BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 06/20/23**
SECTION: SURGERY	**LAST REVIEW DATE: 06/04/24**
	CURRENT EFFECTIVE DATE: 06/04/24
	LAST CRITERIA REVISION DATE: 06/20/23
NEXT ANNUAL REVIEW DATE: 2ND QTR 2025	**ARCHIVE DATE:**

BONE MORPHOGENETIC PROTEIN

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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BONE MORPHOGENETIC PROTEIN

Description:

Two recombinant human bone morphogenetic proteins (rhBMPs) have been extensively studied: recombinant human bone morphogenetic protein-2 (rhBMP-2), applied with an absorbable collagen sponge (Infuse), and recombinant human bone morphogenetic protein-7 (rhBMP-7), applied in putty (OP-1; not currently available in the U.S.). These protein products have been investigated as alternatives to bone autografting in a variety of clinical situations, including spinal fusions, internal fixation of fractures, treatment of bone defects, and reconstruction of maxillofacial conditions.

Bone morphogenetic proteins are members of the transforming growth factors family. At present, some 20 bone morphogenetic proteins have been identified, all with varying degrees of tissue-stimulating properties.

The recombinant human bone morphogenetic proteins (rhBMPs) are delivered to the bone grafting site as part of a surgical procedure; a variety of carrier and delivery systems has been investigated. Carrier systems, which are absorbed over time, maintain the concentration of the rhBMP at the treatment site, provide temporary scaffolding for osteogenesis, and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymers, natural polymers, and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also provide mechanical support.

Use of iliac crest bone graft may be considered not feasible due to situations that may include, *but are not limited to*, prior harvesting of iliac crest bone graft or need for a greater quantity of iliac crest bone graft than available (e.g., for multilevel fusion).

The U.S. Food and Drug Administration has approved the following recombinant human bone morphogenetic protein products and associated carrier and delivery systems including, *but not limited to*:

- INFUSE™ Bone Graft
- INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
- INFUSE™ Bone Graft/Medtronic Interbody Fusion Device
- Divergence-L Anterior/Oblique Lumbar Fusion System
- Pivox™ Oblique Lateral Spinal System

Criteria:

- Use of recombinant human bone morphogenetic protein-2 (Infuse™) in skeletally mature individuals is considered ***medically necessary*** with documentation of **ANY** of the following:

  1. For anterior lumbar interbody fusion procedures when the use of autograft is not feasible

  2. For instrumented posterolateral intertransverse spinal fusion procedures when the use of autograft is not feasible

3. For the treatment of acute, open fracture of the tibial shaft, when the use of autograft is not feasible

- Use of recombinant human bone morphogenetic protein-2 for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Craniomaxillofacial surgery
- Spinal fusion when the use of autograft is feasible

Resources:

Literature reviewed 06/04/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Carragee EJ, Chu G, Rohatgi R, et al. Cancer risk after use of recombinant bone morphogenetic protein-2 for spinal arthrodesis. *J Bone Joint Surg Am*. Sep 4 2013;95(17):1537-45. doi:10.2106/JBJS.L.01483

2. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J*. Jun 2011;11(6):471-91. doi:10.1016/j.spinee.2011.04.023

3. Cooper GS, Kou TD. Risk of cancer after lumbar fusion surgery with recombinant human bone morphogenic protein-2 (rh-BMP-2). *Spine (Phila Pa 1976)*. Oct 1 2013;38(21):1862-8. doi:10.1097/BRS.0b013e3182a3d3b4

4. Cooper GS, Kou TD. Risk of Cancer Following Lumbar Fusion Surgery With Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2): An Analysis Using a Commercially Insured Patient Population. *Int J Spine Surg*. Apr 2018;12(2):260-268. doi:10.14444/50323

5. Dai J, Li L, Jiang C, Wang C, Chen H, Chai Y. Bone Morphogenetic Protein for the Healing of Tibial Fracture: A Meta-Analysis of Randomized Controlled Trials. *PLoS One*. 2015;10(10):e0141670. doi:10.1371/journal.pone.0141670

6. Dettori JR, Chapman JR, DeVine JG, McGuire RA, Junge MR, Norvell DC. Longer follow-up continues to reveal no increased risk of cancer with the use of recombinant human bone morphogenetic protein in spine fusion. *Spine J*. Oct 2019;19(10):1640-1647. doi:10.1016/j.spinee.2019.05.005

7. Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future development. *J Bone Joint Surg Am*. 2003;85-A Suppl 3:82-8. doi:10.2106/00004623-200300003-00014

8. Feng JT, Yang XG, Wang F, He X, Hu YC. Efficacy and safety of bone substitutes in lumbar spinal fusion: a systematic review and network meta-analysis of randomized controlled trials. *Eur Spine J*. Jun 2020;29(6):1261-1276. doi:10.1007/s00586-019-06257-x

9. Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med*. Jun 18 2013;158(12):890-902. doi:10.7326/0003-4819-158-12-201306180-00006

10. Garrison KR, Shemilt I, Donell S, et al. Bone morphogenetic protein (BMP) for fracture healing in adults. *Cochrane Database Syst Rev*. Jun 16 2010;(6):CD006950. doi:10.1002/14651858.CD006950.pub2

11. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am*. Dec 2002;84(12):2123-34. doi:10.2106/00004623-200212000-00001

12. Howard JM, Glassman SD, Carreon LY. Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest. *Spine J*. Jun 2011;11(6):534-7. doi:10.1016/j.spinee.2010.09.001

13. Kaiser MG, Groff MW, Watters WC, 3rd, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. *J Neurosurg Spine*. Jul 2014;21(1):106-32. doi:10.3171/2014.4.SPINE14325

14. Khan TR, Pearce KR, McAnany SJ, Peters CM, Gupta MC, Zebala LP. Comparison of transforaminal lumbar interbody fusion outcomes in patients receiving rhBMP-2 versus autograft. *Spine J*. Mar 2018;18(3):439-446. doi:10.1016/j.spinee.2017.08.230

15. Liu S, Wang Y, Liang Z, Zhou M, Chen C. Comparative Clinical Effectiveness and Safety of Bone Morphogenetic Protein Versus Autologous Iliac Crest Bone Graft in Lumbar Fusion: A Meta-analysis and Systematic Review. *Spine (Phila Pa 1976)*. Jun 15 2020;45(12):E729-E741. doi:10.1097/BRS.0000000000003372

16. Lyon T, Scheele W, Bhandari M, et al. Efficacy and safety of recombinant human bone morphogenetic protein-2/calcium phosphate matrix for closed tibial diaphyseal fracture: a double-blind, randomized, controlled phase-II/III trial. *J Bone Joint Surg Am*. Dec 4 2013;95(23):2088-96. doi:10.2106/JBJS.L.01545

17. Major Extremity Trauma Research C. A Randomized Controlled Trial Comparing rhBMP-2/Absorbable Collagen Sponge Versus Autograft for the Treatment of Tibia Fractures With Critical Size Defects. *J Orthop Trauma*. Aug 2019;33(8):384-391. doi:10.1097/BOT.0000000000001492

18. Mariscal G, Nunez JH, Barrios C, Domenech-Fernandez P. A meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for the posterolateral fusion of the lumbar spine. *J Bone Miner Metab*. Jan 2020;38(1):54-62. doi:10.1007/s00774-019-01025-9

19. North American Spine Society (NASS). NASS Coverage Policy Recommendations: Recombinant Human Bone Morphogenetic Protein (rhBMP-2). 2014, Accessed February 20, 2024. https://www.spine.org/Product-Details?productid=%7B9567DDCC-4EC7-E411-9CA5-005056AF031E%7D

20. Ramly EP, Alfonso AR, Kantar RS, et al. Safety and Efficacy of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) in Craniofacial Surgery. *Plast Reconstr Surg Glob Open*. Aug 2019;7(8):e2347. doi:10.1097/GOX.0000000000002347

21. Ratko TA, Belinson SE, Samson DJ, et al. Bone Morphogenetic Protein: The State of the Evidence of On-Label and Off-Label Use (AHRQ Technology Assessment Report). 2010. Located at: Agency for Healthcare Research and Quality, Rockville, Maryland, USA.

22. Schultz DG. FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion [letter]. Center for Devices and Radiological Health, U.S. Food and Drug Administration. July 1, 2008. Accessed February 20, 2024. https://www.patientsafety.va.gov/docs/alerts/AL09-13MedtronicInfuse.pdf

23. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. *Ann Intern Med*. Jun 18 2013;158(12):877-89. doi:10.7326/0003-4819-158-12-201306180-00005

24. U.S. Food and Drug Administration (FDA). Infuse Bone Graft. Summary of safety and effectiveness data. Accessed February 19, 2024. https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050053B.pdf

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25. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness: InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion Device [P000058]. 2002. Accessed February 20, 2024. https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf

26. United States Senate Finance Committee. Staff report on Medtronic's influence on INFUSE clinical studies. *Int J Occup Environ Health*. Apr-Jun 2013;19(2):67-76. doi:10.1179/2049396713Y.0000000020

27. Valentin-Opran A, Wozney J, Csimma C, Lilly L, Riedel GE. Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Orthop Relat Res*. Feb 2002;(395):110-20. doi:10.1097/00003086-200202000-00011

28. Wu Z, Zhou B, Chen L, Wang X, Abdelrahim MEA, Wei C. Bone morphogenetic protein-2 against iliac crest bone graft for the posterolateral fusion of the lumbar spine: A meta-analysis. *Int J Clin Pract*. Apr 2021;75(4):e13911. doi:10.1111/ijcp.13911

29. Zadegan SA, Abedi A, Jazayeri SB, et al. Bone Morphogenetic Proteins in Anterior Cervical Fusion: A Systematic Review and Meta-Analysis. *World Neurosurg*. Aug 2017;104:752-787. doi:10.1016/j.wneu.2017.02.098

Coding:

CPT: 20930

History:	**Date:**	**Activity:**
Medical Policy Panel	06/04/24	Review with revisions
Medical Policy Panel	06/20/23	Approve guideline
Medical Director (Dr. Deering, Dr. Raja)	04/12/23	Review with revisions

Policy Revisions:

06/04/24 Updated: Resource section

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh íłínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

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Multi-Language Interpreter Services:

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:
اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
.]تماس حاصل نمایید.

Assyrian:
ܐ ܫܟܚ، ܡ ܡ ܩܛܘܩ ܘܡܫܡܫ ܒܗ، ܫܟܚ ܫܟܚ ܚܡܬ ܚܡܬ ܫܟܚ ،Blue Cross Blue Shield of Arizona ܫܟܚ ܫܟܚ ܡܡܚ ܡܡܚ ܡܚܒܫܗ ܡܚܒܫܗ
ܡܫܟ ܡܡܚܘܫܡܚ ܚܫܚܡܚ ܡܚܒܫܗ. ܟܡܡܘܡ ܚܫ ܡ ܡܚܟܚܒ، ܡܟ ܡܚ ܫܟ ܟܫ ܡܫܟ ܡܡܫ 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona
คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799