# 2.01.16

## Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

<table>
<thead>
<tr>
<th>Original Policy Date:</th>
<th>September 12, 2008</th>
<th>Effective Date:</th>
<th>March 1, 2018</th>
</tr>
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<tbody>
<tr>
<td>Section:</td>
<td>2.0 Medicine</td>
<td>Page:</td>
<td>Page 1 of 10</td>
</tr>
</tbody>
</table>

### Policy Statement

Use of platelet-rich plasma (PRP) (i.e., autologous blood-derived preparations) is considered **investigational** for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers, and certain other non-orthopedic conditions.

**Note:** Please refer to the Rationale section of this policy for the non-orthopedic conditions and to Blue Shield of California’s Medication Policy: REGRANEX (becaplermin) for coverage criteria.

### Policy Guidelines

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

**Coding**

There is a CPT category III code for injections of platelet-rich plasma (PRP):

- **0232T:** Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021, or 86965. Code 0232T includes the harvesting and preparation of the PRP.

For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products, but the following CPT code can be used:

- **86999:** Unlisted transfusion medicine procedure

It is questionable whether platelet-rich plasma is appropriately considered a tissue graft, but it has been reported that providers have used the following CPT code to describe the overall procedure:

- **20926:** Tissue grafts, other (e.g., paratenon, fat, demis)

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

There is also a HCPCS code for this treatment:

- **G0460:** Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment

The following HCPCS code represents other human platelet-derived growth factor preparations used to promote wound healing:

- **S9055:** Procuren or other growth factor preparation to promote wound healing

### Description

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

- Bio-Engineered Skin and Soft Tissue Substitutes
- Electrostimulation and Electromagnetic Therapy for Treating Wounds
- Negative Pressure Wound Therapy in the Outpatient Setting
- Noncontact Ultrasound Treatment for Wounds
- Orthopedic Applications of Platelet-Rich Plasma

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Platelet-Rich Plasma

The U.S. Food and Drug Administration (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, title 21, parts 1270 and 1271. Blood products such as 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. These devices are intended to concentrate patient plasma at the point of care during bone grafting procedures. 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.

Rationale

Background

Wound Healing Treatment

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factor (PDGF), 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.

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 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 transforming growth factor, 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 International) and Hemaseel® (Haemacure Corp.) are examples of commercially available fibrin sealants. Autologous fibrin sealants can also be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

**Wound Closure Outcomes**

This review addresses the use of PRP for nonorthopedic indications, which include a number of wound closure–related indications.

For this review, the primary end points of interest for the study of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds1:

- Incidence of complete wound closure
- Time to complete wound closure (reflecting accelerated wound closure)
- Incidence of complete wound closure following surgical wound closure
- Pain control

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens, and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

The portion of this evidence review on platelet-derived wound healing formulae was informed by a 1992 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment that primarily focused on the Procuren process.3 This preparation method is no longer commercially available. Currently, a large number of devices are available for the preparation of platelet-rich plasma (PRP) or PRP gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is unknown whether platelet activation before injection is necessary.4-8
Mixed Wound Types (Chronic and Surgical)

Systematic Reviews

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

This Cochrane review was updated in 2016; it added a new RCT, for a total of 10 RCTs (total N=442 patients). Conclusions about the quality of the overall body of evidence were similar to the 2012 review. For the outcome of overall wound healing, autologous PRP did not significantly increase healing compared with standard treatment (RR=1.19; 95% CI, 0.95 to 1.50; I²=27%, low-quality evidence). For wound healing in foot ulcers in people with diabetes, the evidence suggested that autologous PRP might increase healing compared with standard care (RR=1.22; 95% CI, 1.01 to 1.49; I²=0%, low-quality evidence). It was unclear whether autologous PRP increased wound healing compared with standard care for venous leg ulcers (RR=1.05; 95% CI, 0.29 to 3.88; I²=0% low-quality evidence).

Other systematic reviews reached similar conclusions. For example, one from 2009 identified 42 controlled trials on PRP; of these, 20 were RCTs and were included in the systematic review, which found results to be inconclusive. The 20 RCTs comprised 11 trials on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. An industry-funded systematic review from 2011 included 21 studies of PRP gel for cutaneous wound healing, 12 of which were RCTs. There were 3 main types of wounds, including open chronic wounds, acute surgical wounds with primary closure, and acute surgical wound with secondary closure. Study quality varied considerably, with 3 studies rated as high-quality and 6 rated as poor-quality. Two additional studies could not be rated because they were published only as an abstract and letter. Meta-analysis of the effect of PRP on complete wound healing of chronic wounds was limited by the inclusion of poor-quality studies. No high-quality RCTs showed improvement in complete healing with PRP. A 2015 systematic review of PRP for diabetic foot ulcers identified 6 small RCTs published between 1992 and 2011. Although five of the studies reported positive results with PRP, the studies were small, and the possibility of selective publication bias was not assessed.

Chronic Wounds

Since the publication of the 2015 update to the Cochrane review on PRP for wounds, Escamilla Cardenosa et al (2017) reported on an unblinded RCT comparing PRP and saline for venous ulcer treatment. The trial included 61 patients (102 ulcers) who were randomized to the weekly application of a PRP dressing (31 patients, 55 ulcers) or weekly wet-to-dry dressing changes with saline (30 patients, 47 ulcers) over a 24-week period. The average percentage healed area in the PRP group was 67.7% and 11.2% in the control group (p<0.001). PRP group members had greater reductions in pain with the intervention.

Section Summary: Chronic Wounds

The evidence for autologous PRP for a variety of chronic wounds includes RCTs, which have been summarized in a systematic review. For chronic wounds, including diabetic ulcers, pressure ulcers, and vascular ulcers, the systematic review of RCTs did not find that PRP was associated with improved outcomes.
Acute Surgical or Traumatic Wounds

Surgical Wounds

Aortic Arch Repair

In 2015, Zhou et al reported on a double-blind RCT with 80 patients that assessed the effect of PRP on the amount of blood transfused in the perioperative period for elective ascending and transverse aortic arch repair. An anesthesiologist prepared the PRP so that the surgeon was unaware of the treatment group. The volume of PRP transfused was 726 mL and led to a reduction in transfusion rates for red blood cells, frozen plasma, cryoprecipitate, and platelets by 34% to 70% (p<0.02). Hospital length of stay was also reduced (9.4 days vs 12.7 days). There was no difference in mortality between the 2 groups (1 patient in each group) and no significant differences in postoperative complications or other outcome measures. Corroboration of the effect of PRP on perioperative blood transfusion is needed.

Sternotomy Wounds

In 2015, Serraino et al reported on a large series with historical controls that assessed the occurrence of deep sternal wound infections in patients who underwent cardiac surgery either with (2010-2012, 422 consecutive patients) or without (2007-2009, 671 consecutive patients) application of PRP. The 2 groups were comparable at baseline. At the end of cardiac surgery, PRP gel was applied on the sternum before the closure of subcutaneous tissue. Rates of both deep and superficial wound infection were reduced in the patients treated with PRP (deep: 0.2% vs 1.5%, superficial: 0.5% vs 2.8%). Interpretation of these results is limited by likely differences in treatments over time. RCTs are needed to evaluate this potential use of PRP.

Otolaryngology

In 2016, El-Anwar et al reported on an RCT that evaluated PRP in 44 children (age range, 12-23 months) undergoing repair of a complete cleft palate. Speech and velopharyngeal valve movement on follow-up were evaluated by 3 judges who “usually assessed every patient blindly,” physical examination, video nasoendoscopy, and audio recording of audio perceptual assessment. At 6 months, PRP-treated patients had better nasality grade on audio perceptual assessment (p=0.024) and better velopharyngeal closure on endoscopy (p=0.016).

A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children (age range, 4-15 years). PRP was 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 the patient or a family member for 10 days after surgery. A FACES Pain Scale was used for children ages 4 to 7 years, while a numeric pain rating scale was used for children older than 7 years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the 2 conditions.

Other Wounds

A 2011 Norwegian trial of PRP applied to saphenous vein harvest sites after wound closure found no differences in the incidence of wound infection or cosmetic result.
lower in PRP-treated patients at 2 and 3 weeks (visual analog scale score, 58 PRP vs 80 controls). Although these results are encouraging, additional study with a larger number of patients is needed.

In 2016, Marck et al reported on a randomized, double-blind, within-patient-controlled study in patients with deep dermal to full-thickness burns undergoing split-skin graft, comparing PRP with usual care. The study randomized 52 patients, 50 of whom received the allocated PRP intervention. There were no significant differences in short-term (5-7 days) rates in graft take in the intervention and control areas on each patient. At 3, 6, and 12 months, there were no significant differences in skin appearance or epithelialization scores.

**Section Summary: Acute Surgical or Traumatic Wounds**
The evidence for autologous PRP for a variety of acute and traumatic wounds includes RCTs, which have been summarized in several systematic reviews. For a variety of conditions, studies have either not demonstrated a benefit or have demonstrated small benefits in studies with methodologic limitations.

**Summary of Evidence**

**Platelet-Rich Plasma**
For individuals who have chronic wounds or acute surgical or traumatic wounds who receive 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. 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.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**Association for the Advancement of Wound Care**
The Association for the Advancement of Wound Care developed guideline recommendations for the management of pressure ulcers (2010) and venous ulcers (2015):

- 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)

**National Institute for Health and Care Excellence**
In 2016, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The guidance stated that neither autologous platelet-rich plasma (PRP) gel nor platelet-derived growth factors should be offered in the treatment of diabetic foot ulcers.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
In 2012, the Centers for Medicare & Medicaid Services (CMS) revised its national coverage decision on autologous blood-derived products for chronic nonhealing wounds. This revision replaces prior noncoverage decisions.

The Centers for Medicare & Medicaid Services covers autologous PRP only for patients who have chronic nonhealing diabetic, pressure, and/or venous wounds and when all of the following conditions are met:

- The patient is enrolled in a clinical research study that addresses the following questions using validated and reliable methods of evaluation...
The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic nonhealing diabetic, pressure, and/or venous wounds. The clinical study must address the following:

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, pressure, and/or venous wounds who receive well-defined optimal usual care, along with PRP therapy, experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care for chronic non-healing diabetic, pressure, and/or venous wounds as indicated by addressing at least one of the following:

- Complete wound healing
- Ability to return to previous function and resumption of normal activities
- Reduction of wound size or healing trajectory, which results in the patient's ability to return to previous function and resumption of normal activities

Ongoing and Unpublished Clinical Trials
Some larger studies that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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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 (ongoing)</td>
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<td>NCT02312596a</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>
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<tr>
<td>NCT02312570a</td>
<td>Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Chronic Non-Healing Pressure Ulcers</td>
<td>250</td>
<td>Jul 2018</td>
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<td>NCT02402374a</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>Dec 2018</td>
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<td>NCT02071979a</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>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT02209662a</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>
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<td>NCT02307448a</td>
<td>Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds</td>
<td>1500</td>
<td>Mar 2016 (unknown)</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


**Documentation for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
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<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<td>CPT®</td>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed</td>
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<tr>
<td>HCPCS</td>
<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></td>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
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<tr>
<td></td>
<td>S9055</td>
<td>Procuren or other growth factor preparation to promote wound healing</td>
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**ICD-10 Procedure**

- None

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>09/12/2008</td>
<td>BC BSA Medical Policy adoption 2.01.16. References updated. Coding updated</td>
<td>Medical Policy Committee</td>
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</table>
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.