Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non–Orthopedic Conditions—Regranex (becaplermin)

Policy Number: 2.01.16  
Last Review: 09/2017  
Origination: 09/1999  
Next Review: 09/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for recombinant platelet-derived growth factor (ie, becaplermin) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
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 (for further information on patient selection criteria, see Considerations below.)

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

When Policy Topic is not covered
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:

- Treatment of acute or chronic wounds including nonhealing 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

Considerations
This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 2.01.16.

Becaplermin
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.

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 cm², 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 the 15-g tubes would be required.

**Autologous Blood-Derived Preparations (i.e., Platelet-Rich Plasma)**

In July 2010, a new CPT category III code for injections of platelet-rich plasma became effective: 0232T: Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed. The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021 and 86965. Code 0232T includes the harvesting and preparation of the platelet-rich plasma. For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products but CPT code 86999 (unlisted transfusion medicine procedure) can be used. It has been reported that providers have used CPT code 20926 (tissue graft, other) to describe the overall procedure. It is questionable whether platelet-rich plasma is appropriately considered a tissue graft.

The American Medical Association's Department of Coding instructs that placement of platelet-rich plasma into an operative site is an inclusive component of the operative procedure performed and not separately reported.

**Description of Procedure or Service**

This policy addresses the use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), as a treatment of wounds or other miscellaneous non–orthopedic conditions, including but not limited to treatment of diabetic ulcers, pressure ulcers, and ulcers related to venous stasis.

Results from randomized controlled trials (RCTs) show improved rates of healing with use of recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. Evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat other types of wounds, including ischemic or chronic venous ulcers or acute traumatic wounds.

For PRP treatment, there are numerous small controlled trials for a wide variety of conditions. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors. The oldest and most established evidence is in the area of dental surgery, which is outside the scope of medical policy. Recent literature indicates an increasing number of RCTs for other conditions, and a search of the clinical trials database (available at ClinicalTrials.gov) reveals that many more RCTS are in progress.

Current results of PRP trials are mixed. A recent systematic review found that a greater proportion of studies reported no benefit from PRP than studies that reported a benefit. It is unknown if the mixed results are due to variability in the conditions studied and outcomes measured, to differences in platelet separation technique, concentration or activation, or to differences in the timing and frequency of
administration. Additional studies are needed to resolve these issues.

Rationale
A variety of growth factors have been found to play a role in wound healing, including PDGFs, 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, 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 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 type of transforming growth factors, 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) and Hemaseel® 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) was approved by the U.S. Food and Drug Administration (FDA) in 1997. 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 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 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."

Blood products such as PRP are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products.1 The regulation process for these products is described in FDA’s 21 CFR 1271 of the Code of Federal 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, FDA has not attempted to regulate activated PRP.

There are numerous PRP preparation systems on the market today with FDA clearance. For example, Aurix™ System (previously 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 disposable kit designed for use with the
Magellan Autologous Platelet Separator portable tabletop centrifuge. BioMet Biologics received marketing clearance through FDA’s 510(k) process for a gravitational platelet separation system (GPS®II), 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.

**Recombinant Platelet-Derived Growth Factor (Becaplermin Gel)**

**Diabetic Lower Extremity Ulcers**

This policy regarding the use of becaplermin gel was originally based on a 1999 TEC Assessment,2 which concluded that the evidence supports the conclusion that becaplermin treatment, in conjunction with good wound care, improves the health outcomes of patients with chronic neuropathic diabetic ulcers that meet the patient selection criteria defined here. Becaplermin gel plus good wound care resulted in a 43% complete wound closure rate, compared with 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure. A systematic review from 2014 identified 6 RCTs with a total of 992 patients that compared recombinant plateleterived growth factors (PDGFs) with placebo or standard care.3 There was a combined odds ratio of 1.53 (95% confidence interval [CI], 1.14 to 2.04; p=0.004) favoring recombinant PDGF for complete healing rate.

An industry-sponsored study assessed the effectiveness of recombinant PDGF for diabetic neuropathic foot ulcers in actual clinical practice.4 Subjects (from a cohort of 24,898 patients in wound care centers) whose wounds did not heal over an 8-week observation period were eligible for the study and were retrospectively assessed over a period of 20 weeks or until they healed. Any subject with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25,000 patients treated for foot ulcers, 2394 (9.6%) received recombinant PDGF. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in patients treated with recombinant PDGF. The relative risk, controlling for the propensity to receive PDGF, was 1.32 (95% CI, 1.22 to 1.38) for healing and 0.65 (95% CI, 0.54 to 0.78) for amputation (6.4% in controls vs 4.9% in the PDGF group). Analysis also indicated that those who received PDGF were more likely to be younger, male, and have older wounds, factors not known to affect wound healing. These results support clinical effectiveness of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice.

**Pressure Ulcers**

Rees et al (1999) in the United States conducted a randomized trial focusing on the use of becaplermin gel as a treatment for pressure ulcers.5 Patient selection criteria for this trial are summarized in the Policy Guidelines, but most importantly included full-thickness ulcers and an anatomic location where pressure could be offloaded during treatment. This latter patient selection criterion may limit the number of patients with pressure ulcers who would be considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups and received either a placebo or 1 of 3 doses of becaplermin. All patients received a standardized program of good wound care. In the 2 groups of patients treated with once daily doses of becaplermin (either 0.01% or 0.03%), the incidence of complete healing was significantly improved compared with the placebo group. There was no difference in outcome between the 0.01% and 0.03% groups, suggesting that there is no clinical benefit in increasing the potency above 0.01%. A third group of patients received becaplermin 0.01% twice daily. This group did not report an improved outcome compared with placebo, a finding that is unexplained.

**Hypertensive Leg Ulcers**

In 2011, Senet et al in France published a multicenter, double-blind RCT of becaplermin gel for hypertensive leg ulcers.6 There was no significant difference between the becaplermin (n=28) and control hydrogel (n=31) groups for any of the outcome measures, which included complete closure rates after 8 and 12 weeks, changed ulcer area, and changed ulcer-related pain and quality of life.
**Acute Traumatic Wounds**

Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. A 2005 trial in the United States used alternate assignment to “randomize” 50 patients (fingertip wound area of 1.5 cm or more, with or without phalangeal exposure) to daily treatment with PDGF or surgical reconstruction. Statistical analysis showed that baseline characteristics of the 2 groups were similar for patient age, wound area (2.2-2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that in comparison with the surgical intervention, treatment with recombinant PDGF resulted in faster return to work (10 vs 38 days) and wound healing (25 vs 35 days), less functional impairment (10% vs 22%), and less need for physical therapy (20% vs 56%). Fingertips treated with PDGF were also reported to have satisfactory aesthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed, could lead to improvement in health outcomes for patients with fingertip injury. However, the present study is limited by the small sample size, the method of randomization, and the potential for investigator bias (although examining physicians were blinded to treatment allocation, actual treatment may have been obvious). Additional RCTs are needed.

**Adverse Effects**

Growth factors cause cells to divide more rapidly. For this reason, the manufacturer continued to monitor studies begun before Regranex was approved in December 1997 for any evidence of adverse effects, such as increased numbers of cancers. In a long-term safety study completed in 2001, more deaths from cancer occurred in people who used Regranex than in those who did not. After completion of the study in 2001, an additional study was performed using a health insurance database that covered the period from January 1998 through June 2003. This study identified 2 groups of patients with similar diagnoses, drug use, and use of health services: 1 group used Regranex, and the other group did not. Results of this study showed that there were more deaths from cancer among patients who were given 3 or more prescriptions for treatment with Regranex compared with those who were not treated with Regranex. No single type of cancer was identified; deaths from all types of cancer were observed. In 2008, the U.S. Food and Drug Administration concluded that the increased risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher compared with those who did not use Regranex. The risk of new cancers among Regranex users was not increased compared with nonusers, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

**Section Summary**

Results from RCTs show improved rates of healing with use of recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. The increase in rate of healing must be balanced with the potential for increased risk from cancer. Evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat other types of wounds, including ischemic or chronic venous ulcers or acute traumatic wounds.

**Autologous Blood-Derived Preparations (ie, Platelet-Rich Plasma)**

The policy on platelet-derived wound-healing formulae was originally derived from a 1992 TEC Assessment, which primarily focused on the Procuren process, referred to as a platelet-derived woundhealing formula. This preparation is no longer commercially available. Currently, a large number of devices are available for the preparation of platelet-rich plasma (PRP) or PRP gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is unknown whether platelet activation before injection is necessary.

A number of systematic reviews of the evidence on PRP have been published. A 2012 Cochrane review included 9 RCTs (325 participants) of PRP for treating chronic wounds. This review was restricted to trials where PRP was compared with no additional treatment or placebo. Four RCTs included patients with mixed chronic wounds, 3 included patients with venous leg ulcers, and 2 RCTs included patients with diabetic foot ulcers. Only 1 trial was considered to be at low risk of bias. After a median treatment duration of 12 weeks, there was no significant difference between the PRP and control groups in complete healing of diabetic foot ulcers, venous leg ulcers, or mixed chronic wounds.
There was no significant difference in the area epithelialized in 3 RCTs of mixed chronic wounds. In 2 RCTs of mixed chronic wounds, there was a significant difference favoring PRP in the wound area that was healed. The review concluded that there is no current evidence to suggest that autologous PRP is of value for treating chronic wounds.

Earlier systematic reviews reached similar conclusions. For example, a 2009 systematic review identified 42 controlled trials on PRP, 20 of these were RCTs and included in the systematic review. The 20 RCTs comprised 11 trials on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. An industry-funded systematic review from 2011 included 21 studies of PRP gel for cutaneous wound healing, 12 of which were RCTs. There were 3 main types of wounds, including open chronic wounds, acute surgical wounds with primary closure, and acute surgical wound with secondary closure. Study quality varied considerably, with 3 studies rated as high quality and 6 rated as poor quality. Two additional studies could not be rated because they were published only as an abstract and letter. Meta-analysis of the effect of PRP on complete wound healing of chronic wounds was limited by the inclusion of poor quality studies. There were no high-quality RCTs that showed an improvement in complete healing with PRP.

Key references on PRP for specific indications are described next.

**Acute Traumatic Wounds**
Kazakos et al (2009) reported a prospective RCT that evaluated treatment of acute traumatic wounds (open fractures, closed fractures with skin necrosis, and friction burns) with platelet gel in 59 consecutive patients (27 PRP, 32 controls). Conventional treatment consisted of topical washing and cleaning of the wounds, removal of the necrotic tissue, and dressing with Vaseline gauze every 2 days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel, prepared with specialized tubes and a bench-top centrifuge, was applied to the wounds after surgical débridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. PRP gel was then applied to the wounds once weekly in the outpatient clinic until there was adequate tissue regeneration (mean, 21 days) to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in PRP-treated patients at 2 and 3 weeks (visual analog scale score, 58 PRP vs 80 controls.). Although these results are encouraging, additional study with a larger number of patients is needed.

**Tonsillectomy**
A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children, aged 4 to 15 years. PRP was prepared during the surgery and placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by either the patient or family member for 10 days after surgery. A FACES Pain Scale was used for children aged 4 to 7 years, while a numbered pain scale was used for children older than 7 years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the two conditions.

**Wound Closure**
A 2011 Norwegian trial of PRP applied to saphenous vein harvest sites after wound closure found no difference in the incidence of wound infection or cosmetic result.

**Summary of Evidence**
Results from randomized controlled trials (RCTs) show improved rates of healing with use of recombinant platelet-derived growth factor for diabetic neuropathic ulcers and pressure ulcers. Evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat other types of wounds, including ischemic or chronic venous ulcers or acute traumatic wounds.

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conditions. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors. The oldest and most established evidence is in the area of dental surgery, which is outside the scope of medical policy. Recent literature indicates an increasing number of RCTs for other conditions, and a search of the clinical trials database (available at ClinicalTrials.gov) reveals that many more RCTs are in progress.

Current results of PRP trials are mixed. A recent systematic review found that a greater proportion of studies reported no benefit from PRP than studies that reported a benefit. It is unknown whether the mixed results are due to variability in the conditions studied and outcomes measured, to differences in platelet separation technique, concentration or activation, or to differences in the timing and frequency of administration. Additional studies are needed to resolve these issues.

REFERENCES


Billing Coding/Physician Documentation Information
Regranex is a pharmacy benefit
### Additional Policy Key Words

**2.01.16**

#### Policy Implementation/Update Information

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<td>09/2006</td>
<td>Policy updated to reflect BCBSA policy 2.01.16. Title changed from Growth Factors for Wound Healing – Becaplermin to Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and other Miscellaneous Conditions.</td>
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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for