Clinical Policy Title: Growth factor treatment for wound healing/musculoskeletal uses

Clinical Policy Number: 16.02.02

Effective Date: January 1, 2015
Initial Review Date: August 20, 2014
Most Recent Review Date: June 5, 2018
Next Review Date: June 2019

Related policies:
- CP# 16.03.01 Bioengineered skin substitutes
- CP# 16.03.03 Negative pressure wound therapy
- CP# 14.02.08 Prolotherapy
- CP# 17.03.00 Vacuum assisted closure in surgical wounds

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of recombinant platelet-derived growth factor product becaplermin (Regranex®) gel for the treatment of wound healing to be medically necessary when used as an adjunct to standard wound management and to treat neuropathic diabetic and pressure ulcers extending into the subcutaneous tissue when the following criteria are met (Driver, 2006; Martinez-Zapata, 2016; National Guideline Clearinghouse, 2016; Pourmoussa, 2016; Zhao, 2014):

A. Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet all of the following criteria:
   - The trial and failure of up to three other approved products, if three other products
exist, and then the member must meet the dosing and appropriate indication requirements as needed per member’s plan benefit.

- Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer.
- Full thickness ulcer (i.e., stage III or IV) extending through dermis into subcutaneous tissues.
- Participation in a wound-management program, which includes sharp debridement, pressure relief (i.e., non-weight-bearing), and infection control.

B. Appropriate candidates for becaplermin gel for treatment of pressure ulcers should meet all of the following criteria:

- Full-thickness ulcer (i.e., stage III or IV), extending through dermis into subcutaneous tissues.
- Ulcer in an anatomic location that can be offloaded for the duration of treatment.
- Albumin concentration > 2.5 g/dl.
- Total lymphocyte count > 1,000.
- Normal values of vitamins A and C.

C. Treatment beyond 10 weeks is considered medically necessary when there is evidence of at least a 30 percent reduction in initial ulcer size at 10 weeks following initiation of treatment. Additional treatment beyond 20 weeks of initiation of becaplermin is considered not medically necessary.

D. Application of the gel may be performed by the patient in the home.

E. Other applications of platelet-derived growth factor 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.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of platelet-derived growth factor products are investigational and, therefore, not medically necessary.

This includes, but is not limited to, use in all of the following indications:

- Primary use (injection) for other conditions, such as epicondylitis (i.e., tennis elbow), plantar fasciitis, chronic achilles tendinopathy, anterior cruciate ligament reconstruction, rotator
cuff repair, spinal fusion, tonsillectomy, osteochondral lesions, osteoarthritis or Dupuytren’s contracture.

- Adjunctive use in surgical procedures.

The platelet-derived growth factor products listed below are considered investigational and, therefore, not medically necessary:

- Autologous platelet rich plasma injections (e.g., Procuren®, Magellan®).
- Autologous platelet gel or concentrate (e.g., AutoloGel®).
- Autologous platelet-derived growth factors (e.g., SafeBlood®).

Alternative covered services:

Primary care and specialty care physician evaluation and management.

**Background**

Chronic nonhealing cutaneous wounds are significant health care problems affecting more than five million patients each year, particularly the elderly and those with long-term debilitation (Cytomediix, 2006; McMahon, 1994; Steed, 1992). Conditions that may lead to impaired wound healing include chronic venous insufficiency, diabetes mellitus with consequent diabetic neuropathy, pressure, arterial insufficiency, vasculitis, malignancy and radiation necrosis. While there are many causes of inadequate repair, common reasons for the failure of cutaneous ulcers to heal are decreased skin perfusion, usually due to poor circulation, and infection (Knighton; 1986, Steed; 1992).

The types of nonhealing wounds that may result include venous stasis ulcers, diabetic ulcers of the lower extremity and foot, ulcers on ischemic limbs, and pressure or decubitus ulcers or sores, commonly known as bed sores (Knighton, 1986; McMahon, 1994; Steed, 1992). Patients with diabetes or peripheral vascular disease are especially at risk for lower-extremity amputations, with nonhealing ulcers being one of the most common reasons for amputations. Nonhealing diabetic foot ulcers present substantial costs to the health care system and significantly reduce patient quality of life (Driver, 2006; Hom, 2007; McAleer, 2006).

Platelet-derived growth factors impact chemotaxis and migration, in essence recruiting stem cells to the wound site to promote the healing process. They play a role in angiogenesis and help to start the tissue regeneration and remodeling process. They also attach to cell receptors and control the genetic expression of stem cells via modulation of signal transduction pathways of secondary proteins, resulting in cellular division and differentiation. Researchers have identified a number of growth factors, including platelet-derived growth factor (platelet-derived growth factor); epidermal growth factor (EGF); transforming growth factor-beta (TGF-Beta); vascular endothelial growth factor (VEGF); and insulin growth factor-I (IGF-I).
Platelet-derived growth factor is a major player in wound healing, as witnessed by a number of clinical studies demonstrating a beneficial effect of platelet-derived growth factor on wound healing. Growth factors for wounds are often applied topically. Growth factors can also be incorporated into wound dressings or commercially available skin grafts. Becaplermin is a commercially prepared biotechnology product with recombinant platelet-derived growth factor as an active ingredient. The growth factor is produced in the laboratory by inserting a gene into yeast using genetic engineering techniques to insert the gene for the B-chain of platelet-derived growth factor into the yeast Saccharomyces cerevisiae (Ortho-McNeil, 1999; Steed, 1995).

Becaplermin is indicated for the treatment of patients with lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond, and who have an adequate blood supply to the lower extremities. It is not currently indicated for other ulcers, such as those caused by pressure. It must be used as a topical treatment, in conjunction with the surgical removal of infected and dead tissue, avoidance of weight-bearing activities, and other standard measures for ulcer management (Food and Drug Administration, 1997; Food and Drug Administration, 1998; Ortho-McNeil, 1999). The instructions emphasize the importance of using becaplermin together with a good ulcer-care program, including a strict non-weight bearing and infection control program.

Becaplermin has a relative contraindication of use in patients with a diagnosis of cancer. In 2008, the manufacturer added this black box warning to the labeling for:

“An increased rate of mortality secondary to malignancy was observed in patients treated with three 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.”

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- United Kingdom National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 23, 2018. Searched terms were: "recombinant human platelet-derived growth factor (MeSH)" , "autologous platelet-derived growth factors (MeSH)" and "platelet rich plasma."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic
reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Zhao (2014) conducted a systematic review and meta-analysis to assess the clinical efficacy of topical recombinant human platelet-derived growth factor for treatment of diabetic lower-extremity ulcers where the primary efficacy outcome was complete healing rate. Six randomized controlled trials (RCTs) including 992 patients, comparing platelet-derived growth factor to standard wound care indicated a significantly greater complete healing rate (p=0.014) in patients treated with platelet-derived growth factor. The authors concluded that platelet-derived growth factor is efficacious in the treatment of diabetic lower-extremity ulcers.

Hayes wrote in 2011 that autologous platelet concentrate and gel has potential but unproven benefit in adult patients as treatment of acute surgical soft wounds (surgical incisions or dehiscence) or chronic cutaneous wounds that have failed an adequate course of standard wound therapy. Litmathe (2009) studied autologous platelet-derived growth factor for treatment of wound complications. In a prospective double-blind RCT (n = 44), the team evaluated the efficacy of autologous platelet-derived growth factor for the treatment of wound complications following cardiac surgery in patients at high risk for wound healing complications (e.g., obesity, diabetes, smoking, peripheral vascular disease and heart failure). All patients underwent either isolated coronary artery bypass grafting (CABG) or combined coronary surgery and valve replacement. Autologous platelet-derived growth factor was applied to the wound in the study group (n = 22) but not in the control group (n = 22). There were no statistically significant differences in sternal wound healing or wound healing at the vein harvesting sites. No beneficial effects of autologous platelet-derived growth factor were noted in this study. A RCT from the Diabetic Food Ulcer Study Group (Driver, 2006) found thirteen subjects out of 19 (68.4 percent) responded favorably to a platelet rich plasma gel and nine out of 21 (42.9 percent) of the control wounds healed. Moreover, significantly more PAP gel (13 out of 16, 81.3 percent) than control gel (eight out of 19, 42.1 percent) treated wounds healed (p = 0.036).

An industry-sponsored study by Margolis (2005) assessed the effectiveness of recombinant platelet-derived growth factor on diabetic neuropathic foot ulcers in 24,898 patients in wound-treatment programs whose wounds did not heal after eight weeks. The rate of healing was 26.5 percent in the control group and 33.5 percent in the patients treated with recombinant platelet-derived growth factor. The relative risk, controlling for the propensity to receive platelet-derived growth factor, was 1.32 for healing and 0.65 for amputation (6.4 percent vs. 4.9 percent).

Grazul-Bilska (2003) found healing is a complex biological process that requires cellular interactions.
between a variety of cells, including fibroblasts, myofibroblasts, smooth muscle cells, endothelial cells, keratinocytes and immune cells. These interactions are mediated by numerous factors, such as growth factors, hormones, blood components and second messengers. Several growth factors that are released at the wound site are presumed to be necessary for wound healing. Senet (2003) in an RCT (n = 42) reported no significant difference in outcomes in the treatment of chronic venous ulcers using platelet gel. Steed (1995) noted that becaplermin gel plus good wound care resulted in a 48 percent complete wound-closure rate, compared to 25 percent for patients treated with good wound care alone.

Policy updates:

A systematic review (Pourmoussa, 2016) included 53 studies consisting of prospective and retrospective cohorts as well as several RCTs. Three general categories of cell-based biologic dressings were identified and nine brands were included. Cell-based biologic dressings have shown efficacy in a broad range of scenarios, and studies examining their efficacy have improved our understanding of the pathophysiology of chronic wounds. Amniotic and placental membranes have the widest scope and can be used to treat all subtypes of chronic wounds. Human skin allografts and bioengineered skin substitutes can be used for chronic ulcers but generally require a vascularized wound bed. Autologous platelet rich plasma has shown promise in venous stasis ulcers and decubitus ulcers that have failed conventional treatment. Overall, more research is necessary to determine if these novel therapeutic options will change the current standard of care, but current studies demonstrate encouraging results in the treatment of chronic wounds. Martinez-Zapata (2016) wrote for the Cochrane group that platelet rich plasma may improve the healing of foot ulcers associated with diabetes, but this conclusion is based on low quality evidence from two small RCTs. It is unclear whether platelet rich plasma influences the healing of other chronic wounds. The overall quality of evidence of autologous platelet rich plasma for treating chronic wounds is low. There are very few RCTs evaluating platelet rich plasma. They are underpowered to detect treatment effects, if they exist, and are generally at high or unclear risk of bias. Well-designed and adequately powered clinical trials are needed.

The authors identified a total of ten RCTs inclusive of 442 participants with a range of chronic wounds (e.g., venous leg ulcers, foot ulcers in people with diabetes). The median length of treatment was 12 weeks (range 8 to 40 weeks). They found no clear evidence that autologous platelet rich plasma improves the healing of chronic wounds generally compared with standard treatment (with or without placebo) (risk ratio 1.19, 95 percent confidence interval 0.95 to 1.50). Autologous platelet rich plasma may increase the healing of foot ulcers in people with diabetes compared with standard care (with or without placebo) (risk ratio 1.22, 95 percent confidence interval 1.01 to 1.49). It is unclear if autologous platelet rich plasma affects the healing of venous leg ulcers (risk ratio 1.02, 95 percent confidence interval 0.81 to 1.27). It is unclear if there is a difference in the risk of adverse events in people treated with platelet rich plasma or standard care (risk ratio 1.05, 95 percent confidence interval 0.29 to 3.88).

The National Institute for Health and Clinical Excellence promulgated clinical guidelines in 2016 for treatment of diabetic foot ulcers and made the following recommendations:
“Do not offer the following to treat diabetic foot ulcers, unless as part of a clinical trial:

- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor, epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy."

In 2018, one professional guidelines was added to the summary of clinical evidence.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td><strong>Martinez-Zapata (2016)</strong>&lt;br&gt;Autologous platelet-rich plasma for treating chronic wounds.</td>
<td><strong>Key points:</strong>&lt;br&gt;● Platelet rich plasma may improve the healing of foot ulcers associated with diabetes.&lt;br&gt;● Conclusion is based on low quality evidence from two small RCTs.&lt;br&gt;● It is unclear whether platelet rich plasma influences the healing of other chronic wounds.&lt;br&gt;● The overall quality of evidence of autologous platelet rich plasma for treating chronic wounds is low.&lt;br&gt;● Well-designed and adequately powered clinical trials are needed.</td>
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<td><strong>National Institute for Health and Clinical Excellence (2016)</strong>&lt;br&gt;Diabetic foot problems-inpatient management: full guidance.</td>
<td><strong>Key points:</strong>&lt;br&gt;● Clinical guidelines promulgated in 2016 for treatment of diabetic foot ulcers and made the following recommendations:&lt;br&gt;  - Do not offer the following to treat diabetic foot ulcers, unless as part of a clinical trial:&lt;br&gt;    o Electrical stimulation therapy, autologous platelet rich plasma gel, regenerative wound matrices and dalteparin.&lt;br&gt;    o Growth factors (G-CSF, PDGF, TGF-β).&lt;br&gt;    o Hyperbaric oxygen therapy.”</td>
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<td><strong>Pourmoussa (2016)</strong>&lt;br&gt;An update and review of cell-based wound dressings and their integration into clinical practice.</td>
<td><strong>Key points:</strong>&lt;br&gt;● A systematic review of available biologic dressings describes indications for prescription in clinical practice.&lt;br&gt;● This review included 53 studies consisting of prospective and retrospective cohorts as well as several randomized control trials.&lt;br&gt;● Three general categories of cell-based biologic dressings were identified and nine brands were included.&lt;br&gt;● Cell-based biologic dressings were shown to have efficacy in a broad range of scenarios.&lt;br&gt;● Amniotic and placental membranes were shown to have the widest utility for all subtypes of chronic wounds.&lt;br&gt;● Human skin allografts and bioengineered skin substitutes were shown to have efficacy for chronic ulcers but generally require a vascularized wound bed.&lt;br&gt;● Platelet rich plasma was shown to have promise in venous stasis ulcers and decubitus ulcers that have failed conventional treatment.</td>
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<td><strong>Society for Vascular Surgery (2016)</strong></td>
<td><strong>Key points:</strong></td>
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The management of diabetic foot

- This clinical practice guideline recommends platelet-derived growth factor for diabetic foot ulcers that do not demonstrate improvement as measured by >50% wound area reduction after a minimum of 4 weeks of standard wound therapy. The level of evidence is Grade 1B.


**Key points:**
- Systematic review and meta-analysis to assess the clinical efficacy of topical recombinant human platelet-derived growth factor for treatment of diabetic lower-extremity ulcers.
- The primary efficacy outcome was complete healing rate.
- Six RCTs, including 992 patients, comparing platelet-derived growth factor to standard wound care indicated a significantly greater complete healing rate (p=0.014) in patients treated with platelet-derived growth factor.
- The authors concluded that platelet-derived growth factor is efficacious in the treatment of diabetic lower-extremity ulcers.

Hayes (2011) Autologous Platelet Concentrate and Gel for Wound Healing

**Key points:**
- Wrote that autologous platelet concentrate and gel has potential but unproven benefit in adult patients as treatment of acute surgical soft wounds (surgical incisions or dehiscence) or chronic cutaneous wounds that have failed an adequate course of standard wound therapy.

Litmathe (2009) The use of autologous platelet gel (APG) for high-risk patients in cardiac surgery — is it beneficial?

**Key points:**
- Efficacy of autologous platelet-derived growth factor for treatment of wound complications.
- In a prospective double-blind RCT (n = 44), the team evaluated the efficacy of autologous platelet-derived growth factor for the treatment of wound complications following cardiac surgery in patients at high risk for wound healing complications (e.g., obesity, diabetes, smoking, peripheral vascular disease and heart failure).
- All patients underwent either isolated coronary artery bypass grafting or combined coronary surgery and valve replacement. Autologous platelet-derived growth factor was applied to the wound in the study group (n = 22) but not in the control group (n = 22).
- There were no statistically significant differences in sternal wound healing or wound healing at the vein harvesting sites. No beneficial effects of autologous platelet-derived growth factor were noted in this study.


**Key points:**
- Wound healing is a complex biological process that requires cellular interactions between a variety of cells, including fibroblasts, myofibroblasts, smooth muscle cells, endothelial cells, keratinocytes and immune cells.
- These interactions are mediated by numerous factors, such as growth factors, hormones, blood components and second messengers.
- Several growth factors that are released at the wound site are presumed to be necessary for wound healing.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**


**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<td>Becaplermin (Regranex) gel</td>
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