Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 10/11/2021

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: Orthopedic Applications of Platelet-Rich Plasma is addressed separately in medical policy 00476.

Note: Bioengineered Skin and Soft Tissue Substitutesis 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

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Patient Selection Criteria
Becapleromin

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: Patients 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.

Platelet-Rich Plasma (IE, Autologous Blood-Derived Preparations)

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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.***

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.***

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.

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)

Regranex®‡

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 débridement, 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…."

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 patients 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 patients 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.

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

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.

Recombinant PDGFs
For individuals who have diabetic lower-extremity ulcers who receive recombinant PDGF, the evidence includes 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 a meaningful improvement in the net health outcome.

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes RCTs and systematic reviews. 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 a meaningful 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 the effects of the technology on health outcomes.

Platelet-Rich Plasma

For individuals who have chronic wounds or acute surgical or traumatic 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 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 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.

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Additional Information
Not applicable

Supplemental Information

Practice Guidelines and Position Statements

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)
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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.

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 patients 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 patients 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 patients with diabetic ulcers who are treated with autologous PRP have better outcomes (complete wound healing) when compared to patients 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."

CMS is currently seeking public comments on this proposed decision during a public comment period that is open through January 20, 2021. The expected completion date for this national coverage analysis reconsideration is March 21, 2021.

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT02312596a	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	250	Jul 2021
NCT02312570a	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	250	Jul 2021
NCT02307448a	Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds	80	Dec 2022
NCT02402374a	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
Unpublished			
NCT02071979a	Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)	1500	Jan 2018(terminated; updated 01/16/18)
NCT02213952	Efficacy of Autologous Platelet-Rich Plasma in the Treatment of Vascular Ulcers in Primary Care: Clinical Trial Phase III	0	Dec 2017 (withdrawn Feb 2020)

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

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Policy History

Original Effective Date: 06/16/2010
Current Effective Date: 10/11/2021

06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. New policy.
05/05/2011	Medical Policy Committee approval
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.

Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions

Policy # 00262
Original Effective Date: 06/16/2010
Current Effective Date: 10/11/2021

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.

Next Scheduled Review Date: 09/2022

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 2020 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.

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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	0232T, 36513
HCPCS	G0460, P9020, S0157, S9055
ICD-10 Diagnosis	E11.40-E11.49, E11.610-E11.69, E13.40-E13.49, E13.61-E13.69, I70.25, I70.35, I70.45, I70.55, I70.65, I70.75, L72.0-L72.9, L89.006-L89.96, L98.411-L98.419, L98.421-L98.429, L98.491-L98.499

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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.