Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Electrostimulation and Electromagnetic Therapy for the Treatment of Chronic Wounds is addressed separately in medical policy 00030.

Note: Therapeutic use of Stem Cells, Blood and Bone Marrow Products is addressed separately in medical policy 00476.

Note: Bioengineered Skin and Soft Tissue Substitutes addressed separately in medical policy 00572.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider recombinant platelet-derived growth factor (PDGF [i.e., becaplermin]) when used as an adjunct to standard wound management to be **eligible for coverage**** for the following indications:

- Neuropathic diabetic ulcers extending into the subcutaneous tissue
- Pressure ulcers extending into the subcutaneous tissue

Patient Selection Criteria
Becaplermin

Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet ALL of the following criteria:

- Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer; AND

- Full-thickness ulcer (i.e., Stage III or IV), extending through dermis into subcutaneous tissues; AND
- Participation in a wound-management program, which includes sharp debridement, pressure relief (i.e., non-weight-bearing), and infection control.

Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet ALL of the following criteria:

- Full-thickness ulcer (i.e., Stage III or IV), extending through dermis into subcutaneous tissues; AND
- Ulcer in an anatomic location that can be off-loaded for the duration of treatment; AND
- Albumin concentration > 2.5 dL; AND
- Total lymphocyte count > 1,000; AND
- Normal values of vitamins A and C.

Note: Individuals are typically treated once daily for up to 20 weeks or until complete healing. Application of the gel may be performed by the patient in the home.

Note: Becaplermin is available in 2-, 7.5-, and 15-g tubes and is applied in a thin continuous layer, about 1/16 of an inch thick, i.e., the thickness of a dime. The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm^2, treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the15-g tubes would be required.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers other applications of recombinant platelet-derived growth factor (ie, becaplermin) including, but not limited to, ischemic ulcers, ulcers related to venous stasis, and ulcers not extending through the dermis into the subcutaneous tissue to be **investigational.***

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

Background/Overview

Wound Healing Treatment

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factor (PDGF), epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of PDGF, transforming growth factors (that function as a mitogen for fibroblasts, smooth muscle cells, and osteoblasts), and vascular endothelial growth factors. Recombinant PDGF also has been extensively investigated for clinical use in wound healing.

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing various growth factors, and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and accelerate healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a transforming growth factor, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

PRP is distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel®‡ (Baxter International) and Hemaseel®‡ (Haemacure Corp.) are examples of commercially available fibrin sealants. Autologous fibrin sealants can also be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

Wound Closure Outcomes

This review addresses the use of recombinant PDGF products and PRP for nonorthopedic indications, which include a number of wound closure-related indications.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

For this review, the primary endpoints of interest for the study of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:

- Incidence of complete wound closure;
- Time to complete wound closure (reflecting accelerated wound closure);
- Incidence of complete wound closure following surgical wound closure;
- Pain control.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Becaplermin

In 1997, becaplermin gel (Regranex®‡; Smith & Nephew), a recombinant PDGF product, was approved by the FDA for the following labeled indication:

"Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers.

The efficacy of Regranex Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers … has not been evaluated…." Regranex is not intended to be used in wounds that close by primary intention."

In 2008, the manufacturer added the following black box warning to the labeling for Regranex®‡: "An increased rate of mortality secondary to malignancy was observed in individuals treated with 3 or more tubes of Regranex Gel in a postmarketing retrospective cohort study. Regranex Gel should only be used when the benefits can be expected to outweigh the risks. Regranex Gel should be used with caution in individuals with known malignancy."

In 2018, the "Boxed Warning" and "Warnings and Precautions" were changed to remove "increased rate of cancer mortality" and "cancer mortality," respectively.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

Platelet-Rich Plasma
The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Blood products such as PRP are included in these regulations.

Under these regulations, certain products including blood products such as PRP are exempt and therefore, do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.

Numerous PRP preparation systems have been cleared for marketing by the FDA through the 510(k) process. These devices are intended to concentrate patient plasma at the point of care during bone grafting procedures. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), has been suggested as a treatment for wounds or other miscellaneous non-orthopedic conditions, including but not limited to, diabetic ulcers, pressure ulcers, venous stasis ulcers, and surgical and traumatic wounds.

Summary of Evidence
Recombinant Platelet-Derived Growth Factors
For individuals who have diabetic lower-extremity ulcers who receive recombinant PDGF, the evidence includes randomized controlled trials (RCTs) and systematic reviews. The relevant outcomes are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity. Results have shown improved rates of healing with use of

recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes a single RCT. The relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Results have shown improved rates of healing with use of recombinant PDGF for pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have venous stasis leg ulcers or acute surgical or traumatic wounds who receive recombinant PDGF, the evidence includes small RCTs. The relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. The level of evidence does not permit conclusions whether recombinant PDGF is effective in treating other wound types, including chronic venous ulcers or acute traumatic wounds. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Platelet-Rich Plasma

For individuals who have chronic wounds who receive PRP, the evidence includes meta-analyses of a number of small controlled trials. The relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. In meta-analyses of individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure and healing time, but moderate to high risk of bias and imprecision preclude drawing conclusions on other important outcomes such as recurrence, infection, amputation, and quality of life. In individuals with venous ulcers, PRP did not demonstrate an improvement over the control groups in complete wound closure, recurrence, wound infection or quality of life, although imprecision likely precluded identifying differences on these outcomes. In individuals with pressure ulcers, although PRP reduced wound size, other important outcomes such as complete wound closure were not measured. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute surgical or traumatic wounds who receive PRP, the evidence includes systematic reviews and a number of small controlled trials. The relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Current

results of trials using PRP are mixed and the studies are limited in both size and quality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Physicians

In 2015, the American College of Physicians (ACP) published guidelines on treatment of pressure ulcers. The guidelines noted that "although low-quality evidence suggests that dressings containing PDGF [platelet-derived growth factors] promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings." A search of the ACP website on December 1, 2020 found that this 2015 guideline is now listed as inactive.

Association for the Advancement of Wound Care

The Association for the Advancement of Wound Care developed guideline recommendations for the management of pressure ulcers (2010) and venous ulcers (2015):

- Pressure ulcer: "Growth factors are not indicated for PU [pressure ulcers] at this time." (level C evidence - no RCTs available comparing growth factors with A-level dressings)
- Venous ulcer: "Platelet-derived growth factor has shown no significant effects on VU [venous ulcer healing or recurrence]." (level A evidence)

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The guidance stated that neither autologous platelet-rich plasma gel nor platelet-derived growth factors should be offered in the treatment of diabetic foot ulcers.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
In 2012, the Centers for Medicare & Medicaid Services (CMS) revised its national coverage decision on autologous blood-derived products for chronic non-healing wounds. This revision replaces prior noncoverage decisions.

The Centers for Medicare & Medicaid Services covers autologous PRP only for individuals who have chronic non-healing diabetic, pressure, and/or venous wounds and when all of the following conditions are met:

"The patient is enrolled in a clinical research study that addresses the following questions using validated and reliable methods of evaluation…

"The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic non-healing diabetic, venous and/or pressure wounds. The clinical study must address:

"Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure wounds who receive well-defined optimal usual care, along with PRP therapy, experience clinically significant health outcomes compared to individuals who receive well-defined optimal usual care for chronic non-healing diabetic, venous and/or pressure wounds as indicated by addressing at least 1 of the following:

- Complete wound healing?
- Ability to return to previous function and resumption of normal activities?
- Reduction of wound size or healing trajectory which results in the patient's ability to return to previous function and resumption of normal activities?"

In response to a formal request from Nuo Therapeutics on May 9, 2019, CMS began a fourth reconsideration of its national coverage decision. To inform this reconsideration, the Mayo Evidence-based Practice Center performed a technology assessment that was published by Qu et al (2020) and its results are described above in the Rationale section. Following their review of this evidence, on December 21, 2020, CMS posted a Proposed Decision Memorandum that proposes to

expand its 2012 Coverage with Evidence Development decision to cover any use of autologous PRP "...for the treatment of chronic non-healing diabetic wounds under section 1862(a)(1)(A) of the Social Security Act (the Act)." This decision is based on the evidence described above that is sufficient "...to demonstrate that individuals with diabetic ulcers who are treated with autologous PRP have better outcomes (complete wound healing) when compared to individuals who receive standard care." CMS additionally noted that a limitation of the evidence is that "None of these studies addressed whether or not PRP affected a patient's ability to return to previous function and resumption of normal activities, or resulted in reduction of wound size or healing trajectory as an intermediary towards a formal endpoint of a patient's ability to return to previous function and resumption of normal activities."

For other chronic non-healing wounds, "CMS proposes that coverage of autologous PRP for the treatment of all other chronic non-healing wounds will be determined by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act."

In April 2021, CMS published an updated decision memo following the fourth reconsideration of the national coverage analysis stating that CMS will "cover autologous platelet-rich plasma (PRP) for the treatment of chronic non-healing diabetic wounds under section 1862(a)(1)(A) of the Social Security Act (the Act) for a duration of 20 weeks, when prepared by devices whose FDA cleared indications include the management of exuding cutaneous wounds, such as diabetic ulcers. Coverage of autologous PRP for the treatment of chronic non-healing diabetic wounds beyond 20 weeks will be determined by local Medicare Administrative Contractors (MACs).

Coverage of autologous PRP for the treatment of all other chronic non-healing wounds will be determined by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act."

Ongoing and Unpublished Clinical Trials
Some larger studies that might influence this review are listed in Table 1.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05979584	Platelet Rich Plasma VS Platelet Fibrin Plasma in Treatment of Diabetes Foot Ulcer: a Randomized Controlled Trial	56	Dec 2024
NCT02312596[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Non-Healing Diabetic Foot Ulcers	200	Dec 2021
NCT02312570[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	200	Dec 2021
NCT02307448[a]	Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds	80	Dec 2022
NCT02402374[a]	Randomized, Placebo-controlled, Blind-assessor Study to Evaluate the Safety and Efficacy of Autologous Platelet Rich Plasma Gel Prepared With the RegenKit-BCT Plus Family of Kits for the Treatment of Diabetic Foot Ulcer	192	Dec 2020 (unknown)
Unpublished			
NCT02071979[a]	Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)	1500	Jan 2018 (terminated; updated 01/18)

NCT: national clinical trial; PRP: autologous platelet-rich plasma.
[a] Denotes industry-sponsored or cosponsored trial.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

References

1. U.S. Food and Drug Administration. Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds -- Developing Products for Treatment. Rockville, MD: Food and Drug Administration; 2006 June.
2. U.S. Food and Drug Administration (FDA). Tissue and Tissue Products. 2016; http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/.
3. Crovetti G, Martinelli G, Issi M, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci. Apr 2004; 30(2): 145-51. PMID 15062754
4. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound heaing. Plast Reconstr Surg. Nov 2004; 114(6): 1502-8. PMID 15509939
5. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. J Extra Corpor Technol. Mar 2004; 36(1): 28-35. PMID 15095838
6. Castillo TN, Pouliot MA, Kim HJ, et al. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. Feb 2011; 39(2): 266-71. PMID 21051428
7. Mazzucco L, Balbo V, Cattana E, et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang. Aug 2009; 97(2): 110-8. PMID 19392780
8. Zhao XH, Gu HF, Xu ZR, et al. Efficacy of topical recombinant human platelet-derived growth factor for treatment of diabetic lower-extremity ulcers: Systematic review and meta-analysis. Metabolism. Oct 2014; 63(10): 1304-13. PMID 25060693
9. Sridharan K, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: mixed treatment comparison analysis of randomized clinical trials. Br J Clin Pharmacol. Mar 2018; 84(3): 434-444. PMID 29148070
10. Margolis DJ, Bartus C, Hoffstad O, et al. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Repair Regen. 2005; 13(6): 531-6. PMID 16283867
11. Rees RS, Robson MC, Smiell JM, et al. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. Wound Repair Regen. 1999; 7(3): 141-7. PMID 10417749

12. Senet P, Vicaut E, Beneton N, et al. Topical treatment of hypertensive leg ulcers with platelet-derived growth factor-BB: a randomized controlled trial. Arch Dermatol. Aug 2011; 147(8): 926-30. PMID 21482863
13. Freedman BM, Oplinger EH, Freedman IS. Topical becaplermin improves outcomes in work related fingertip injuries. J Trauma. Oct 2005; 59(4): 965-8. PMID 16374289
14. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. May 25 2016; 2016(5): CD006899. PMID 27223580
15. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. Oct 17 2012; 10: CD006899. PMID 23076929
16. Carter MJ, Fylling CP, Parnell LK. Use of platelet rich plasma gel on wound healing: a systematic review and meta-analysis. Eplasty. 2011; 11: e38. PMID 22028946
17. Picard F, Hersant B, Bosc R, et al. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: A review and a proposal for a new standard care. Wound Repair Regen. Sep 2015; 23(5): 638-43. PMID 26019054
18. Del Pino-Sedeño T, Trujillo-Martín MM, Andia I, et al. Platelet-rich plasma for the treatment of diabetic foot ulcers: A meta-analysis. Wound Repair Regen. Mar 2019; 27(2): 170-182. PMID 30575212
19. Li Y, Gao Y, Gao Y, et al. Autologous platelet-rich gel treatment for diabetic chronic cutaneous ulcers: A meta-analysis of randomized controlled trials. J Diabetes. May 2019; 11(5): 359-369. PMID 30182534
20. Qu W, Wang Z, Hunt C, Morrow AS, Urtecho M, Amin M, Shah S, Hasan B, Abd-Rabu R, Ashmore Z, Kubrova E, Prokop LJ, Murad MH. Platelet-Rich Plasma for Wound Care in the Medicare Population. Technology Assessment Program Project ID 040-353-492. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/prp/prp-wound-care.pdf.
21. Deng J, Yang M, Zhang X, et al. Efficacy and safety of autologous platelet-rich plasma for diabetic foot ulcer healing: a systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. May 19 2023; 18(1): 370. PMID 37202812
22. Martínez-Zapata MJ, Martí-Carvajal A, Solà I, et al. Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion. Jan 2009; 49(1): 44-56. PMID 18954394

23. Qu S, Hu Z, Zhang Y, et al. Clinical Studies on Platelet-Rich Plasma Therapy for Chronic Cutaneous Ulcers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Wound Care (New Rochelle). Feb 2022; 11(2): 56-69. PMID 33607926
24. Ahmed M, Reffat SA, Hassan A, et al. Platelet-Rich Plasma for the Treatment of Clean Diabetic Foot Ulcers. Ann Vasc Surg. Jan 2017; 38: 206-211. PMID 27522981
25. Alamdari DH, Asadi M, Rahim AN, et al. Efficacy and Safety of Pleurodesis Using Platelet-Rich Plasma and Fibrin Glue in Management of Postoperative Chylothorax After Esophagectomy. World J Surg. Apr 2018; 42(4): 1046-1055. PMID 28986682
26. Chen HY, Chen CX, Liang Y, Wang J. Efficacy of autologous platelet rich gel in the treatment of refractory diabetic foot. Chin J New Clin Med. 2008; 17:1-2.
27. Driver VR, Hanft J, Fylling CP, et al. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage. Jun 2006; 52(6): 68-70, 72, 74 passim. PMID 16799184
28. Elsaid A, El-Said M, Emile S, et al. Randomized Controlled Trial on Autologous Platelet-Rich Plasma Versus Saline Dressing in Treatment of Non-healing Diabetic Foot Ulcers. World J Surg. Apr 2020; 44(4): 1294-1301. PMID 31811339
29. Friese G, Herten M, Scherbaum WA. The use of autologous platelet concentrate activated by autologous thrombin (APC+) is effective and safe in the treatment of chronic diabetic foot ulcers-a randomized controlled trial. In: eds. Proceedings of the Fifth International Symposium on the Diabetic Foot, May September 12, 2007, Noordwijkerhout, The Netherlands. 2007.
30. Game F, Jeffcoate W, Tarnow L, et al. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomized controlled trial. Lancet Diabetes Endocrinol. Nov 2018; 6(11): 870-878. PMID 30243803
31. Gude W, Hagan D, Abood F, et al. Aurix Gel Is an Effective Intervention for Chronic Diabetic Foot Ulcers: A Pragmatic Randomized Controlled Trial. Adv Skin Wound Care. Sep 2019; 32(9): 416-426. PMID 31436621
32. Habeeb T, AA E, H M. Platelet-rich plasma (PRP) bio-stimulant gel dressing in treating chronic non-healing leg and foot ulcers; cost and effectiveness. Randomized Controlled Clinical Trial. 2021.
33. Helmy Y, Farouk N, Ali Dahy A, et al. Objective assessment of Platelet-Rich Plasma (PRP) potentiality in the treatment of Chronic leg Ulcer: RCT on 80 patients with Venous ulcer. J Cosmet Dermatol. Oct 2021; 20(10): 3257-3263. PMID 33880860

34. Hossam EM, Alserr AHK, Antonopoulos CN, et al. Autologous Platelet Rich Plasma Promotes the Healing of Non-Ischemic Diabetic Foot Ulcers. A Randomized Controlled Trial. Ann Vasc Surg. May 2022; 82: 165-171. PMID 34896242
35. Jeong SH, Han SK, Kim WK. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. Plast Reconstr Surg. Mar 2010; 125(3): 944-52. PMID 20195121
36. Kakagia DD, Kazakos KJ, Xarchas KC, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. J Diabetes Complications. 2007; 21(6): 387-91. PMID 17967712
37. Karimi R, Afshar M, Salimian M, et al. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. Nurs Midwifery Stud. 2016;5(3):e30314.
38. Li L, Wang C, Wang Y, He LP, Yang YZ, Chen LH, et al. Impact of topical application of autologous platelet-rich gel on medical expenditure and length of stay in hospitals in diabetic patients with refractory cutaneous ulcers. Sichuan Da Xue Xue Bao Yi Xue Ban. 2012;43(5):7625
39. Li L, Chen D, Wang C, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: A prospective, randomized clinical trial. Wound Repair Regen. 2015; 23(4): 495-505. PMID 25847503
40. Liu GY, Deng XL, Sun Y, Wang MZ, Gao J, Gou J. Effect of autologous platelet-rich gel on the treatment of diabetic foot ulcers. J Xi'an Jiaotong Univ (Med Sci). 2016;37:264-267.
41. Liao X, Liang JX, Li SH, et al. Allogeneic Platelet-Rich Plasma Therapy as an Effective and Safe Adjuvant Method for Chronic Wounds. J Surg Res. Feb 2020; 246: 284-291. PMID 31622885
42. Meamar R, Ghasemi-Mobarakeh L, Norouzi MR, et al. Improved wound healing of diabetic foot ulcers using human placenta-derived mesenchymal stem cells in gelatin electrospun nanofibrous scaffolds plus a platelet-rich plasma gel: A randomized clinical trial. Int Immunopharmacol. Dec 2021; 101(Pt B): 108282. PMID 34737130
43. Ma L. Clinical efficacy of autologous platelet rich gel in the treatment of diabetic foot and diabetic chronic cutaneous ulcer. Chin J Mod Drug Appl.2014;8:86-88
44. Miłek T, Baranowski K, Zydlewski P, et al. Role of plasma growth factor in the healing of chronic ulcers of the lower legs and foot due to ischemia in diabetic patients. Postepy Dermatol Alergol. Dec 2017; 34(6): 601-606. PMID 29422826
45. Qi KQ, ChenTJ PJL, Shang XL. The application of autologous platelet-rich gel in the treatment of diabetic foot ulcers. Chin J Diabetes. 2014;22: 1102-1105.

46. Rainys D, Cepas A, Dambrauskaite K, et al. Effectiveness of autologous platelet-rich plasma gel in the treatment of hard-to-heal leg ulcers: a randomized control trial. J Wound Care. Oct 02 2019; 28(10): 658-667. PMID 31600109
47. Saad Setta H, Elshahat A, Elsherbiny K, et al. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. Int Wound J. Jun 2011; 8(3): 307-12. PMID 21470370
48. Saldalamacchia G, Lapice E, Cuomo V, et al. A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers. Nutr Metab Cardiovasc Dis. Dec 2004; 14(6): 395-6. PMID 15853123
49. Serra R, Grande R, Butrico L, et al. Skin grafting and topical application of platelet gel in the treatment of vascular lower extremity ulcers. Acta Phlebologica. 2014 01 Dec;15(3):129-36.
50. Singh SP, Kumar V, Pandey A, et al. Role of platelet-rich plasma in healing diabetic foot ulcers: a prospective study. J Wound Care. Sep 02 2018; 27(9): 550-556. PMID 30204574
51. Steed DL, Goslen JB, Holloway GA, et al. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. Diabetes Care. Nov 1992; 15(11): 1598-604. PMID 1468291
52. Steed DL, Edington HD, Webster MW. Recurrence rate of diabetic neurotrophic foot ulcers healed using topical application of growth factors released from platelets. Wound Repair Regen. 1996; 4(2): 230-3. PMID 17177818
53. Mohammadi Tofigh A, Tajik M. Comparing the standard surgical dressing with dehydrated amnion and platelet-derived growth factor dressings in the healing rate of diabetic foot ulcer: A randomized clinical trial. Diabetes Res Clin Pract. Mar 2022; 185: 109775. PMID 35149167
54. Xie J, Fang Y, Zhao Y, et al. Autologous Platelet-Rich Gel for the Treatment of Diabetic Sinus Tract Wounds: A Clinical Study. J Surg Res. Mar 2020; 247: 271-279. PMID 31706541
55. Yang L, Gao L, Lv Y, et al. Autologous platelet-rich gel for lower-extremity ischemic ulcers in patients with type 2 diabetes. International Journal of Clinical and Experimental Medicine. 2017 30 Sep;10(9):13796-801.
56. Zhang L Qiang D, Sun YH. Clinical observation of autologous platelet rich gel in the treatment of diabetic foot ulcers. Ningxia Med J. 2016;38:809-811.
57. Zhou XP, Gong YX, Yang ZD, Wang W. Application value analysis of autologous platelet gel in refractory skin ulcer of diabetic patients. World Lat Med Inform. 2015;15:19-20
58. Zhu SF, Liu H, Li L, Wang XF. Preliminary application of autologous platelet rich gel in diabetic neuropathic ulcers. Med Innov China. 2012;9:18-19.

59. Centers for Medicare & Medicaid Services (CMS). National Coverage Analysis (NCA) Tracking Sheet for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R4). 2020; https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=300&NCDId=217.
60. Gupta A, Channaveera C, Sethi S, et al. Efficacy of Intralesional Platelet-Rich Plasma in Diabetic Foot Ulcer. J Am Podiatr Med Assoc. May 01 2021; 111(3). PMID 33231614
61. Qu W, Wang Z, Hunt C, et al. The Effectiveness and Safety of Platelet-Rich Plasma for Chronic Wounds: A Systematic Review and Meta-analysis. Mayo Clin Proc. Sep 2021; 96(9): 2407-2417. PMID 34226023
62. Oliveira BGRB, Carvalho MR, Ribeiro APL. Cost and effectiveness of Platelet Rich Plasma in the healing of varicose ulcer: Meta-analysis. Rev Bras Enferm. 2020; 73(4): e20180981. PMID 32609173
63. Fang Q, Zhang Y, Tang L, et al. Clinical Study of Platelet-Rich Plasma (PRP) for Lower Extremity Venous Ulcers: A Meta-Analysis and Systematic Review. Int J Low Extrem Wounds. Dec 2023; 22(4): 641-653. PMID 34665051
64. Saha S, Patra AC, Gowda SP, et al. Effectiveness and safety of autologous platelet-rich plasma therapy with total contact casting versus total contact casting alone in treatment of trophic ulcer in leprosy: An observer-blind, randomized controlled trial. Indian J Dermatol Venereol Leprol. 2020; 86(3): 262-271. PMID 31997794
65. Shehab AW, Eleshra A, Fouda E, et al. Randomized prospective comparative study of platelet-rich plasma versus conventional compression in treatment of post-phlebitic venous ulcer. Vascular. Dec 2023; 31(6): 1222-1229. PMID 35603798
66. Zhou SF, Estrera AL, Loubser P, et al. Autologous platelet-rich plasma reduces transfusions during ascending aortic arch repair: a prospective, randomized, controlled trial. Ann Thorac Surg. Apr 2015; 99(4): 1282-90. PMID 25661906
67. Serraino GF, Dominijanni A, Jiritano F, et al. Platelet-rich plasma inside the sternotomy wound reduces the incidence of sternal wound infections. Int Wound J. Jun 2015; 12(3): 260-4. PMID 23692143
68. Zhu S, Gao J, Yu W, et al. Platelet-rich plasma influence on the sternal wounds healing: A meta-analysis. Int Wound J. Nov 2023; 20(9): 3794-3801. PMID 37350616
69. El-Anwar MW, Nofal AA, Khalifa M, et al. Use of autologous platelet-rich plasma in complete cleft palate repair. Laryngoscope. Jul 2016; 126(7): 1524-8. PMID 27075516
70. Sidman JD, Lander TA, Finkelstein M. Platelet-rich plasma for pediatric tonsillectomy patients. Laryngoscope. Oct 2008; 118(10): 1765-7. PMID 18622315

71. Almdahl SM, Veel T, Halvorsen P, et al. Randomized prospective trial of saphenous vein harvest site infection after wound closure with and without topical application of autologous platelet-rich plasma. Eur J Cardiothorac Surg. Jan 2011; 39(1): 44-8. PMID 20634084
72. Mohamadi S, Norooznezhad AH, Mostafaei S, et al. A randomized controlled trial of effectiveness of platelet-rich plasma gel and regular dressing on wound healing time in pilonidal sinus surgery: Role of different affecting factors. Biomed J. Dec 2019; 42(6): 403-410. PMID 31948604
73. Slaninka I, Fibír A, Kaška M, et al. Use of autologous platelet-rich plasma in healing skin graft donor sites. J Wound Care. Jan 02 2020; 29(1): 36-41. PMID 31930949
74. Kazakos K, Lyras DN, Verettas D, et al. The use of autologous PRP gel as an aid in the management of acute trauma wounds. Injury. Aug 2009; 40(8): 801-5. PMID 18703188
75. Marck RE, Gardien KL, Stekelenburg CM, et al. The application of platelet-rich plasma in the treatment of deep dermal burns: A randomized, double-blind, intra-patient controlled study. Wound Repair Regen. Jul 2016; 24(4): 712-20. PMID 27169627
76. Yeung CY, Hsieh PS, Wei LG, et al. Efficacy of Lyophilised Platelet-Rich Plasma Powder on Healing Rate in Patients With Deep Second Degree Burn Injury: A Prospective Double-Blind Randomized Clinical Trial. Ann Plast Surg. Feb 2018; 80(2S Suppl 1): S66-S69. PMID 29369904
77. Huang H, Sun X, Zhao Y. Platelet-rich plasma for the treatment of burn wounds: A meta-analysis of randomized controlled trials. Transfus Apher Sci. Feb 2021; 60(1): 102964. PMID 33127309
78. Imam MS, Alotaibi AAS, Alotaibi NOM, et al. Efficiency of platelet-rich plasma in the management of burn wounds: A meta-analysis. Int Wound J. Sep 30 2023. PMID 37776166
79. Qaseem A, Humphrey LL, Forciea MA, et al. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. Mar 03 2015; 162(5): 370-9. PMID 25732279
80. Association for the Advancement of Wound Care (AAWC). Guideline of Pressure Ulcer Guidelines. Malvern, PA: AAWC; 2010.
81. Association for the Advancement of Wound Care (AAWC). International Consolidated Venous Ulcer Guideline (ICVUG). 2015; https://aawconline.memberclicks.net/assets/appendix%20c%20guideline%20icvug-textformatrecommendations-final%20v42%20changessaved18aug17.pdf.
82. National Institute for Health and Clinical Excellence (NICE). Diabetic foot problems: prevention and management [NG19]. 2019; https://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-pdf-1837279828933.

83. Centers for Medicare and Medicaid Services (CMS). National coverage determination (NCD) for blood-derived products for chronic non-healing wounds (270.3). Effective date of version August 2, 2012. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=217&ncdver=5&NCAId=260.
84. Centers for Medicare & Medicaid Services (CMS). Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R3). 2012; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=260.
85. Centers for Medicare & Medicaid Services (CMS). CMS Manual System: Pub 100-3 Medicare National Coverage Determinations (Transmittal 127). 2010 Oct; https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R127NCD.pdf..
86. Centers for Medicare & Medicaid Services (CMS). Decision Memo for Autologous Blood Derived Products for Chronic Non-Healing Wounds (CAG-00190R2). 2008; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=208.
87. Qu W, Wang Z, Hunt C, Morrow AS, Urtecho M, Amin M, Shah S, Hasan B, Abd-Rabu R, Ashmore Z, Kubrova E, Prokop LJ, Murad MH. Platelet-Rich Plasma for Wound Care in the Medicare Population. Technology Assessment Program Project ID 040-353-492. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/prp/prp-wound-care.pdf.
88. Centers for Medicare & Medicaid Services (CMS). National Coverage Analysis (NCA) for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R4). 2021; https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=300.

Policy History

Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024
06/03/2010 Medical Policy Committee approval
06/16/2010 Medical Policy Implementation Committee approval. New policy.
05/05/2011 Medical Policy Committee approval

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

05/18/2011	Medical Policy Implementation Committee approval. No change to coverage.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding revised
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Removed orthopedic applications of platelet rich plasma from the policy. Title change.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/10/2019	Coding update
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

09/01/2022 Medical Policy Committee review
09/14/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023 Medical Policy Committee review
06/14/2023 Medical Policy Implementation Committee approval. "Based on review of available data, the Company considers use of platelet-rich plasma (ie, autologous blood-derived preparations for the treatment of acute or chronic wounds including, but not limited to surgical wounds and non-healing ulcers to be investigational" was moved to policy 00476. Title changed to Recombinant platelet-derived growth factor (Becaplermin).
06/06/2024 Medical Policy Committee review
06/12/2024 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 06/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Recombinant platelet-derived growth factor (Becaplermin)

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 07/08/2024

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	Delete codes effective 07/01/2023: 0232T, 36513
HCPCS	S0157 Delete codes effective 07/01/2023: G0460, G0465, P9020, S9055
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.