

## Corporate Medical Policy

### Growth Factors in Wound Healing

<b>File Name:</b>	growth_factors_in_wound_healing
<b>Origination:</b>	4/1993
<b>Last CAP Review:</b>	11/2011
<b>Next CAP Review:</b>	11/2012
<b>Last Review:</b>	11/2011

#### Description of Procedure or Service

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This policy addresses the use of blood-derived growth factors, including recombinant platelet-derived growth factors and platelet rich plasma, as a treatment of wounds or other musculoskeletal conditions, including but not limited to adjunctive use in surgical procedures and treatment of diabetic ulcers, ulcers related to venous stasis, lateral epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture.

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, 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 has also 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 the 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, platelet-rich plasma has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus platelet-rich plasma has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, platelet-rich plasma may be injected directly into the tissue. Platelet-rich plasma has also been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren's contracture. Injection of platelet-rich plasma for tendon and ligament pain is theoretically related to prolotherapy. However, prolotherapy involves injection of chemical irritants that are intended to stimulate inflammatory responses and induce release of endogenous growth factors.

Platelet-rich plasma 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; Tisseal (Baxter) and Hemaseal are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This policy does not address the use of fibrin sealants.

A recombinant PDGF product, becaplermin gel (Regranex®, McNeil Pharmaceutical) has been approved by the U.S. Food and Drug Administration (FDA). The labeled indication is as follows: "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

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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 this 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 post-marketing 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."

A number of commercially available centrifugation devices are used for the preparation of platelet-rich plasma. For example, AutoloGel™ (Cytomedix) and SafeBlood® (SafeBlood Technologies) are two related but distinct autologous blood-derived preparations that can be prepared at the bedside for immediate application. Both Autologel and SafeBlood have been specifically marketed for wound healing. Other devices may be used in the operating room setting, such as Medtronic Electromedic, Elmd-500 Autotransfusion system, the Plasma Saver device, or the Smart PreP device. The Magellan Autologous Platelet Separator System (Medtronic) includes a disposables kit designed for use with the Magellan Autologous Platelet Separator portable tabletop centrifuge. BioMet Biologics received marketing clearance through the FDA's 510(k) process for a gravitational platelet separation system (GPSII), which uses a disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. 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.

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

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**BCBSNC will provide coverage for Growth Factors in Wound Healing when it is medically necessary because the medical criteria and guidelines below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Growth Factors in Wound Healing are covered

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Recombinant platelet-derived growth factor (i.e., becaplermin) may be considered **medically necessary** when used as an adjunct to standard wound management for the following indications

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

**(See Policy Guidelines section below for further information regarding patient selection criteria.)**

## When Growth Factors in Wound Healing are not covered

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Other applications of becaplermin are considered **investigational**, including, but not limited to, ischemic ulcers, ulcers related to venous stasis, and ulcers not extending through the dermis into the subcutaneous tissue.

Use of autologous blood-derived preparations (i.e., platelet-rich plasma) is considered **investigational**. This includes, but is not limited to, use in the following situations:

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- Treatment of acute or chronic wounds including non-healing ulcers
- Adjunctive use in surgical procedures
- Primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture.

## Policy Guidelines

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

1. 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
2. Full-thickness ulcer (i.e., Stage III or IV), extending through dermis into subcutaneous tissues
3. 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:

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

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.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable Codes: S0157, S9055, 0232T*

*Code 0232T should not be reported with 20550-20551, 20600-20610, 20926, 76942, 77002, 77012, 77021, 86965*

*CPT code 20926 should not be billed for application of recombinant or autologous platelet-derived growth factors.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual - 3/96

Medical Policy Advisory Group - 1/99

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BCBSA Medical Policy Reference Manual - 7/99  
USPDI, 1999, Volume 1, 19th Edition, p. 550-551  
Medical Policy Advisory Group - 12/99  
Specialty Matched Consultant Advisory Panel - 10/2000  
Medical Policy Advisory Group - 10/2000  
BCBSA Medical Policy Reference Manual; Policy 2.01.16; Review date 7/12/02  
Specialty Matched Consultant Advisory Panel - 8/2002  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 7/17/03.  
ECRI. Platelet Gel for Chronic, Nonhealing Wounds [Hotline Request]. 2003/11/05 retrieved on 7/2/04 from [http://www.ta.ecri.org/Hotline/Prod/summarydetail.aspx?doc\\_id=7793&q=%22Growth+Factors&anm](http://www.ta.ecri.org/Hotline/Prod/summarydetail.aspx?doc_id=7793&q=%22Growth+Factors&anm)  
Specialty Matched Consultant Advisory Panel - 8/2004  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 11/9/04  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 9/27/05  
Specialty Matched Consultant Advisory Panel - 8/2006  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 4/17/07  
FDA Update of Safety Review. Follow-up to the March 27, 2008, Communication about the Ongoing Safety Review of Regranex (becaplermin). June 6, 2008. Retrieved on July 11, 2008 from [http://www.fda.gov/cder/drug/early\\_comm/becaplermin\\_update\\_200806.htm](http://www.fda.gov/cder/drug/early_comm/becaplermin_update_200806.htm)  
FDA Updated labeling for Regranex. Retrieved on July 11, 2008 from [http://www.fda.gov/cder/drug/infopage/becaplermin/regranex\\_cbe\\_ibl.pdf](http://www.fda.gov/cder/drug/infopage/becaplermin/regranex_cbe_ibl.pdf)  
Specialty Matched Consultant Advisory Panel - 9/4/08  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 11/12/2009  
BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.16, 4/14/2011

## Policy Implementation/Update Information

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12/92	Evaluated: Investigational
7/96	Reaffirmed: National Association reviewed 3/96. No changes.
1/99	Reaffirmed: Medical Policy Advisory Group
8/99	Reformatted, Medical Term Definitions added
12/99	Medical Policy Advisory Group
10/00	Specialty Matched Consultant Advisory Panel review. No change recommended in criteria. System coding changes. Medical Policy Advisory Group review. No change in criteria. Approve. See Also: Keratinocyte Allografts
11/01	Coding format change.
0/02	Specialty Matched Consultant Advisory Panel review 8/15/02. New policy statement on becaplermin gel for treatment of pressure ulcers under "When Growth Factors for Wound Healing are Covered". Under when not covered, removed "pressure ulcers" from third bullet. Added codes S0157 and S9055. System coding changes. See Also: Bioengineered Skin for Treatment of Skin Ulcers (Name of Keratinocyte Allografts policy changed)
4/04	Benefits Application and Billing/Coding sections updated for consistency. Corrected

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- references to match file name in policy.
- 9/9/04 Specialty Matched Consultant Advisory Panel review. No changes to criteria. Description section updated to add information regarding Autologel, Safeblood and chronic non-healing ulcers. Added "See Also: Bioengineered Skin for Treatment of Skin Ulcers (Name of Keratinocyte Allografts policy changed)" to Policy Implementation/Update Information section following 10/02 entry.
- 11/27/06 Description section revised. Under When Covered #1-adequate tissue oxygenation may be determined by transcutaneous partial pressure of oxygen or "an ankle-brachial index (ABI) of 0.7 or greater, or if an ABI is not obtainable, then a toe pressure of 40 or greater". Under When Not Covered added "Autologous blood-derived preparations (i.e., platelet-rich plasma) are considered investigational as a primary procedure for other miscellaneous conditions including, but not limited to, epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture." Medical Terms and Reference sources added. (pmo)
- 10/6/08 Description section updated to include FDA indications for Regranex Gel and recently added Black Box Warning. Reference sources added. Specialty Matched Consultant Advisory Panel review 9/4/08. No changes to criteria. (pmo)
- 4/13/2010 Description section revised. Revised section "When not covered" to include "Autologous blood-derived preparations (i.e., platelet-rich plasma) are considered investigational as a primary procedure for other miscellaneous conditions including, but not limited to: Treatment of acute or chronic wounds including non-healing ulcers, Adjunctive use in surgical procedures, Primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture" Policy Guidelines updated. Resource added. (mco)
- 6/22/2010 Policy Number(s) removed (amw)
- 8/31/2010 Coding update. CPT 0232T added to Billing/Coding section. (adn)
- 12/21/10 Description section extensively revised. Specific criteria in the Covered/Not Covered sections and in the Policy Guidelines were rearranged for clarity. Intent of policy is unchanged. Specialty Matched Consultant Advisory Panel review 11/29/10. Policy accepted as drafted. (adn)
- 12/20/11 Added coding instructions to Billing/Coding section. No change to policy statement or coverage criteria. Specialty Matched Consultant Advisory Panel review 11/30/10. (adn)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.