Introduction

Special substances that are found in the blood may help cells to grow and divide. Some of these “blood-derived growth factors”, including some platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), have been used to treat wounds and skin ulcers. Some of these growth factors have been made in the lab by manipulating genetic material such as DNA. These are called “recombinant” blood-derived growth factors. Other growth factors come from your own body. These are called “autologous” blood-derived growth factors. This policy discusses the use of recombinant and autologous blood-derived growth factors when treating wounds and skin ulcers.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

### Treatment | Medical Necessity
--- | ---
Recombinant platelet-derived growth factor (ie, Recgranex® [becaplermin]) | Recombinant platelet-derived growth factor (ie, Becaplermin [Regranex®]) may be considered medically necessary when used as an adjunct to standard wound management for the following indications (for information on patient selection criteria, see Additional Guidelines section below):
- 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
- Ulcers not extending through the dermis into the subcutaneous tissue

### Treatment | Investigational
--- | ---
Use of autologous blood-derived preparations (ie, platelet-rich plasma [PRP]) | Use of autologous blood-derived preparations (ie, platelet-rich plasma [PRP]) is considered investigational for the treatment of all acute or chronic wounds including surgical wounds and non-healing ulcers.

### Additional Guidelines
**Becaplermin Gel (Regranex®)**
- Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet **ALL** of the following criteria:
  - Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer
  - Full-thickness ulcer (ie, Stage III or IV), extending through the dermis into subcutaneous tissues

AND
Additional Guidelines

- Participation in a wound-management program, which includes sharp debridement, pressure relief (ie, non-weight bearing), and infection control

- Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet ALL of the following criteria:
  - Full-thickness ulcer (ie, Stage III or IV), extending through the dermis into subcutaneous tissues
  - Ulcer is in an anatomic location that can be off-loaded for the duration of treatment
  - Albumin concentration >2.5 dl
  - Total lymphocyte count >1,000
  - 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-g, 7.5-g, and 15-g tubes and is applied in a thin continuous layer, about 1/16 of an inch thick (ie, the thickness of a dime). The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm², treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the 15-g tubes would be required.

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

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

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>86999</td>
<td>Unlisted transfusion medicine procedure</td>
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<tr>
<td></td>
<td><strong>HCPCS</strong></td>
</tr>
<tr>
<td>G0460</td>
<td>Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment</td>
</tr>
<tr>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
</tr>
<tr>
<td>S0157</td>
<td>Becaplermin gel 0.01%, 0.5 gm</td>
</tr>
<tr>
<td>S9055</td>
<td>Procuren or other growth factor preparation to promote wound healing</td>
</tr>
<tr>
<td></td>
<td>(Please note that Procuren may no longer be available but this code is used to report other growth factor preparations that promote wound healing.)</td>
</tr>
</tbody>
</table>

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**Related Information**

**Benefit Application**

Becaplermin is used as part of a program of wound management, as described in the **Additional Guidelines**. Utilization for becaplermin gel is potentially high, particularly if used for off-label indications, or if used outside the setting of adequate and diligent standard wound management.

**Evidence Review**

**Description**

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), has been suggested as a treatment of wounds or other miscellaneous non–orthopedic conditions, including but not limited to, diabetic ulcers, pressure ulcers, ulcers related to venous stasis, and surgical and traumatic wounds.
Background

A variety of growth factors have been found to play a role in wound healing, including PDGFs, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of PDGF, transforming growth factors (that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts), and vascular endothelial growth factors. Recombinant PDGF also has been extensively investigated for clinical use in wound healing.

Autologous platelet concentrate suspended in plasma, also known as PRP, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing various growth factors, and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and accelerate healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

PRP is distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and Hemaseel® are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This policy does not address the use of fibrin sealants.

Wound closure Outcomes

This review addresses the use of recombinant PDGF products and PRP for nonorthopedic indications, which include a number of wound closure-related indications.

For the purposes of this review, the primary end points of interest for studies of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

1. Incidence of complete wound closure
2. Time to complete wound closure (reflecting accelerated wound closure)
3. Incidence of complete wound closure following surgical wound closure
4. Pain control

Summary of Evidence

Recombinant Platelet-Derived Growth Factors

For individuals who have diabetic lower-extremity ulcers or pressure ulcers who receive recombinant platelet-derived growth factors (PDGF), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. Results have shown improved rates of healing with the use of recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have venous leg ulcers or acute surgical or traumatic wounds who receive recombinant PDGF, the evidence includes small RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The level of evidence does not permit conclusions whether recombinant PDGF is effective in treating other wound types, including chronic venous ulcers or acute traumatic wounds. The evidence is insufficient to determine the effects of the technology on health outcomes.

Platelet-Rich Plasma

For individuals who have chronic wounds or acute surgical or traumatic wounds who receive platelet-rich plasma (PRP), the evidence includes a number of small controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The potential benefit of PRP has received considerable interest due to its appeal as a simple, safe, low-cost, and minimally invasive method of applying growth factors. Current results of trials using PRP are mixed and the studies are limited in both size and quality. The evidence is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

Some larger studies that might influence this review are listed in **Table 1**.

### Table 1. Summary of Key Clinical Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02307448</td>
<td>Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds</td>
<td>1500</td>
<td>Mar 2016 (ongoing)</td>
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<tr>
<td>NCT02402374</td>
<td>Randomized, Placebo-controlled, Blind-assessor Study to Evaluate the Safety and Efficacy of Autologous Platelet Rich Plasma Gel Prepared With the RegenKit-BCT Plus Family of Kits for the Treatment of Diabetic Foot Ulcer</td>
<td>192</td>
<td>Nov 2016 (ongoing)</td>
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<tr>
<td>NCT02213952</td>
<td>Efficacy of Autologous Platelet-Rich Plasma in the Treatment of Vascular Ulcers in Primary Care: Clinical Trial Phase III</td>
<td>150</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02312596</td>
<td>A Prospective, Randomized Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Non-Healing Diabetic Foot Ulcers</td>
<td>250</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT02312570</td>
<td>Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Chronic Non-Healing Pressure Ulcers</td>
<td>250</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT02071979</td>
<td>Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)</td>
<td>1500</td>
<td>Dec 2021</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02209662</td>
<td>A Multi-Center, Randomized Trial Comparing the Effectiveness of APIC-PRP to Control, When Added to Standard of Care in the Treatment of Non-healing Diabetic Foot Ulcers</td>
<td>274</td>
<td>Dec 2015 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

**American College of Physicians**

In 2015, the American College of Physicians (ACP) published guidelines on treatment of pressure ulcers. The guidelines noted that “although low quality evidence suggests that dressings containing PDGF [platelet-derived growth factors] promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings.”

**Association for the Advancement of Wound Care**

In 2010, the Association for the Advancement of Wound Care developed guidelines on pressure ulcers and on venous ulcer:

- Pressure ulcer: “Growth factors are not indicated for PU [pressure ulcers] at this time” (level C evidence – no RCTs available comparing growth factors with A-level dressings).

- Venous ulcer: “Platelet derived growth factor has shown no significant effects on VU [venous ulcer] healing or recurrence” (level A evidence).

**National Institute for Health and Care Excellence**

In January 2016, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The guidance states that neither autologous platelet-rich plasma gel nor PDGF should be offered in the treatment of diabetic foot ulcers.

**Medicare National Coverage**

In 2012, Medicare revised its national coverage decision on autologous blood-derived products for chronic nonhealing wounds. This replaces noncoverage decisions from 2004 and 2008.

The Centers for Medicare and Medicaid Services covers autologous PRP only for patients who have chronic nonhealing diabetic, pressure, and/or venous wounds and when specific conditions are met.
Regulatory Status

Regranex®

In 1997, becaplermin gel (Regranex®; Smith & Nephew), a recombinant platelet-derived growth factor product, was approved by the U.S. Food and Drug Administration (FDA) for the following labeled indication:

Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp débridement, pressure relief and infection control, REGRANEX Gel increases the complete healing of diabetic ulcers.

The efficacy of REGRANEX Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers ... has not been evaluated....

In 2008, the manufacturer added this black box warning to the labeling for Regranex®: “An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of Regranex Gel in a postmarketing 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.”

Platelet-Rich Plasma

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Blood products such as platelet-rich plasma (PRP) are included in these regulations.

Under these regulations, certain products including blood products such as PRP are exempt and therefore, do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.2

Numerous PRP preparation systems have been cleared for marketing by the FDA through the 510(k) process. 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.
References

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>05/05/97</td>
<td>Add to Medicine Section - New Policy</td>
</tr>
<tr>
<td>08/17/99</td>
<td>Replace Policy - Revised policy; addresses becaplermin gel.</td>
</tr>
<tr>
<td>10/08/02</td>
<td>Replace Policy - Policy reviewed with changes: new policy statement on becaplermin gel for treatment of pressure ulcers.</td>
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<tr>
<td>10/16/03</td>
<td>Replace Policy - Policy updated; no change in policy statement. Information regarding Autologel and SafeBlood provided. Title updated by removing Platelet and adding Blood.</td>
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<tr>
<td>01/11/05</td>
<td>Replace Policy - Policy updated focusing on autologous blood derived wound healing products; reference added; no change in policy statement.</td>
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<tr>
<td>01/10/06</td>
<td>Presented at January MPC - Policy revised; policy statement added regarding miscellaneous use of platelet-rich plasma as a primary procedure. Description and rationale now include discussion of platelet-rich plasma. MPC requested further research before adopting.</td>
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<tr>
<td>02/14/06</td>
<td>Replace Policy - Policy revised per MPC request of removing description regarding fibrin sealant and surgical indications (primary wound closure).</td>
</tr>
<tr>
<td>06/16/06</td>
<td>Update Scope and Disclaimer - No other changes</td>
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<tr>
<td>07/10/07</td>
<td>Replace Policy - Policy updated with literature search; references added; policy statement unchanged.</td>
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<tr>
<td>08/12/08</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement.</td>
</tr>
<tr>
<td>01/13/09</td>
<td>Code Updates - Codes Q4102 and Q4103 added, effective 1/1/09.</td>
</tr>
<tr>
<td>10/13/09</td>
<td>Replace Policy - Policy updated with literature search; policy statement updated to include “acute” wounds for PRP. References added.</td>
</tr>
<tr>
<td>12/27/10</td>
<td>Codes Updated - CPT code 0232T added to policy; no other changes.</td>
</tr>
<tr>
<td>06/13/11</td>
<td>Replace Policy - Policy updated with literature search, reference numbers 11-14, 18, 19, 23, 24 added, policy statements unchanged. ICD-10 codes added to policy. CPT coding related to platelet-rich plasma also updated. Title changed to “Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions.”</td>
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<tr>
<td>03/22/12</td>
<td>Minor update, Related Policies updated with 7.01.113 and 1.01.16.</td>
</tr>
<tr>
<td>06/26/12</td>
<td>Replace policy. Policy updated with literature search through February 2012, references added and reordered; some references removed; policy statements unchanged. Codes Q4102 and Q4103 removed; these do not apply to this policy and appear on 7.01.113.</td>
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<tr>
<td>07/25/12</td>
<td>Related Policies Update: 8.01.52 and 8.01.55 have been added.</td>
</tr>
<tr>
<td>08/24/12</td>
<td>Update Related Policies – Remove 1.01.16 as it was archived. Update coding section – ICD-10 codes are now effective 10/01/2014.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>07/23/13</td>
<td>Replace policy. Policy updated with literature search through March 8, 2013; references added and reordered; policy statements unchanged.</td>
</tr>
<tr>
<td>03/17/14</td>
<td>Update Related Policies. Remove 7.01.100 as it was archived.</td>
</tr>
<tr>
<td>09/23/14</td>
<td>Update Related Policies. Add 7.01.142.</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy title changed to “Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions.” Orthopedic applications of platelet-rich plasma (PRP) policy statements removed from this policy and placed in new Policy No. 2.01.98. Coding table in Policy Guidelines updated to match Coding section of policy. Policy updated with literature review through April 15, 2015; references 1 and 3 added. Policy statements removed as noted, others remain unchanged. CPT code 20926 removed; platelet-rich plasma is not considered a tissue graft. ICD-9 and ICD-10 codes removed; these were for informational purposes only.</td>
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<tr>
<td>09/01/15</td>
<td>Update Related Policies. Add 7.01.149</td>
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<tr>
<td>10/16/15</td>
<td>Update Related Policies. Remove 7.01.142.</td>
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<tr>
<td>04/01/16</td>
<td>Annual Review, approved March 8, 2016. Policy updated with literature review through October 29, 2015; references 16 and 18-19 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/22/17</td>
<td>Policy moved to new format. No changes to policy statements.</td>
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</table>

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  - Information written in other languages

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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at http://www.hhs.gov/ocr/office/file/index.html.

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Deutsche (German):
