PLATELET DERIVED GROWTH FACTORS FOR TREATMENT OF WOUNDS

Policy Number: 2011T0523E
Effective Date: May 1, 2011

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVERAGE RATIONALE</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>2</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>6</td>
</tr>
<tr>
<td>CENTERS FOR MEDICARE AND MEDICAID SERVICES</td>
<td>6</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>7</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>7</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>9</td>
</tr>
</tbody>
</table>

INSTRUCTIONS FOR USE
This Medical policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this medical policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

COVERAGE RATIONALE

Platelet Derived Growth Factors
When used according to U.S. Food and Drug Administration (FDA) approved indications, becaplermin (Regranex® Gel) is proven for the treatment of lower extremity diabetic neuropathic ulcers.
In June 2008, the U.S. Food and Drug Administration (FDA) announced the addition of a boxed warning to the labeling of becaplermin (Regranex Gel). Please see the U.S. Food and Drug Administration section for more information.

Platelet Rich Plasma
Autologous platelet rich plasma (e.g., Procuren®, AutoloGel®, or SafeBlood®) is unproven for the treatment of wounds.
The better designed studies do not demonstrate that autologous platelet rich plasma such as Procuren, AutoloGel or SafeBlood improves health outcomes in patients with wounds. The remaining studies have design flaws that do not allow confidence in analyzing final study results. The clinical utility of autologous platelet rich plasma remains to be determined in larger well-designed controlled clinical trials comparing their use with standard wound care.

Platelet Derived Growth Factors for Treatment of Wounds: Medical Policy

Related Medical Policies:
- Apheresis
- Bone or Soft Tissue Healing and Fusion Enhancement Products

Related Coverage Determination Guidelines: None
**BACKGROUND**

*Platelet-Derived Growth Factors:* Platelet-derived growth factors are applied directly to the wound surface to promote growth of skin, soft tissue, and blood vessels. Recombinant DNA technology has been used to produce a recombinant human platelet-derived growth factor (rPDGF, rPDGF-BB, or rhPDGF-BB). Becaplermin (tradename Regranex Gel) is not an autologous product, but is a commercially prepared biotechnology product with recombinant PDGF as the active ingredient. The growth factor is produced in the laboratory by inserting a gene into yeast.

*Platelet Rich Plasma:* AutoloGel and SafeBlood are autologous preparations in which blood is drawn from the patient and centrifuged to create platelet-rich plasma that is applied to the wound. Procuren® an autologous product that has been used as treatment in the past for chronic wound healing, but it is no longer manufactured or commercially available.

**CLINICAL EVIDENCE**

**Becaplermin:** The earlier studies evaluating recombinant PDGF or becaplermin for chronic diabetic ulcers were well-designed with large sample sizes. Results of these studies demonstrate that becaplermin, in conjunction with good wound care, is efficacious in accelerating wound closure of chronic diabetic ulcers. (Embil et al., 2000; Ehrlich and Freedman, 2002; Wieman et al., 1998; Smiell et al., 1999) Significant increases in the incidence of complete wound closure and decreases in the time to achieve complete wound healing were observed in patients receiving the study medication compared with those receiving placebo.

A total of 922 patients with full-thickness diabetic neuropathic ulcers were entered into 1 of 5 randomized prospective blinded clinical trials comparing treatment of recombinant PDGF with placebo gel. Results showed that patients treated with PDGF had a significant increase in complete healing and decreased time to complete healing compared with patients given placebo (Steed, 2006).

**Platelet Rich Plasma:** A prospective, randomized, controlled, blinded multicenter study initially included 72 patients with diabetic foot ulcers who were treated with autologous platelet-rich plasma gel or control (saline gel). Thirty-two patients were excluded from the final protocol because of protocol violations and failure to complete treatment. Significantly more wounds healed in patients treated with platelet-rich plasma gel (13 out of 16 or 81.3%) than patients treated with control gel (8 out of 19 or 42.1%) (Driver et al., 2006). Study limitations include small sample size, study supported by manufacturer, protocol violations occurring during the study period, and high rate of patient dropouts.

A prospective, randomized, controlled trial was conducted to evaluate autologous platelet concentrate used during blepharoplasty surgery in 33 patients. The study showed that although there were statistically significant differences in edema using autologous platelet gel, trends towards improvement in postoperative ecchymosis and edema were not significant (Vick et al., 2006). Study limitations include small sample size, no external controls, and lack of blinding.

In a controlled study by Stacey et al. (2000), 86 patients with chronic venous ulcers were randomly assigned to receive autologous platelet lysate or placebo. The results of the study demonstrated no major difference in healing outcome between the treatment and control groups.

Within a prospective randomized study, Buchwald et al. (2008) evaluated whether intraoperative use of autologous platelet gel on the leg during a coronary artery bypass graft (CABG) could reduce the incidence of postoperative wound healing disturbances. The application group (AG) included 35 patients and was compared to a control group (CG) that also had 35 patients. The platelet gel, as well as the thrombin required to activate the platelets, was prepared from autologous patient blood during the operation. Wound healing was photographically documented...
after surgery, and the patients were contacted by telephone on day 50 after surgery to obtain information on wound healing status. During the primary clinical stay, no statistically significant differences were recorded in the number of hematomas, postoperative leg swelling, or pain level. Large-area hematomas were less frequent in the application group. In the follow-up 51 days after surgery, 17.6% (6/34) of the patients from the AG and 31.4% (11/35) of the patients from the CG showed leg wound healing disturbances. The investigators concluded that despite optimum application of the autologous platelet gel to the wound, no clinically relevant differences were found between the groups, either during the primary clinic stay or in the follow-up period.

Kazakos et al. (2008) conducted a study to assess the benefits of using autologous platelet-rich plasma (PRP) gel in the treatment of acute limb soft tissue wounds. Fifty-nine patients with acute wounds (open fractures, closed fractures with skin necrosis and friction burns) were randomized into two groups. Group A (32 patients) were treated with conventional dressings and Group B (27 patients) were managed with local application of PRP gel. The rate of wound healing rate was significantly faster in Group B at week 1, 2 and 3. The investigators concluded that PRP gel treatment can be a valuable and effective aid in the management of acute trauma wounds. The value of this study is limited by the small sample size.

Almdahl et al. (2010) evaluated if spraying of wounds after open long saphenous vein harvesting with platelet-rich plasma (PRP) gel might reduce the frequency of harvest site infections. A total of 140 patients undergoing first-time coronary artery bypass grafting were randomized into two groups of 70 patients. Both groups had standard surgical leg wound closure and care except topical application of platelet-rich plasma as adjunctive treatment in the active treatment group. End points were wound infection and cosmetic result at 6 weeks. The follow-up was 100% complete. Nine patients (13%) in the treatment group and eight (11%) in the control group experienced harvest site infection. The overall cosmetic result was also similar between the groups, but the top score was borderline and more frequent in the treatment group. The investigators concluded that topical application of autologous platelet-rich plasma on vein harvest wounds did not reduce the rate of surgical site infection.

Córdoba-Fernández et al. (2010) analyzed the use of autologous platelet gel in the surgical treatment of ingrown toe nails in a within-patient clinical trial. Thirty-five healthy volunteers (70 feet) underwent surgical treatment for bilateral ingrown hallux nails. Recovery time (days), postoperative pain (analog chromatic scale), and inflammation (digital circumference) at 48 hours postoperative were the outcomes of interest. Recovery time and postoperative pain were less in the experimental group, although the differences of means were not statistically significant. The investigators concluded that local application of APG in surgical ingrown toenail wounds may produce a slight increase in acute inflammatory phase dermal wound healing, but it does not cause a statistically significant reduction in recovery times or postoperative pain.

Villela and Santos (2010) systematically reviewed evidence regarding the use of platelet-rich plasma (PRP) for the topical treatment of chronic leg ulcers. The systematic review of the literature was performed according to the steps recommended by the Cochrane Collaboration with studies published until July 2008. Among 18 selected studies, 7 (39%) of these studies were randomized clinical trials. Five of the seven randomized clinical trials studied ulcers of diabetic etiology. The results of meta-analysis showed that PRP favors the healing process (95% CI: 2.94-20.31). According to the reviewers, the present systematic review and meta-analysis show that there is scientific evidence regarding favorable outcomes of the use of PRP for the treatment of diabetic ulcer. The reviewers stated that the sample size of the studies analyzed was small.

Martínez-Zapata et al. (2009) performed a systematic review to evaluate autologous plasma rich in platelets (PRP) for tissue regeneration. The main outcomes were tissue regeneration and safety. Relative risks (RRs) and standardized mean differences (SMDs) were calculated to show pooled estimates for these outcomes. When the results heterogeneity was more than 50 percent, a sensitivity analysis was performed. Twenty RCTs were included (11 of oral and maxillofacial surgery, 7 of chronic skin ulcers, and 2 of surgery wounds). Four RCTs evaluated the depth
reduction in gingival recession in chronic periodontitis; the SMD was 0.54 mm, favorable to PRP. Three RCTs evaluated the clinical attachment level in chronic periodontitis; the SMD was 0.33 mm. Six RCTs assessed the complete skin epithelialization in wound ulcers; the RR was 1.40. Only 6 RCTs reported adverse effects without differences between groups. The investigators concluded that PRP improves the gingival recession but not the clinical attachment level in chronic periodontitis. In the complete healing process of chronic skin ulcers, the results are inconclusive. There are little data about PRP safety. There are several methodologic limitations and, consequently, future research should focus on strong and well-designed RCTs that assess the efficacy and safety of PRP.

A meta-analysis of treatment of chronic diabetic wounds found that platelet releasate and becaplermin have improved healing rates over standard care, and becaplermin was less expensive and more effective than platelet releasate after 20 weeks of treatment. Baseline effectiveness for standard care, becaplermin, platelet releasate, and wound care center care were 30.9%, 43.0%, 36.8%, and 35.6% respectively. Data for this meta-analysis was obtained from published clinical trials, meta-analyses, and data on 26,599 patients with wounds (Kantor and Margolis, 2001).

Frykberg et al. (2010) conducted a prospective case series to evaluate how a physiologically relevant concentration of an autologous platelet-rich plasma (PRP) gel affects initial wound healing trajectories of chronic, nonhealing wounds of various etiologies. Using convenience sampling methods, 49 patients with 65 nonhealing wounds (mean duration 47.8 weeks) were prescribed PRP gel. The most common wounds were pressure ulcers (n = 21), venous ulcers (n = 16) and diabetic foot ulcers (n = 14). Mean wound area and volume were 19 cm² and 36.2 cm³, respectively. Following a mean of 2.8 weeks with 3.2 applications, reductions in wound volume (mean 51%, SD 43.1), area (39.5%, SD 41.2), undermining (77.8%, SD 28.9), and sinus tract/tunneling (45.8%, SD 40.2) were observed. For all wound etiologies, 97% of wounds improved. According to the investigators, the results of this study suggest the application of this PRP gel can reverse nonhealing trends in chronic wounds. These findings require confirmation in a statistically robust randomized controlled trial.

Marquez De Aracena Del Cid et al. (2009) evaluated the efficiency of the subconjunctival application of autologous regenerative factor-rich plasma (RFRP) in a study of 35 patients with different degrees of ocular alkali burns. The patients were classified into moderate and relevance groups according to the severity of the burn. A control group underwent conventional topical medical treatment. A further group was added to the severe chemical burn group, which received autohemotherapy. The clinical evolution of the lesions and the period in which the pathology prevented the patient from working were studied; monitoring was carried out until the patient had healed. In the moderate chemical burns, there was a significant reduction in corneal and conjunctival epithelization times, sick leave duration, and healing time when the patients were treated with RFRP in comparison to traditional treatment was reported. RFRP showed, at least as effective and less side effects than the autohemotherapy. The limitation of this study is small sample size.

Spyridakis et al. (2009) evaluated 52 patients with pilonidal sinus disease who underwent open excision and secondary closure of the surgical wound (n = 22) or additional local postoperative infusion of platelet-derived growth factors (n = 30). Duration of total wound healing and time to return to normal activities were evaluated. Wound-healing rates were much greater for the platelet group. Complete healing of the surgical wound required 24 days for the platelet group while the respective time for the control group was more than 30 days. According to the investigators, the study provides evidence that the use of platelet-derived growth factors directly to the surgical wound enhances the healing process resulting in faster recovery of patients surgically treated for pilonidal sinus disease. Study limitations include lack of blinding or randomization.
A study by Mazzucco et al. (2004) evaluated patients with dehiscent sternal wounds and patients with necrotic skin ulcers who were treated with autologous platelet gel and retrospectively compared with patients having similar lesions but undergoing traditional treatment. In patients with dehiscent sternal wounds, the healing rate and hospital stay were significantly reduced. Patients with necrotic skin ulcers required a shorter time to have surgery. Study limitations include lack of blinding or randomization, use of historical controls, and non-reporting of inclusion/exclusion criteria.

Margolis et al. (2001) conducted a retrospective cohort study of 26,599 patients from the Curative Health Services database who were treated with platelet releasate or standard wound therapy. The authors determined that more diabetic neuropathic foot ulcers treated with platelet releasate healed by 32 weeks than ulcers treated with standard wound therapy (50% versus 41% respectively). The study did not control for glycemic control or microbiologic status of the wound and commencement of treatment was not standardized.

Yilmaz et al. (2009) investigated the effectiveness of platelet-rich plasma (PRP) and bovine derived xenograft (BDX) combination in the treatment of deep intrabony defects with an emphasis on the evaluation of early wound healing. A total of 85 intrabony defects with an intrabony component of 3 mm or more were selected in 20 advanced chronic periodontitis patients. Defects were surgically treated with PRP/BDX. At 12 months, all clinical and radiographic parameters were improved. Two weeks after surgery, primary closure was maintained in 95% of the defect sites. According to the investigators, treatment with a combination of PRP and BDX leads to a significantly favorable clinical and radiographic improvement in deep intrabony periodontal defects. This study was not randomized or controlled.

Cervelli et al. (2010) evaluated 30 patients with lesions with differentiating etiopathogenesis all localized on the inferior limb, who were treated with PRP and autologous fat grafts. The study results demonstrated an improvement from minor to moderate in 100% of patients after 3 weeks, healing in less than 6 weeks in 47% of patients, and complete wound healing in 57% of patients within 3 months. The investigators concluded that the combination of PRP and autologous adipose graft to regenerate tissue and epithelialization with wound closure, resulted in a significant healing-time reduction. These findings require confirmation in a statistically robust randomized controlled trial.

In a pilot study, Alissa et al. (2010) investigated the effect of autologous platelet-rich plasma (PRP) on the healing of hard and soft tissues of extraction sockets. Patients undergoing tooth extraction under intravenous sedation were asked to participate in the trial. Patients were followed up to 3 months post-extraction. Twelve patients (15 sockets) were randomly allocated to the PRP group and 11 patients (14 sockets) to the control group. Soft tissue healing was significantly better in patients treated with PRP. These findings require confirmation in a larger study.

There is very limited evidence from several randomized controlled and prospective controlled trials that autologous platelet concentrate and gel may hasten healing and reduce postoperative pain in wounds caused by acute surgical incision or dehiscence and in chronic cutaneous wounds that have failed a sufficient course of standard wound therapy. However, the evidence is conflicting, with several trials reporting no significant effect of autologous platelet concentrate (APC) or autologous platelet gel (APG) on wound healing. Overall, the evidence is too limited and methodologically flawed to draw definitive conclusions regarding the clinical efficacy of APC or APG (Hayes, 2007).

A guideline developed by Agency for Healthcare Research and Quality (AHRQ) for the treatment of pressure ulcers indicates that the use of topical agents such as growth factors has not been sufficiently established to warrant a recommendation of these agents as treatment for pressure ulcers (AHRQ, 1994).
In December 1997, the FDA approved becaplermin for the treatment of patients with lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. According to FDA labeled indications, Becaplermin should be used in combination with standard ulcer wound care. This is the first FDA-approved biotechnology product to treat deep diabetic foot and leg ulcers. See the following Web site for more information: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080471.htm. Accessed January 2011.

In June 2008, the FDA announced the addition of a boxed warning to the labeling of Regranex Gel 0.01% (becaplermin). The new labeling indicates that Regranex (becaplermin) Gel is contraindicated in patients with a known hypersensitivity to any component of this product (e.g., parabens) or a known neoplasm(s) at the site(s) of application. The warnings in the new labeling indicate that Regranex Gel contains becaplermin, a recombinant human platelet-derived growth factor, which promotes cellular proliferation and angiogenesis. The benefits and risks of becaplermin treatment should be carefully evaluated before prescribing. Becaplermin should be used with caution in patients with a known malignancy. Malignancies distant from the site of application have occurred in becaplermin users in both a clinical study and in postmarketing use, and an increased rate of death from systemic malignancies was seen in patients who have received 3 or more tubes of Regranex Gel. See the following Web site for more information: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116909.htm. Accessed January 2011.

The AutoloGel Process Centrifuge is one of several devices cleared for marketing by FDA for point-of-care preparation of platelet-rich plasma (PRP) from a sample of a patient’s blood (see listings under product code JQC for additional devices). However, the AutoloGel System is currently the only autologous PRP product cleared by the FDA specifically for treatment of chronic wounds. See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed January 2011.

In April 2003, the FDA approved the use of the GPS™ Platelet Separation Kit. The GPS™ separation kit aids separation of the patient’s own blood components by density through the use of the GPS™-Thermo International Equipment Company (IEC) centrifuge. The GPS separation kit permits platelet rich plasma to be rapidly prepared from a small volume of the patient’s blood that is drawn at the time of treatment. The GPS Platelet Separation Kit is designed for use in the clinical laboratory or intraoperatively at point of care, for the safe and effective preparation of platelet poor plasma and platelet concentrate from a small sample (50-60 ml) of whole blood. See the following Web site for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=10974. Accessed January 2011.

Additional Products
Platelet-enriched plasma, platelet-rich concentrate, autologous platelet gel, platelet releasate, Magellan® Autologous Platelet Separator, Platelet Separator SmartPReP® Centrifuge System, Fibrinet Autologous Fibrin & Platelet System

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover blood-derived products for wound healing. See the National Coverage Determination (NCD) for Blood Derived Products for Chronic Non-Healing Wounds (270.3) available at: http://www.cms.hhs.gov/ncd/viewncd.asp?ncd_id=270.3&ncd_version=4&basketcncd%3A270%2E3%2E%3A4%3ABlood%2DDerived%2BRequiredProducts%2B%2BChronic%2BNon%2BHealing%2BWounds.

Platelet Derived Growth Factors for Treatment of Wounds: Medical Policy

Proprietary Information of UnitedHealthcare. Copyright 2011 United HealthCare Services, Inc.

**APPLICABLE CODES**

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>HCPCS Code (Proven)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0157</td>
<td>Becaplermin gel 0.01%, 0.5 gm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT Code (Unproven)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Code (Unproven)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S9055</td>
<td>Procuren or other growth factor preparation to promote wound healing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>707.10</td>
<td>Ulcer of lower limb, unspecified</td>
</tr>
<tr>
<td>707.11</td>
<td>Ulcer of thigh</td>
</tr>
<tr>
<td>707.12</td>
<td>Ulcer of calf</td>
</tr>
<tr>
<td>707.13</td>
<td>Ulcer of ankle</td>
</tr>
<tr>
<td>707.14</td>
<td>Ulcer of heel and midfoot</td>
</tr>
<tr>
<td>707.15</td>
<td>Ulcer of other part of foot</td>
</tr>
<tr>
<td>707.19</td>
<td>Ulcer of other part of lower limb</td>
</tr>
</tbody>
</table>

Coding Clarification: The above diagnosis codes should be billed with 249.80, 249.81, 250.80, 250.81, 250.82 or 250.83 to specify diabetic ulcers.

**REFERENCES**


Proprietary Information of UnitedHealthcare. Copyright 2011 United HealthCare Services, Inc.


**POLICY HISTORY/REVISION INFORMATION**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/01/2011</td>
<td>• No change to coverage rationale or lists of applicable codes</td>
</tr>
<tr>
<td></td>
<td>• Archived previous policy version 2010T0523D</td>
</tr>
</tbody>
</table>