93.01%, respectively, noninferiority $P < 0.0001$). There was no difference in the rate of adverse events (83.64% and 82.47% in the i-Factor™ and autograft groups, respectively, $P = 0.8814$). Overall success rate consisting of fusion, NDI, neurological success and safety success was higher in i-Factor™ subjects than in autograft subjects (68.75% and 56.94%, respectively, $P = 0.0382$). Improvements in visual analogue scale (VAS) pain and short form health survey (SF-36v2) scores were clinically relevant and similar between the groups. A high proportion of patients reported good or excellent Odom outcomes (81.4% in both groups). Authors note that i-Factor™ met all four FDA mandated noninferiority success criteria and demonstrated safety and efficacy in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy and i-Factor™ and autograft groups demonstrated significant postsurgical improvement and high fusion rates.

Arnold et al. (3) reported on a 2-yr follow-up of the prospective, randomized, controlled, parallel, single-blinded noninferiority multicenter pivotal FDA IDE trial. Subjects randomly received either autograft (n =154) or i-Factor™ (n =165) in a cortical ring allograft and followed using radiological, clinical, and patient-reported outcomes. At 2 years, the fusion rate was 97.30% and 94.44% in i-Factor™ and autograft subjects, respectively (P =.2513), and neurological success rate was 94.87% (i-Factor™) and 93.79% (autograft; P =.7869). Neck Disability Index improved 28.30 (i-Factor™) and 26.95 (autograft; P =.1448); VAS scale arm pain

improved 5.43 (i-Factor™) and 4.97 (autograft) (p =.2763); VAS neck pain improved 4.78 (i-Factor™) and 4.41 (autograft; P =.1652), SF-36v2 Physical Component Score improved 10.23 (i-Factor™) and 10.18 (autograft; P =.4507), and SF-36v2 Mental Component Score improved 7.88 (i-Factor™) and 7.53 (autograft; P =.9872). The composite endpoint of overall success (fusion, NDI improvement >15, neurological success, and absence of re-operations) was greater in i-Factor™ subjects compared to autograft subjects (69.83% and 56.35%, respectively, P =.0302). Twelve (7.45%) i-Factor™ subjects and 16 (10.53%) autograft subjects underwent re-operation (P =.3411). There were no allergic reactions associated with i-Factor™. Use of i-Factor™ in anterior cervical discectomy and fusion is effective and safe, and results in similar outcomes compared to local autograft bone at 2 years following surgery.

Arnold et al. (5) reported on a 6-year follow-up of the prospective, randomized, controlled, parallel, single-blinded noninferiority multicenter pivotal FDA Investigational Device Exemption study demonstrated the superiority of i-Factor™ compared with local autograft bone in single-level ACDF at 12 and 24 months postoperatively in a composite end point of overall success. The objective of this analyses was to report the final, 6-year clinical and radiological outcomes of the FDA post-approval study. Radiographic fusion was achieved in 99% (103/104) and 98.2% (109/111) in i-Factor™ and local autograft subjects, mean NDI improvement from baseline was 28.6 (24.8, 32.3) in the i-Factor™ and 29.2 (25.6, 32.9) in the control group, respectively (noninferiority P < .0001). The neurological success rate at 6 years was 95.9% (70/73) in i-Factor™ subjects and 93.7% (70/75) in local autograft subjects (noninferiority P < .0001). Safety outcomes were similar between the 2 groups. Secondary surgery on the same or different cervical levels occurred in 20/106 (18.9%) i-Factor™ subjects and 23/114 (20.2%) local autograft subjects (P = .866). Secondary outcomes (pain, SF-36 physical component score and mental component score) in i-Factor™ subjects were similar to those in local autograft subjects. i-Factor™ met all 4 FDA-mandated noninferiority success criteria and demonstrated safety and efficacy in single-level anterior cervical discectomy and fusion for cervical radiculopathy through 6 years postoperatively. Safety outcomes are acceptable, and the clinical and functional outcomes observed at 12 and 24 months remained at 72 months.

ECRI Institute

<u>i-Factor™ Peptide Enhanced Bone Graft (Cerapedics, Inc.) for Treating Cervical Degenerative Disc Disease</u>

A 2019 ECRI (7) report noted that evidence from a pivotal RCT suggests that i-Factor™ used in a standard anterior cervical discectomy and fusion procedure that uses a metallic anterior plate fixation system and allograft ring structural graft, produces the same fusion and complication rates as autologous bone graft. Confirmation in additional studies is needed.

ECRI noted that the pivotal RCT was a noninferiority trial and reported fusion rates that were not statistically different at 1- and 2-year follow-up (1, 2): i-Facto™r 89% (1 year) and 97% (2 year) versus autologous bone graft 86% (1 year) and 94% (2 year). Severe adverse events (AEs) at 1 year were also not statistically different between groups: i-Factor™ 27% versus bone graft 23%. Reoperation rates at 2-year follow-up were 7% for i-Factor™ and 11% for bone graft. Evidence limitations state that available evidence is derived from one well-designed RCT.

Additional RCTs comparing i-Factor™ Peptide Enhanced Bone Graft with other cervical degenerative disc disease treatments and reporting on patient-oriented outcomes are needed to verify findings.

i-Factor™ Bone Graft (Cerapedics, Inc.) for Lumbar Fusion Procedures

i-Factor™ has been used off-label for lumbar spinal fusion incorporating interbody fusion devices. A 2021 ECRI report (6) focused on how well it works for lumbar fusion and how it compares with autograft and allograft bone. Limited evidence from1 double-blind RCT, 1 comparative study and 2 before-and-after studies suggest that i-Factor™ is safe and effective for lumbar spine fusion in some patients; however, too few patients have been studied to conclude whether i-Factor™ works better than autografts, allografts, or other bone graft materials.

ECRI noted that 1 small nonrandomized comparison study (8) in which patients served as their own controls found that in the short-term, i-Factor™ Bone Grafts worked better than autologous bone to facilitate formation of bridging bone inside hollow spaces in the cages used during posterior lumbar interbody fusion procedures. At 24-month follow-up, no statistically significant dark line above difference was observed in the presence of intracage bridging bone (93.33% autograft versus 95.56% i-Factor™; p =NS). i-Factor™ migration outside the cage occurred more than autograft migration. One patient had no bridging bone in the i-Factor™ cage but had bridging bone all around the cage. In addition, 1 single-center case series (9) reported fusion rates of 97.5% (single-level), 81% (double-level), and 100% (triple-level) at a mean 24 months after anterior lumbar interbody fusion using i-Factor™ bone graft. Authors also reported significant improvements from baseline in function and quality-of-life scores ($p<0.05$). Evidence from the RCT and single-center case series suggest fusion rates are better with i-Factor™ than with allograft; however, improved fusion did not lead to improved pain, disability, or quality of life (QOL). Additional RCTs comparing i-Factor™ with autografts, allografts, and other bone graft materials are needed to validate these findings and address evidence gaps.

ECRI also noted on the 2 before and after studies of patients undergoing lateral lumbar interbody fusion (ALIF). The reported Oswestry disability index (ODI) scores were lowered from a mean of 36.84 to 23.47 in patients. (10) It was also stated that “The use of i-FACTOR™ bone graft substitute demonstrates promising results for facilitating successful fusion and improving clinical outcomes in patients who undergo ALIF surgery for degenerative spinal pathologies." (9)

Summary Of Evidence

Some studies suggest that i-Factor™ is safe and effective in select patients; however, too few patients have been studied to conclude whether i-Factor™ works better than autografts, allografts, or other bone graft materials. Evidence from the RCT and single-center case series suggest fusion rates are better with i-Factor™ than with allograft; however, improved fusion did not improve pain, disability, or quality of life. Based on available literature, the use of i-Factor™ peptide enhanced bone graft product during spinal surgery is considered experimental, investigational and/or unproven. Additional long term RCTs comparing i-Factor™ with

autografts, allografts, and other bone graft materials are needed to validate prior findings and address evidence gaps.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04610021	Prospective i-Factor™ Analysis Fusion Rate and Quality of Life	128	Mar 2027 (not yet recruiting)
NCT05144126	Safety, Radiological and Patient Reported Outcomes of i-FACTOR™+ Matrix Bone Graft Device - A Canadian, Multicenter, Post-Market Clinical Investigation	300	Sep 2025 (not yet recruiting)
Unpublished			
NCT02895555	The Clinical Effect of i-FACTOR™ Versus Allograft in Non-instrumentated Posterolateral Fusion in The IVANOS-study	102	Jan 2016
NCT01618435	The Clinical Effect of i-FACTOR™ Versus Allograft in Non-instrumented Posterolateral Spondylodesis Operation in the Elderly With Spinal Stenosis Due to Degenerative Spondylolisthesis (IVANOS)	108	May 2018

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	20930
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

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7. ECRI Institute. i-Factor™ Peptide-enhanced Bone Graft (Cerapedics, Inc.) for Treating Cervical Degenerative Disc Disease; 2019 Oct (Product Brief).
8. Lauweryns P, Raskin Y. Prospective analysis of a new bone graft in lumbar interbody fusion: results of a 2- year prospective clinical and radiological study. Int J Spine Surg. February 3, 2015; 9:2. PMID 25709887
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10. Asad, S, Dubey, A, Dubey, A, and Sutterlin, C. Clinical Outcomes after Minimally Invasive Trans-Psoas Lateral Lumbar Interbody Fusion for the Treatment of Adult Degenerative Scoliosis: Four Years' Multicenter Study. Indian Journal of Neurosurgery. 2020; 9(3):225-229.

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/31/2025	Document became inactive.
04/01/2024	Reviewed. No changes.
05/01/2023	Document updated with literature review. Coverage unchanged. Reference 1 and 5 added.
12/01/2022	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. Reference 8 added; 4 and 5 updated.
12/15/2020	Reviewed. No changes.
12/15/2019	New medical document. Use of i-Factor peptide enhanced bone graft product during spinal surgery is considered experimental, investigational and/or unproven.