

<b>POLICY TITLE</b>	<b>RECOMBINANT AND AUTOLOGOUS PLATELET-DERIVED GROWTH FACTORS AS A TREATMENT OF WOUND HEALING AND OTHER CONDITIONS (FORMERLY BLOOD/PLATELET-DERIVED GROWTH FACTORS FOR WOUND HEALING)</b>
<b>POLICY NUMBER</b>	<b>MP-2.033</b>

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## I. POLICY

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

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**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure for these indications. This includes, but is not limited to, use in the following situations:

- 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

#### **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

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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 cm<sup>2</sup>, 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.

## ***Cross-reference:***

**MP-2.061** Prolotherapy

**MP-1.117** Bone Morphogenetic Protein

## **II. PRODUCT VARIATIONS**

*[N] = No product variation, policy applies as stated*

*[Y] = Standard product coverage varies from application of this policy, see below*

[N] Capital Cares 4 Kids

[N] PPO

[N] Indemnity

[N] SpecialCare

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[N] HMO

[Y] SeniorBlue HMO\*

[Y] SeniorBlue PPO\*

[N] POS

[Y] FEP PPO\*\*

\* CMS covers autologous platelet-rich plasma (PRP) only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when the patient is enrolled in a research study which meets the requirements specified in the CMS Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R3). The decision memo can be found at: <http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=260>.

\*\* Refer to FEP Medical Policy Manual MP-2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions. The FEP Medical Policy manual can be found at: <http://bluewebportal.bcbs.com>.

## III. DESCRIPTION/BACKGROUND

This policy addresses the use of blood-derived growth factors, including recombinant platelet-derived growth factors and platelet-rich plasma (PRP), 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.

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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.

### **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

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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.

#### **IV. RATIONALE**

This policy was created in 1996 and updated periodically using the MEDLINE database. The most recent update was performed through March 8, 2013. Following is a summary of key references to date, focusing on randomized controlled trials (RCTs).

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

Diabetic Neuropathic Ulcers: This policy regarding the use of becaplermin gel was originally based on a 1999 TEC Assessment, (1) 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 to 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure.

An industry-sponsored study assessed the effectiveness of recombinant platelet-derived growth factors (PDGF) on diabetic neuropathic foot ulcers in actual clinical practice. (2) 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 assessed over a period of 20 weeks or until they healed. Any individual with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25,000 patients treated for foot ulcers, 2,394 (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 the patients treated with recombinant PDGF. The relative risk, controlling for the propensity to receive PDGF, was 1.32 for healing and 0.65 for amputation (6.4% vs. 4.9%, respectively). 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.

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**Pressure Ulcers:** Results of a randomized study focusing on the use of becaplermin gel as a treatment of pressure ulcers was published in 1999. (3) The patient selection criteria for this study are summarized in the Policy Guidelines section, but most importantly included full-thickness ulcers and an anatomic location where pressure could be off-loaded 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 100 or 300 µg/g), the incidence of complete healing was significantly improved compared to the placebo group. There was no difference in outcome between the 100 and 300 µg/g group, suggesting that there is no clinical benefit in increasing the dose above 100 µg/g. A third group of patients received becaplermin 100 µg/g twice a day. This group did not report an improved outcome compared to placebo, a finding that is unexplained.

**Hypertensive Leg Ulcers:** In 2011, Senet et al. published results of a multicenter randomized double-blind controlled trial of becaplermin gel as a treatment of hypertensive ulcers. (4) 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. One study 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. (5) Statistical analysis showed that the baseline characteristics of the two 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, respectively) and wound healing (25 vs. 35 days, respectively) and a reduction in functional impairment (10% vs. 22%, respectively) and need for physiotherapy (20% vs. 56%, respectively). Fingertips treated with PDGF were also reported to have satisfactory esthetic 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 the investigators did blind the examining physician from treatment allocation, the actual treatment may have been obvious). Additional RCTs are needed.

**Adverse Effects:** Growth factors cause cells to divide more rapidly. It is for this reason that the manufacturer continued to monitor studies begun before Regranex was approved in December

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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 use it. Following the report of the study completed in 2001, an additional study was performed using a health insurance database that covered the period from January 1998 through June 2003. This study used the database to identify two groups of patients with similar diagnoses, drug use, and use of health services, one of which used Regranex and one group that did not. The results of this study showed that deaths from cancer were higher for patients who were given 3 or more prescriptions for treatment with Regranex than those who were not treated with Regranex. No single type of cancer was identified, but deaths from all types of cancer combined were observed. In 2008, the U.S. Food and Drug Administration (FDA) concluded that the increase in the risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher than in those patients who did not use Regranex. The risk of getting new cancers among Regranex users was not increased compared to non-users, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

**Conclusions:** Results from randomized controlled trials show improved rates of healing with use of recombinant platelet-derived growth factor 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 (i.e., Platelet-Rich Plasma)**

The policy on platelet-derived wound-healing formula was originally derived from a 1992 TEC Assessment, (6) which primarily focused on the Procuren process, referred to as a platelet-derived wound-healing formula. This preparation is no longer commercially available. At the present time, there are a large number of devices 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 are variable, and it is also uncertain whether platelet activation prior to injection is necessary. (7-11)

A number of systematic reviews of the evidence on PRP have been published. A 2012 systematic review included 23 randomized trials and 10 prospective cohort studies that compared PRP to placebo, corticosteroids, or a standard procedure. (12) For most of the studies the outcome measures differed, but 6 RCTs (n=358) and 3 prospective cohort studies (n=88) reported results of PRP using a visual analog score (VAS) and were combined for analysis. These studies assessed injuries to the acromion, rotator cuff, lateral humeral epicondyle, anterior cruciate ligament (ACL), patella, tibia, and spine. Follow-up ranged from 6 weeks to 24 months. Of 22 RCTs that evaluated functional outcomes, 6 showed a functional

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benefit of PRP, 15 showed no difference between PRP and the control, and 1 showed a significant functional advantage for the control group. Interpretation of this systematic review is limited by the combination of a wide variety of conditions, as well as the lack of standardization of platelet-separation techniques and outcome measures in the primary literature.

A 2012 Cochrane review included 9 RCTs (325 participants) on PRP for treating chronic wounds. (13) This review was restricted to studies where PRP was compared with no additional treatment or a 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 study was considered to be at low risk of bias. After a median treatment time 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 have come to 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. (14) The 20 RCTs comprised 11 studies on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. A 2010 systematic review of autologous growth factor injections in chronic tendinopathy found no high-quality studies using PRP. (15) An industry-funded systematic review from 2011 included 21 studies on PRP gel for cutaneous wound healing, 12 of which were RCTs. (16) 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 was found to vary 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. The meta-analysis of the effect of PRP on complete wound healing of chronic wounds is 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 below.

**Achilles Tendinopathy:** A single center, randomized, double-blind, placebo-controlled trial of PRP injection in patients with chronic midportion Achilles tendinopathy was reported by de Vos et al. in 2010. (17) Fifty-four patients were randomized to receive PRP or saline injection, and all patients performed eccentric exercises. The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire evaluating pain score and activity level was completed at baseline and at 6, 12, and 24 weeks. The mean VISA-A score improved significantly after 24



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weeks in both groups, and the between-group difference was not statistically significant. There were no significant differences on secondary measures of patient satisfaction and number of patients returning to their desired sport. The authors conclude that “in patients treated with an eccentric exercise program, a PRP injection compared with saline injection did not result in greater improvement in pain and activity.”

Acute Traumatic Wounds: Kazakos and colleagues reported a prospective controlled study of the treatment of acute traumatic wounds with platelet gel in 59 consecutive patients (27 PRP and 32 controls). (18) 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 debridement 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 of 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 the PRP-treated patients at 2 and 3 weeks (VAS score of 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of subjects is needed.

Anterior Cruciate Ligament (ACL) Reconstruction: Nin and colleagues randomized 100 patients undergoing arthroscopic patellar tendon allograft anterior cruciate ligament reconstruction; platelet-enriched gel was used in one group (n=50), and a non-gel group (n=50) served as control. (19) The use of platelet-derived growth factors (PDGF) on the graft and inside the tibial tunnel in patients treated with bone-patellar tendon-bone allografts had no discernable clinical or biomechanical effect at 2-year follow-up.

Lateral Epicondylitis (Tennis Elbow): A double-blind randomized trial of PRP for lateral epicondylitis was reported by Peerbooms and colleagues in 2010, with 2-year follow-up reported by Gosens et al. in 2011. (20, 21) One hundred patients with chronic (longer than 6 months) epicondylitis were randomized, 49 to receive corticosteroid injection and 51 to receive PRP injection. Success was defined as 25% reduction in pain on VAS or Disabilities of the Arm, Shoulder, and Hand (DASH) outcomes measure score after 1 year without a re-intervention. Initially, mean VAS was 70.1 in the PRP-treated patients and 65.8 in the corticosteroid group. DASH scores were 161.3 and 131.2, respectively (p<0.001). At 4 and 8 weeks after injection, outcomes on VAS and DASH scores were significantly better in the corticosteroid group. At 12 weeks, between-group differences were not significant. After 1 year, 73% of PRP and 49% of corticosteroid-treated patients met criteria for success on pain VAS; 73% of the PRP group and 51% the steroid group were successful using DASH outcome

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measures ( $p=0.005$ ). At 2 years, both VAS and DASH scores were significantly better in the PRP group (21.3 and 17.6, respectively) compared to the corticosteroid group (42.4 and 36.5). Success on the DASH was achieved by 73% of the PRP group and 39% of the corticosteroid group, while more patients in the corticosteroid group (47% vs. 14%) had deteriorated at 2 years.

In 2013, Krogh et al. reported a double-blind placebo-controlled RCT in 60 patients with chronic lateral epicondylitis. (22) Patients were randomized to receive either a blinded injection of PRP, saline, or corticosteroid injection. In order to maintain blinding, a blood sample was taken from all patients, and patients were blindfolded during the blood sampling and injections. At 1 month, corticosteroid injections reduced pain to a greater extent than either PRP or saline. At 3-month follow-up, there was no significant difference between the groups in the primary endpoint of pain reduction. Corticosteroid injection was more effective than saline or PRP in reducing color Doppler activity and tendon thickness.

Long-Bone Nonunion: A 2012 Cochrane review found only one small ( $n=21$ ) RCT of PRP for long-bone healing. (23) However, only studies where PRP was compared with no additional treatment or a placebo were included in the review; therefore the authors did not include the larger RCT by Calori et al. described below.

Calori et al. compared application of PRP or recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of long-bone nonunions in an RCT with 120 patients and 10 surgeons. (24) Inclusion criteria were post-traumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and in 21 cases in the PRP group. Computer-generated randomization was developed to create two homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, the patients underwent surgery for nonunion, including bone grafts according to the surgeon's choice (66.6% of rhBMP-7 and 80% of PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the PRP group (68%) compared with the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13–14% with PRP.

Osteochondral Lesions: In 2012, Mei-Dan et al. reported a quasi-randomized trial of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronate or PRP. (25) At 28-week follow-up, scores on the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale (AHFS) improved to a greater extent in the PRP group (from 68 to 92) than the hyaluronate group (from 66 to 78). Subjective global function also improved to a greater extent in the PRP group (from 58 to 91) than the hyaluronate group (from 56 to 73). Interpretation of the composite measures of VAS pain and

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VAS function is limited by differences in the groups at baseline. Neither the patients nor the evaluators were blinded to treatment in this small study.

Osteoarthritis: Several RCTs from Europe and Asia have been reported, with mixed results. A double-blind study from 2012 randomized 109 patients with knee chondropathy or osteoarthritis (Kellgren-Lawrence grades I, II, or III) to 3 weekly injections of PRP (previously frozen aliquot) or hyaluronic acid. (26) At 12 months of follow-up, there was significant improvement on International Knee Documentation Committee (IKDC), VAS, Tegner, and KOOS scores in both groups, but no significant difference between the groups. Another RCT from 2012 compared 4 intra-articular injections of PRP or hyaluronic acid in 120 patients with gonarthrosis (early stage knee arthritis, Kellgren-Lawrence grades I, II, or III). (27) At 4 weeks, both groups showed improvement in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores compared to baseline. In this non-blinded study, WOMAC scores for the PRP group continued to improve over 24 weeks (79.6 at baseline, 49.6 at 4 weeks and 36.5 at 24 weeks), whereas WOMAC scores in the hyaluronic acid group declined in the post-treatment period (75.4 at baseline, 49.6 at 4 weeks, and 65.1 at 24 weeks). In 2013, Patel et al. reported a double-blind placebo-controlled RCT with 78 patients (156 knees). This study compared a single injection of PRP, 2 injections of PRP, or a single injection of saline. Adverse effects at the time of injection were observed in 22% of patients in the 1 injection PRP group and 44% in the 2 injection PRP group, compared to none in the saline group. At 6-month follow-up, WOMAC scores had improved in the 2 PRP groups but not in the control group. VAS pain scores improved from 4.54 to 2.16 after a single injection of PRP and from 4.64 to 2.54 after 2 injections of PRP. VAS scores did not change in the placebo-control group (from 4.57 at baseline to 4.61 at 6-month follow-up).

A 2009 series from Europe described a prospective study of intra-articular injection of PRP in 100 consecutive patients affected by chronic degenerative cartilage lesions. (28) Fifty-eight knees presented with a degenerative chondral lesion, 33 with early osteoarthritis, and 24 had advanced osteoarthritis. Three injections were administered at 21-day intervals. Evaluation was conducted in 91 patients (91% follow-up) before and at the end of the 3 treatments and at 6 and 12 months after treatment. The IKDC objective score improved from 46% (of normal and nearly normal knees) to 78% at the end of therapy, declining to 67% at 12-month follow-up. The IKDC subjective score improved from 41 to 63 after treatment, with a score of 61 at 12-month follow-up. Treatment was less effective in older, heavier, and more advanced osteoarthritis patients than in younger patients with less severe chondral damage. Patellar Tendon: In 2012, de Almeida et al. reported a small (n=27) randomized trial of the effect of PRP gel on the harvest site of the patellar tendon during anterior cruciate ligament (ACL) reconstruction. (29) VAS for pain in the postoperative period was significantly lower in the PRP group compared to the control group (3.8 vs. 5.1). At 6 months, assessment by magnetic resonance imaging (MRI) showed a smaller gap in the patellar tendon in the PRP group (4.9

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mm vs. 9.4 mm), but there was no significant difference between groups for the Tegner questionnaire or isokinetic testing.

Plantar Fasciitis: The 2012 systematic review by Sheth et al. identified 3 studies that evaluated the effect of autologous blood injections. (12) No controlled trials have been identified that evaluated the effect of PRP for plantar fasciitis.

Rotator Cuff Repair: There are a number of small double-blind RCTs that have evaluated the efficacy of PRP in combination with repair of the rotator cuff. A majority of these studies show no significant benefit of PRP. For example, Castricini et al. randomized 88 patients with a rotator cuff tear to arthroscopic repair without (n=45) or with (n=43) augmentation with platelet-rich fibrin matrix. (30) At average follow-up of 20.2 months (range, 16-30 months), both groups demonstrated statistically significant improvement in the primary endpoint (Constant scores evaluating pain, activities of daily living, range of movement, and power), but the between-group difference was not significant. In 2012, Rodeo et al. reported an RCT arthroscopic rotator cuff tendon repair with or without PRP (platelet rich fibrin matrix) in 79 patients. (31) Follow-up at 6 weeks, 3 months, and 12 months postoperatively found no significant differences between the PRP and control groups for tendon healing, tendon vascularity, manual muscle strength, or clinical rating scales. Logistic regression analysis suggested that PRP might have a negative effect on healing.

A double-blind quasi-randomized trial from 2013 assigned 60 patients in alternating order to receive rotator cuff surgery with or without PRP (platelet rich fibrin matrix). (32) Mean surgery time was increased by about 10 minutes in the PRP group. At 1-year follow-up, there was no significant difference between the groups in VAS pain scores, narcotic use, recovery of motion, simple shoulder test (SST), and American Shoulder and Elbow Surgeons (ASES) shoulder scores. Mean University of California-Los Angeles (UCLA) scores were slightly lower in the PRP group (27.94 vs. 29.59). There were no significant differences between the groups on MRI scans at 3 to 5 month follow-up.

In 2012, Gumina et al. reported an RCT of platelet-leukocyte membrane in 80 patients with full-thickness rotator cuff tear randomized to arthroscopic repair with or without PRP. (33) Both age and Constant score were significantly different at baseline. At a mean 13-month follow-up, the SST and the change in Constant score did not differ significantly between the 2 groups. Independent evaluation with MRI found that rotator cuff retears occurred only in the control group and that the use of the PRP membrane resulted in significantly better repair integrity.

Randelli et al. randomized 53 patients in a double-blind study to arthroscopic rotator cuff repair with or without PRP. (34) VAS pain scores in the PRP group were lower than controls at baseline (4.8 vs. 6.4) through 30 days after surgery (1.1 vs. 2.4). At 3 months after surgery,

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the PRP group had higher scores on Constant scores (65.0 vs. 57.8) and the Simple Shoulder Test (8.9 vs. 7.1), UCLA (26.9 vs. 24.2) and strength in external rotation (3.0 vs. 2.1). There was no difference in functional outcomes between the groups at 6, 12, and 24 months after surgery and no difference in the healing rate measured by magnetic resonance imaging (MRI) at 1 year or more after surgery. This study is limited by the difference in VAS between the groups at baseline.

A small double-blind RCT of PRP for rotator cuff healing without surgical repair was reported by Rha et al. in 2012. (35) In this study, 39 patients with tendinosis or a partial tear were randomized to 2 sessions of dry needling or 2 PRP injections. For dry needling, a needle was passed through the lesion of the tendon approximately 40-50 times. PRP was injected into or around the lesion under ultrasound guidance. Both groups showed an improvement in the Shoulder Pain and Disability Index (SPDI) over the 6 months of the study. At 2 weeks, 3 months and 6 months after the treatment, the mean SPDI score was significantly better in the PRP group (17.7 vs. 29.5). Range of motion was generally not different between the groups.

Conclusions: The literature on PRP for rotator cuff repair consists of a number of small double-blind RCTs that have evaluated the efficacy of PRP membrane or matrix combined with surgical repair of the rotator cuff. Results are mixed, with a majority of studies showing little or no benefit of PRP.

Spinal Fusion: No randomized trials on PRP in spinal fusion were identified; however, 2 controlled studies found no difference in fusion rates with use of a platelet gel or platelet glue. (36, 37)

Subacromial Decompression Surgery: Everts and colleagues reported a rigorously conducted, small (n=40) double-blinded RCT of platelet and leukocyte-rich plasma (PLRP) gel following open subacromial decompression surgery in a carefully selected patient population. (38) Blood was drawn from all patients after induction of anesthesia to maintain blinding. PLRP with autologous thrombin was injected into both the subacromial intracapsular space and the subcutaneous layer covering the incision during wound closure. Postoperative examinations at 1, 2, 4, and 6 weeks were performed by independent evaluators; unique patient identifier codes were used to maintain patient and investigator blinding. Neither self-assessed nor physician-assessed instability were improved. Both subjective pain and use of pain medication were lower in the PLRP group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the PLRP group (close to 4 in the control group and close to 2 in the PLRP group), and only 1 patient (5%) was taking pain medication compared to 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvement in the PLRP group across the 6-week assessment period, while patients reported improvements in activities of daily living such as ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

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**Tonsillectomy:** A double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children, aged 4 to 15 years. (39) The 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 the children aged 4 to 7 years, while a numbered pain scale was used for children older than 7 years. Diaries from 83% of the patients showed no differences in pain, medication doses, activity, and days eating solid foods between the two conditions.

**Wound Closure:** A study of PRP applied to saphenous vein harvest sites after wound closure found no difference in the incidence of wound infection or cosmetic result. (40)

### **Summary**

Results from randomized controlled trials show improved rates of healing with use of recombinant platelet-derived growth factor (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 platelet-rich plasma (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 online at: [www.clinicaltrials.gov](http://www.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. Therefore, PRP as a primary treatment for acute or chronic wounds, or as an adjunct to surgical procedures, is considered investigational.

### **Practice Guidelines and Position Statements**

In 2009, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) issued guidance on use of autologous blood injection for tendinopathy. (41) NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for

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tendinopathy is inadequate in quantity and quality. NICE recommends this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

In 2013, NICE issued guidance on use of autologous blood injection (with or without techniques for producing PRP) for plantar fasciitis. (42) NICE concluded that the evidence on autologous blood injection for plantar fasciitis raises no major safety concerns but that the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. In addition, physicians should ensure that patients understand the uncertainty about the procedure's efficacy, be aware of alternative treatments and be provided with clear written information.

## V. DEFINITIONS

**DIABETIC NEUROPATHIC ULCER** is a lesion of the skin or mucous membranes marked by inflammation, necrosis, and sloughing of damaged tissue. A diabetic neuropathic ulcer is caused by damage to the autonomic motor and/or sensory nerves that result from metabolic or vascular derangement in patients with longstanding diabetes mellitus.

**STAGE III ULCER** is full thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia.

**STAGE IV ULCER** is full thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supportive structures.

## VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

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## VII. DISCLAIMER

*Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

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## IX. CODING INFORMATION

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

### Covered when medically necessary:

CPT Codes®								
20926	86999							

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<b>HCPCS Code</b>	<b>Description</b>
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
S0157	Becaplermin gel 0.01%, 0.5 gm
S9055	Procuren or other growth factor preparation to promote wound healing

<b>ICD-9-CM Diagnosis Code*</b>	<b>Description</b>
250.60-250.63	DIABETES WITH NEUROLOGICAL MANIFESTATIONS, TYPE II OR UNSPECIFIED TYPE, NOT STATED AS UNCONTROLLED
250.80-250.83	DIABETES WITH OTHER SPECIFIED MANIFESTATIONS
707.0	PRESSURE ULCER
707.1	ULCER OF LOWER LIMBS, EXCEPT PRESSURE ULCER
707.8	CHRONIC ULCER OF OTHER SPECIFIED SITE
707.9	CHRONIC ULCER OF UNSPECIFIED SITE

\*If applicable, please see Medicare LCD or NCD for additional covered diagnoses and procedures.

### Investigational; therefore not covered:

<b>CPT Codes®</b>							
0232T							

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**Investigational when used for, but not limited to: treatment of acute or chronic wounds including non healing, adjunctive use in surgery procedures and primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture**

<b>HCPCS Code</b>	<b>Description</b>
P9020	PLATELET RICH PLASMA, EACH UNIT

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The following ICD-10 diagnosis codes will be effective October 1, 2014

<b>ICD-10-CM Diagnosis Code*</b>	<b>Description</b>
E11.40-E11.43	Diabetes with neurological manifestations code range
E11.49	Diabetes with other diabetic neurological complication
L89.000-L89.95	Pressure ulcer code range
L97.121-L97.929	Pressure ulcer lower limbs and foot code range
L98.491-L98.499	Non pressure chronic ulcer of skin and other sites

\*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

## X. POLICY HISTORY

<b>MP-2.033</b>	<b>CAC 11/26/02</b>
	<b>CAC 12/2/03</b>
	<b>CAC 8/30/05</b>
	<b>CAC 10/25/05</b>
	<b>CAC 11/28/06</b>
	<b>CAC 11/27/07</b>
	<b>CAC 11/25/08</b>
	<b>CAC 11/24/09</b> consensus. References and background updated. Addition of “acute” wounds to the investigational indication of autologous blood-derived preparations (i.e., platelet-rich plasma)
	<b>CAC 11/30/10</b> Consensus Review. No changes in policy statement. References updated.
	<b>CAC 4/26/11</b> Adopt BCBSA. Title changed to Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions. A statement was added to the policy that recombinant platelet-derived growth factor is considered medically necessary for pressure ulcers extending into the subcutaneous tissue. Medicare variation removed.
	<b>CAC 6/26/12</b> Consensus. FEP variation added to reference MP-2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions. No change to policy statements.
	<b>8/6/12</b> Medicare variation added to reference Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R3). Memo dated Aug. 2, 1012.
	<b>7/24/13</b> Admin coding review complete--rsb

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>RECOMBINANT AND AUTOLOGOUS PLATELET-DERIVED GROWTH FACTORS AS A TREATMENT OF WOUND HEALING AND OTHER CONDITIONS (FORMERLY BLOOD/PLATELET-DERIVED GROWTH FACTORS FOR WOUND HEALING)</b>
<b>POLICY NUMBER</b>	<b>MP-2.033</b>

	<b>9/24/13 CAC.</b> Consensus. No change to policy statements. Added policy guidelines. Rational section added. References updated.
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