Title

Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions

Related Policy:
Wound Healing, #435

Description

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 (discussed in policy No. 2.01.26). 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; Tissel (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.

Regulatory Status
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 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.

When services are covered for commercial products and for Medicare HMO Blue and Medicare PPO Blue[1]

We cover recombinant platelet-derived growth factor (i.e., Becaplermin) when used as an adjunct to standard wound management for the following indications (for further information on patient selection criteria, see "Note" below.)

- Neuropathic diabetic ulcers extending into the subcutaneous tissue, and
- Pressure ulcers extending into the subcutaneous tissue.

Note: 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,
- 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,
- Ulcer in an anatomic location that can be off-loaded for the duration of treatment,
- Albumin concentration >2.5 dL,
- Total lymphocyte count >1,000, and
- Normal values of vitamins A and C.

When services are not covered for commercial products and for Medicare HMO Blue and Medicare PPO Blue[1]

We do not cover other applications of Becaplermin, including, but not limited to, ischemic ulcers, ulcers related to venous stasis, and ulcers not extending through the dermis into the subcutaneous tissue.

We do not cover autologous blood-derived preparations (i.e., platelet-rich plasma) including, but not limited to, the following:

- 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.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed	Prior to performance of service
Blue Cross Blue Shield of Massachusetts Provider Appeals PO Box 986065 Boston, MA 02298	Blue Cross Blue Shield of Massachusetts Case Creation/Medical Policy One Enterprise Drive Quincy, MA 02171 Tel: 1-800-327-6716 Fax: 1-888-641-5330

Authorization Information

For Managed Care members:

- Authorizations are required for these services; *see **Managed Care Guidelines** for additional requirements.*

For Indemnity and PPO members:

- Authorizations are required for these services; *see **Indemnity and PPO Guidelines** for additional requirements.*

Managed Care Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- **For Medicare HMO Blue members:** The service must meet the criteria for coverage noted in this policy, be medically necessary, prescribed by a plan physician and provided by a network provider.
- **For Medicare HMO Blue members:** Referrals are required for all visits to a specialist.
- For all other Managed Care plans, any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorization is required for an inpatient admission.

Indemnity and PPO Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- Authorization is required for an inpatient admission.
- Authorizations are not required for most outpatient services as determined by the individual's subscriber certificate.

- Referrals to a specialist are not required.

Other information

For our Medical Technology Assessment Guidelines, see document #350.

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

HCPCS code:
Recombinant Platelet-derived Growth Factor

- **S0157:** Becaplermin gel 0.01%, 0.5 gm

The procedure noted below will reject as non-covered, ***for commercial products and for Medicare HMO Blue and Medicare PPO Blue products,*** leaving **no** patient balance, as this procedure does not meet our Medical Technology Assessment Guidelines.

HCPCS code:

- **S9055:** Procuren or other growth factor preparation to promote wound healing.

Policy update history

Issued 6/88. Reviewed 1/99; no changes in coverage were made. Reviewed 3/04 MPG Pulmonology, Allergy and ENT/Otolaryngology, no changes is coverage were made. Reviewed 12/04 MPG Plastic Surgery and Dermatology, no changes in coverage were made. Reviewed 3/05 MPG Pulmonology, Allergy and ENT/Otolaryngology, no changes in coverage were made. Reviewed 3/06 MPG-Pulmonology, Allergy, ENT/Otolaryngology, no changes in coverage were made. Reviewed 12/06 MPG-Plastic Surgery and Dermatology, no changes in coverage were made. Reviewed 3/07 MPG- Pulmonology, Allergy and ENT/Otolaryngology, no changes in coverage were made. 6/07 comparison review of BCBSA national policy Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and Other Miscellaneous Condition. BCBSMA medical policy clarified to more specifically benchmark BCBSA's coverage and investigational language, which also represents present day BCBSMA claims processing. Reviewed 3/08 MPG- Pulmonology, Allergy and ENT/Otolaryngology, no changes in coverage were made. 9/08 comparison review of the BCBSA national medical policy, Recombinant and Autologous Platelet-Derived Growth Factor as a Primary Treatment of Wound Healing and other Miscellaneous Condition; policy statements unchanged which BCBSMA continues to benchmark. Reviewed 12/08 MPG-Plastic Surgery and Dermatology, no changes in coverage were made. Reviewed 3/09 MPG-Pulmonology, Allergy/Asthma/Immunology and ENT/ Otolaryngology, no changes in coverage were made. Updated 11/09 based on the comparison review of the BCBSA national policy, Recombinant and Autologous Platelet-Derived Growth Factor as a Primary Treatment for Wound Healing and Other Miscellaneous Conditions. BCBSA clarified their investigational non-covered indications with the addition: autologous blood-derived preparations used in the treatment for acute non-healing wounds; BCBSMA benchmarks this national policy clarification. Reviewed 12/2009 MPG Plastic Surgery and Dermatology, no changes in coverage were made. Updated 5/1/2010 to clarify non-coverage of autologous blood-derived preparations for adjunctive use in surgical procedures, and to issue a new policy document #186, Recombinant Platelet-derived Growth Factor (PDGF). Recombinant Platelet-derived Growth Factor (PDGF) was previously addressed under policy #435,

Wound Healing. Reviewed 12/2010 MPG Plastic Surgery and Dermatology, no coverage changes were made. Reviewed 11/2011 MPG – Plastic Surgery and Dermatology, no changes in coverage.

References

References for footnote 1:

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22. CMS Manual System. Pub. 100-03 Medicare National Coverage Determinations, July 30, 2004.

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Footnotes

[1] Based on BCBSA national policy 2.01.16, Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions, reviewed 11/2009.