DRAFT

BlueCross BlueShield of Alabama

Name of Policy:
Autologous Platelet Derived Growth Factors as a Primary Treatment of Wound Healing and Other Miscellaneous Conditions

Policy #: 241
Category: Other
Latest Review Date: June 2010
Policy Grade: C

Background:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Description of Procedure or Service:
A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factor, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous wound healing factors are derived from the patients' blood. Topically applied platelet-derived growth factors (PDGF) have been most extensively investigated for clinical use in wound healing.

Platelets are a rich source of platelet-derived growth factors, including transforming growth factors (which function as a mitogen for fibroblasts, smooth muscle cells an osteoblasts) and vasculare endothelial growth factors. Autologous platelet concentrate suspended in plasma, also know as platelet rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride 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. Activated platelets then degranulate, releasing the various growth factors.
Platelet rich plasma must be distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incisions sites. Fibrin glue is created from platelet poor plasma, and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tissel (Baxter) and Hemaseal are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet poor plasma.

A recombinant PDGF product, becaplermin gel (Regranex®, McNeil Pharmaceutical) has been approved as follows: "Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers. The efficacy of Regranex Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers has not been evaluated." In 2008, the manufacturer added this **black box** warning to the labeling for Regranex, “An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a post-marketing retrospective cohort study. REGRANEX Gel should only be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy.”

A number of commercially available centrifugation devices are used for the preparation of platelet-rich plasma. For example, AutoloGel™ (Cytomedix) and Safe Blood (SafeBlood technologies) are two related but distinct autologous blood-derived preparations that can be prepared at the bedside for immediate application. Both Autologel and SafeBlood have been specifically marketed for wound healing. Other devices may be used in the operating room setting, such as Medtronic Electromedic, Elmd-500 Autotransfusion system, the Plasma Saver device, or the Smart PreP device. The Magellan Autologous Platelet Separator System (Medtronic) includes a disposables kit designed for use with the Magellan Autologous Platelet Separator portable tabletop centrifuge. BioMet Biologics received marketing clearance through the FDA’s 510(k) process for a gravitational platelet separation system (GPSII), which uses a disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

Procuren® (Curative Technologies, Inc.) is an autologous product that is derived from the patients' own blood cells; blood is collected from the patient and sent to a specialized laboratory for processing and then returned to the patient for topical use. Originally, Procuren was offered as part of a program of wound care management by Wound Care Centers, which are operated by Curative Technologies, Inc. As of 2002, Procuren is no longer marketed.

Policy:

Effective for dates of service on or after July 1, 2010:

Autologous blood derived preparations (i.e., platelet rich plasma) do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage when used to:

- **Treat chronic non-healing wounds;** or
- As a **primary procedure** for conditions, including, but not limited to epicondylitis (i.e. tennis elbow), plantar fasciitis, Dupuytren's contracture, cartilage degeneration, or degenerative disc disease;
- Or **adjunctive use in surgical procedures**

Recombinant platelet-derived growth factor (i.e., becaplermin) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when used as an adjunct to standard wound management for the following indications:

- Neuropathic diabetic ulcers extending into the subcutaneous tissue
- Pressure ulcers extending into the subcutaneous tissue

Candidates for becaplermin gel for **neuropathic ulcers must 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 (i.e., stage III or IV), extending through dermis into subcutaneous tissues
- Participation in a wound-management program, which includes sharp debridement, pressure relief, and infection control

Candidates for becaplermin gel for the treatment of **pressure ulcers must meet all** of the following criteria:

- Full-thickness ulcer (stage III or IV), extending in to the subcutaneous tissue
- Ulcer 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

Treatments are normally for 20 weeks or complete healing.

Effective for dates of service ~~on or after~~ May 1, 2010 through June 30, 2010:

Autologous blood derived preparations (i.e., platelet rich plasma) do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage when used to:

- **Treat chronic non-healing wounds;** or
- As a **primary procedure** for conditions, including, but not limited to epicondylitis (i.e. tennis elbow), plantar fasciitis, Dupuytren's contracture, cartilage degeneration, or degenerative disc disease.

The use of platelet rich plasma as an **adjunct to surgery** in periodontal, plastic/reconstructive, or orthopedic procedures is an integral part of the global procedure and not eligible for separate reimbursement when billed by the surgeon.

This policy does not address the use of fibrin sealants.
This policy does not address the use of recombinant PDGF products

Recombinant platelet-derived growth factor (i.e., becaplermin) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when used as an adjunct to standard wound management for the following indications:

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- 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, and infection control

Candidates for becaplermin gel for the treatment of **pressure ulcers must meet all** of the following criteria:

- Full-thickness ulcer (stage III or IV), extending in to the subcutaneous tissue
- Ulcer 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

Treatments are normally for 20 weeks or complete healing.

Effective for dates of service May 1 2005 through May 1, 2010:
Autologous blood derived preparations (i.e., platelet rich plasma) do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage when used to:

- **Treat chronic non-healing wounds;** or
- As a **primary procedure** for conditions, including, but not limited to epicondylitis (i.e. tennis elbow), plantar fasciitis, Dupuytren's contracture, cartilage degeneration, or degenerative disc disease.

The use of platelet rich plasma as an **adjunct to surgery** in periodontal, plastic/reconstructive, or orthopedic procedures is an integral part of the global procedure and not eligible for separate reimbursement when billed by the surgeon.

This policy does not address the use of fibrin sealants.
This policy does not address the use of recombinant PDGF products

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

A literature search focusing on different preparation of platelet rich plasma did not identify any controlled clinical trials. Several articles did describe different methods of preparation of autologous platelet rich plasma, and noted the variability in platelet concentration and viability depending on the preparation. In addition, the literature search focused on other indications for platelet rich plasma as a primary treatment. One abstract was identified that described the use of a single percutaneous injection of platelet rich plasma as a treatment of lateral epicondylitis in a case series of 20 patients. Anecdotally, platelet rich plasma has also been investigated as a treatment of plantar fasciitis or Dupuytren's contracture, but no published studies were identified.

In 2004, Medicare announced the following policy regarding autologous blood-derived products for chronic non-healing cutaneous woods:

"The CMS issued a national Medicare non-coverage determination in 1992 related to platelet-derived wound healing formulas containing growth factors to treat non healing wounds based on a lack of sufficient published data to determine its efficacy and safety. Upon reconsideration, CMS continues to believe that the clinical effectiveness of autologous blood derived products, both platelet derived growth factors in a platelet poor plasma and platelet rich plasma (PRP) are not adequately proven in scientific literature. Therefore, autologous blood derived produces remain nationally non-covered for chronic non-healing cutaneous wounds as not reasonable and necessary under section 1861(a) of the Social Security Act."

The November 2005 issue of *CPT® Assistant* states the following: "The instillation of the platelets by the surgeon into the surgical site would not warrant additional CPT code reporting as this is considered an integral part of the total procedure performed; therefore, the instillation is not separately reportable as there is no significant, additional physician work involved".

A November 2006 review for autologous platelet derived growth factors did not reveal any new literature that would alter the current non-coverage decision for this policy.

November 2007 Update
A literature search identified a small multicenter randomized controlled trial from the OASIS Diabetic Ulcer study Group that compared an acellular biomaterial from pig small intestine submucosa (OAISIS wound matrix) with recombinant PDGF. This industry sponsored trial found 49% healing in 37 OASIS-treated patients in comparison with 28% in 36 PDGF-treated patients (p= 0.55). Additional studies with a greater number of subjects are needed to compare efficacy between these 2 wound-healing agents. There is no additional information to alter the policy statement.

April 2009 Update
An April 2009 review of PRP identified emerging literature on beneficial effects of PRP for chronic non-healing tendon injuries including lateral epicondylitis, plantar fasciitis, cartilage degeneration due to sports injuries and degenerative disc disease. However, there are few controlled trials and mostly anecdotal or case reports or involve small sample size. Lillte is documented in the literature regarding the expected timeframe of tendon healing post-PRP injection. Also, there are no studies to date that review the need of post-PRP injection rehabilitation. However, it is assumed that physical/occupational therapy and restoring the kinetic chain will help facilitate recovery post injection.

April 2010 Update
Recombinant Platelet-Derived Growth Factor (Becaplermin Gel)
This policy regarding the use of becaplermin gel was originally based on a 1999 TEC Assessment that offered the following observations and conclusions:

- The evidence supports the conclusion that becaplermin treatment, in conjunction with good wound care, improves the health outcomes of patients with chronic neuropathic diabetic ulcers that meet the patient selection criteria defined here. Becaplermin gel plus good wound care resulted in a 43% complete wound-closure rate, compared to 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure.
- Evidence is insufficient to determine the effect of becaplermin gel in treatment of other types of ulcers, including ischemic, chronic venous, or chronic pressure ulcers.
- It should be emphasized that the beneficial effects of becaplermin were achieved within the setting of a controlled clinical trial protocol. Results of the clinical trials clearly tied the efficacy of becaplermin treatment to the overall intensity of the wound management effort. Variations in standard care, including infection control, debridement type and frequency, non-weight-bearing compliance and methods, and patients' glycemic control all influence ulcer healing. Whether this comprehensive degree of wound care is

maintained in a community practice or home care setting is a concern. The magnitude of becaplermin effect, as demonstrated in clinical trials, can be expected only in settings that adhere to good wound care practices.

Results of a randomized study focusing on the use of becaplermin gel as a treatment of pressure ulcers has also been published. Patient selection criteria include full-thickness ulcers and an anatomic location where pressure could be off-loaded during treatment. This latter patient selection criterion may limit the number of patients with pressure ulcers who would be considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups, and received either a placebo or 1 of 3 doses of becaplermin. All patients received a standardized program of good wound care. In the 2 groups of patients treated with once daily doses of becaplermin (either 100 or 300 µg/g), the incidence of complete healing was significantly improved compared to the placebo group. There was no difference in outcome between the 100 and 300 µg/g group, suggesting that there is no clinical benefit in increasing the dose above100 µg/g. A third group of patients received becaplermin 100 µg/g twice a day. This group did not report an improved outcome compared to placebo, a finding that is unexplained.

An industry-sponsored study assessed the effectiveness of recombinant platelet-derived growth factors (PDGF) on diabetic neuropathic foot ulcers in actual clinical practice. Subjects (from a cohort of 24,898 patients in wound-care centers) whose wounds did not heal over an 8-week observation period were eligible for the study and assessed over a period of 20 weeks or until they healed. Any individual with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25,000 patients treated for foot ulcers, 2,394 (9.6%) received recombinant PDGF. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in the patients treated with recombinant PDGF. The relative risk, controlling for the propensity to receive PDGF, was 1.32 for healing and 0.65 for amputation (6.4% vs. 4.9%). Analysis also indicated that those who received PDGF were more likely to be younger, male, and have older wounds, factors not known to affect wound healing. These results support clinical effectiveness of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice. Also identified in the literature search was a small multicenter randomized controlled trial from the OASIS Diabetic Ulcer Study Group that compared an acellular biomaterial from pig small intestine submucosa (OAISIS wound matrix) with recombinant PDGF. This industry-sponsored trial found 49% healing in 37 OASIS-treated patients in comparison with 28% in 36 PDGF-treated patients ($p = 0.55$). Additional studies with a greater number of subjects are needed to compare efficacy between these two wound-healing agents.

Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. One study used alternate assignment to “randomize” 50 patients (fingertip wound area of 1.5 cm or more, with or without phalangeal exposure) to daily treatment with PDGF or surgical reconstruction. Statistical analysis showed that the baseline characteristics of the two groups were similar for patient age, wound area (2.2–2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that in comparison with the surgical intervention, treatment with recombinant PDGF resulted in faster return to

work (10 vs. 38 days) and wound healing (25 vs. 35 days), and a reduction in functional impairment (10% vs. 22%) and need for physiotherapy (20% vs. 56%). Fingertips treated with PDGF were also reported to have satisfactory esthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed, could lead to improvement in health outcomes for patients with finger tip injury. However, the present study is limited by the small sample size, the method of randomization, and the potential for investigator bias (although the investigators did blind the examining physician from treatment allocation, the actual treatment may have been obvious). Additional randomized controlled trials are needed.

Growth factors cause cells to divide more rapidly. It is for this reason that the manufacturer continued to monitor studies begun before Regranex was approved in December 1997 for any evidence of adverse effects such as increased numbers of cancers. In a long-term safety study completed in 2001, more deaths from cancer occurred in people who used Regranex than in those who did not use it. Following the report of the study completed in 2001, an additional study was performed using a health insurance database that covered the period from January 1998 through June 2003. This study used the database to identify two groups of patients with similar diagnoses, drug use, and use of health services, one of which used Regranex and one group that did not. The results of this study showed that deaths from cancer were higher for patients who were given 3 or more prescriptions for treatment with Regranex than those who were not treated with Regranex. No single type of cancer was identified, but deaths from all types of cancer combined were observed. In 2008, the U.S. Food and Drug Administration (FDA) concluded that the increase in the risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher than in those patients who did not use Regranex. The risk of getting new cancers among Regranex users was not increased compared to non-users, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

Autologous Blood-Derived Preparations (i.e., Platelet-Rich Plasma)
The policy on platelet-derived wound-healing formula was originally derived from a 1992 TEC Assessment, which primarily focused on the Procuren process, referred to as a platelet-derived wound-healing formula. This preparation is no longer commercially available. A literature search for different preparations of PDGFs was performed for the period of 1999 to June 2005 using the MEDLINE database. Several articles described different methods of preparation of autologous platelet-rich plasma (PRP) and noted variability in platelet concentration and viability depending on the preparation.

A 2009 systematic review identified 42 controlled trials on PRP, 20 of these were randomized controlled trials (RCTs) and included in the systematic review. The 20 RCTs comprised 11 studies on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. Four of the 11 studies on oral and maxillofacial (dental) surgery were combined to analyze the efficacy of PRP in patients with chronic periodontitis. The mean effect showed a greater reduction in patients in the PRP group for depth reduction of gingival recession of 0.54 mm. The mean effect for 3 studies assessing the clinical attachment level was not significant, although the studies were heterogeneous. When only the 2 studies including patients at severe stages were considered, there was a 0.89 mm advantage for the PRP group. Of the 7 RCTs assessing PRP for skin ulcers, 6 could be combined for the measure of complete ulcer

epithelialization. The observed relative risk ratio of 1.40 was not significant between the experimental and controls groups. Two low quality RCTs assessed the use of PRP in surgery wounds; both studies tended to favor the PRP group, but were not statistically significant. The authors concluded that PRP improved the gingival recession but not the clinical attachment level in chronic periodontitis. Results were inconclusive for the healing of skin ulcers, and there were little safety data. Non-randomized controlled studies were identified, but not reviewed, for chronic elbow tendinosis, muscle strains, lumbar spinal fusions, and other orthopedic procedures.

Tendon, Ligament and Muscle

Percutaneous injection of PRP as a treatment of lateral epicondylitis was assessed in a small prospective controlled study with 20 patients. Criteria for participation included elbow epicondylar pain for longer than 3 months and at least 60 of 100 on a VAS with failure of conservative therapy (a standardized stretching and strengthening protocol, and some combination of non-steroidal medication, bracing, or corticosteroid injections). Twenty (15%) of the 140 patients evaluated met the inclusion/exclusion criteria. Fifteen patients were treated with PRP and 5 patients were injected only with bupivacaine with epinephrine into the skin, subcutaneous tissue and directly into the area of maximum tenderness. Either 2–3 mL PRP or 2–3 mL bupivacaine with epinephrine was injected into the common extensor or flexor tendon using a single skin portal with 5 penetrations of the tendon (peppering technique). Although drawing 55 mL of blood in control patients (to conceal the treatment allocation) was not permitted by the institutional review board, participants were informed that the needling alone was expected to improve symptoms. All participants were given a standardized post-treatment stretching and strengthening program. At 4 weeks after the procedure, PRP-treated patients reported a mean 46% improvement (80 to 43) in Visual Analogue Scale (VAS) pain scores and a 42% improvement (50 to 71) in Mayo elbow scores. Control patients reported a mean 17% improvement (86 to 71) in VAS and 20% improvement (50 to 60) in Mayo elbow scores. The PRP-treated patients continued to improve over follow-up. At a mean of 26 months' follow-up PRP-treated patients reported a 93% reduction in pain compared with before the procedure. Follow-up was limited in the control patients as 3 of 5 (60%) had either sought treatment outside of the protocol or had formally withdrawn from the study by 8 weeks. No complications were noted in either group at any time. Mishra and colleagues report that a double-blind prospective trial with 230 patients has been initiated in the United States using this protocol. No additional studies of PRP treatment of lateral epicondylitis were identified in a 2009 systematic review of injection therapies. Anecdotally, PRP has also been investigated as a treatment of plantar fasciitis or Dupuytren's contracture, but no published studies were identified.

Kazakos and colleagues reported a prospective controlled study of the treatment of acute traumatic wounds with platelet gel in 59 consecutive patients (27 PRP and 32 controls). Conventional treatment consisted of topical washing and cleaning of the wounds, removal of the necrotic tissue, and dressing with Vaseline gauze every 2 days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel, prepared with specialized tubes and a bench-top centrifuge, was applied to the wounds after surgical debridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. PRP gel was then applied to the wounds once weekly in the

outpatient clinic until there was adequate tissue regeneration (mean of 21 days) to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in the PRP-treated patients at 2 and 3 weeks (VAS score of 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of subjects is needed.

A 2009 report from Europe described a prospective study of intra-articular injection of PRP in 100 consecutive patients affected by chronic degenerative cartilage lesions. Patients had a history of pain or swelling of the knee for at least 4 months and imaging findings on radiograph or magnetic resonance imaging (MR) of degenerative changes in the joint; 58 knees presented with a degenerative chondral lesion, 33 with early osteoarthritis, and 24 had advanced osteoarthritis. Exclusion criteria included systemic disorders, axial malalignment, severe cardiovascular diseases, infections, or immunodepression. Three injections were administered at 21-day intervals. During the treatment period, rest or mild activities such as an exercise bike or mild exercises in a pool were indicated. Gradual resumption of normal sport or recreational activities was allowed as tolerated. Five patients were lost to follow-up and 4 did not complete treatment (1 patient had swelling after the first treatment). Evaluation was conducted in 91 patients (91% follow-up) before and at the end of the 3 treatments, and at 6 and 12 months after treatment. The International Knee Documentation Committee (IKDC) objective score improved from 46% (of normal and nearly normal knees) to 78% at the end of therapy, declining to 67% at 12-month follow-up. The IKDC subjective score improved from 41 to 63 after treatment, with a score of 61 at 12-month follow-up. Treatment was less effective in older, heavier, and more advanced osteoarthritis patients than in younger patients with less severe chondral damage. The authors commented that randomized studies with longer follow-up are needed, and that additional studies are in progress to further evaluate this relatively simple, low cost, and minimally invasive method of applying growth factors.

Use of autologous PDGF as a primary treatment of soft-tissue injuries is in an early stage, and randomized controlled trials are lacking. Evidence is insufficient to permit conclusions concerning the effect of this technology on health outcomes.

Adjunct to Surgical Procedures

Soft tissue

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

the PLRP group across the 6-week assessment period, while patients reported improvements in activities of daily living such as ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

Another double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children, aged 4 to 15 years of age. The PRP was prepared during the surgery and placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by either the patient or family member for 10 days after surgery. A FACES pain scale was used for the children aged 4 to 7 years, while a numbered pain scale was used for children older than 7 years. Diaries from 83% of the patients showed no differences in pain, medication doses, activity, and days eating solid foods between the two conditions. The possibility that the PRP was rapidly sloughed off the tonsil beds was discussed as a potential explanation for the lack of effect in controlling post-tonsillectomy pain.

Bone

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

No randomized trials on PRP in spinal fusion were identified, however, 2 controlled studies found no difference in fusion rates with use of a platelet gel or platelet glue. (19, 20) The investigators of a prospective study published in 2009 concluded that the theoretical benefits of platelet glue were not clinically evident, and that further investigation to find a more stable carrier and optimal implantation time is needed.

Summary

The potential benefit of PRP has been of considerable interest for a wide variety of conditions. Although clear evidence of a health benefit is lacking, the appeal of a simple, safe, low cost, and minimally invasive method of applying growth factors is apparent. The oldest and most established evidence is in the area of dental surgery, which is outside the scope of medical policy. Recent literature indicates an increasing number of RCTs for other conditions, and a search of the clinical trials database (www.clinicaltrials.gov) reveals that many more RCTS are in progress. Overall, there is a limited but rapidly developing literature on the safety and efficacy of this novel treatment. Therefore, PRP as a primary treatment for acute or chronic wounds, or as an adjunct to surgical procedures, is considered investigational.

Technology Assessments, Guidelines and Position Statements
In 2009, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) issued guidance on use of autologous blood injection for tendinopathy. NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy is inadequate in quantity and quality. NICE recommends this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

Medicare National Coverage
In 2004, Medicare announced the following policy regarding autologous blood-derived products for chronic non-healing cutaneous wounds:

"The CMS [Centers for Medicare and Medicaid Services] issued a national Medicare noncoverage determination in 1992 related to platelet-derived wound healing formulas containing growth factors to treat non healing wounds based on a lack of sufficient published data to determine its efficacy and safety. Upon reconsideration, CMS continues to believe that the clinical effectiveness of autologous blood derived products, both platelet derived growth factor in a platelet poor plasma, and platelet rich plasma (PRP) are not adequately proven in scientific literature. Therefore, autologous blood derived products remain nationally non-covered for chronic non healing cutaneous wounds as not reasonable and necessary under section 1861(a) of the Social Security Act."

In 2008, CMS determined that the evidence was inadequate to conclude that autologous PRP for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds improved health outcomes in the Medicare population. Therefore, CMS determined that PRP is not reasonable and necessary for the treatment of these indications. Consequently, CMS issued a non-coverage determination for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds, and maintains the current non-coverage for chronic, non-healing cutaneous wounds.

Nationally Non-Covered Indications
- On reconsideration, the clinical effectiveness of autologous PDGF products continues to be not adequately proven in scientific literature. As the evidence is insufficient to conclude that autologous PDGF in a platelet-poor plasma is reasonable and necessary, it remains non-covered for treatment of chronic, non-healing cutaneous wounds.
- In addition, the evidence is not adequate to determine that autologous PRP is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds.
- Coverage for treatments using becaplermin, a non-autologous growth factor for chronic, non-healing subcutaneous wounds, will remain nationally non-covered under Part B based on §1861(s)(2)(A) and (B) of the Social Security Act because this product is usually administered by the patient.

Key Words:

Autologous platelet derived growth factors, autologous blood derived preparations, platelet-derived growth factors, PDGF, platelet rich plasma, PRP, autologous platelet gel, Autologel, SafeBlood, Medtronic Electromedic, Elmd-500 Autotransfusion system, Plasma Saver, Smart PreP, wound healing, autologous platelet gel, platelet gel, platelet concentrate, autologous blood-derived products, platelet-derived wound healing formulas, epicondylitis, tennis elbow, plantar fasciitis, Dupuytren's contracture, becaplermin, becaplermin gel, recombinant platelet-derived growth factor

Approved by Governing Bodies:

Autologous platelet gel is not FDA approved for use as a biologic agent.
Combining PRP with thrombin and calcium to create a gel is considered to be the practice of medicine.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
BellSouth/AT&T contracts: No special consideration
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan.
Wal-Mart: Special benefit consideration may apply. Refer to member's benefit plan.
Pre-certification requirements: Not applicable
Pre-determination requirements: Pre-determinations will be performed as a courtesy review at the request of the physician and/or subscriber.

Coding:

HCPCS code: **S9055** Procuren or other growth factor preparation to promote wound Healing
S0157 Becaplermin gel 0.01%, 0.5gm
P9020 Platelet rich plasma

CPT code: **22899** Unlisted procedure, spine
27599 Unlisted procedure, femur or knee
29999 Unlisted procedure, arthroscopy
41899 Unlisted procedure, dentoalveolar structures

Effective July 1, 2010:
0232T Injection(s) platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed

CPT code 20926 (Tissue graft, other) should not be billed for application of recombinant and autologous platelet derived growth factors.

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Policy History:

Medical Policy Group, May 2005 **(3)**
Medical Policy Group, June 2005
Medical Policy Group, July 2005 **(2)**
Medical Policy Administration Committee, July 2005
Available for comment August 6-September 19, 2005
Medical Policy Group, November 2006 **(1)**
Medical Policy Group, November 2007 **(1)**
Medical Policy Group, February 2009 **(2)**
Medical Policy Administration Committee, May 2009
Available for comment April 9-May 23, 2009

Medical Policy Group, April 2010 **(1)** Policy updated, Description, Key Points, Policy Update, Key Words
Medical Policy Administration Committee, May 2010
Available for comment May 7-June 21, 2010
Medical Policy Group, June 1010 **(2)**
Medical Policy Administration, June 2010
Available for comment June 18-August 2, 2010

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review)in Blue Cross and Blue Shield's administration of plans contracts.