Clinical Review Criteria

Autologous Platelet Derived Wound Healing Factors for Treatment of:
- Non Healing Cutaneous Wounds (Procuren)
- Non-Healing Fractures and the Associated GEM 21STM Device
- Platelet Rich Plasma Injections for the Treatment of Tendinopathy

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Criteria
See the wound care treatment criteria.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background
Wound healing is a dynamic process that involves a complex interaction of several cellular and biochemical events. Tissue repair begins with a clot formation and platelet degranulation which release the growth factors necessary for wound repair. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed.

Treatment of chronic non-healing cutaneous wounds has challenged health care providers for generations, and various strategies including devices, biologics and drug have been used to accelerate the healing process. These agents are designed to affect one of processes involved in healing (Robson 1999).

Advances in biology of wound healing, showed that macrophages and platelets are the chief regulatory cells in the repair process. Platelets are known for their role in haemostasis where they help prevent blood loss at site of vascular injury. They adhere, aggregate, and form a procoagulant surface leading to thrombin generation and fibrin formation. Activated platelets release potent locally acting growth factors substances that initiate division and migration of fibroblasts and formation of new capillaries promoting wound healing (Knighton 1986, Fu 2005).

Becaplermin, a topical treatment with platelet derived growth factor as its active ingredient was approved by the FDA in 1997 to treat diabetic foot and leg ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply.

Platelet derived growth factor (Procuren) for the treatment of non-healing cutaneous wounds was reviewed by MTAC in February 1999, and failed MTAC evaluation criteria due to the lack of scientific evidence to determine its safety and efficacy. It is being re-reviewed based on requests for coverage from Eastern WA.
Bone Fracture Healing (GEM 21STM)
Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracellular matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been, and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008).

In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007).

The GEM 21STM a device for bone grafting material containing a therapeutic tri-calcium phosphate or PDGF was approved by the FDA for peridontally related defects in November 2005.

Tendinopathy
Tendinopathy is a general term that is used to describe a tendon injury. It is characterized by pain, stiffness, and loss of strength in the affected area. Treatments for tendinopathy include, but are not limited to: rest, anti-inflammatory medication, analgesia, orthotics, physical therapy, and local steroid injections. Another more recent technology that has been proposed for the treatment of tendinopathy is platelet rich plasma injections into the ailing tendon (Kampa 2010).

Platelets are small nonneculeated bloods cells that are involved in wound healing. The exact mechanism by which platelet rich plasma promotes tendon healing is unclear; however, it is thought that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release growth factors and cytokines. The alpha granules release: platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010).

Platelet rich plasma is derived from anti-coagulated autologous whole blood, which is centrifuged to concentrate platelets in plasma. Normal platelet counts in the blood range from 150,000-350,000 μL. The goal of the devices used to create platelet rich plasma is to raise the concentration to at least one million platelets per μL. After separation, the platelet rich plasma must be clotted to allow for delivery to the desired site. This clotting leads to platelet activation, resulting in the release of growth factors and cytokines. Bovine thrombin, calcium chloride, and type I collagen are different agents used to stimulate platelet activation (clotting) (Foster 2009).
One of the advantages of this approach is that because the platelet rich plasma is derived from the patient’s own blood there is a low chance of rejection. However, the optimal dose range has not been defined.

The injection of platelet rich plasma is a procedure and therefore not regulated by the FDA. However, several devices used in the preparation of platelet rich plasma have received FDA approved.

**Medical Director Clinical Review and Policy Committee**

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<tr>
<th>Date</th>
<th>Evidence Conclusion</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>07/14/08</td>
<td>The committee did not approve this service for coverage as there is insufficient evidence in the published literature.</td>
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<tr>
<td>4/5/2011</td>
<td>The committee did not approve this service for tendinopathy as there is insufficient evidence in the published literature.</td>
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**Medical Technology Assessment Committee (MTAC)**

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<th>Date</th>
<th>Evidence Conclusion</th>
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<tr>
<td>2/10/99</td>
<td>Procuren The published evidence on the effect of Procuren for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren as compared to placebo and the other trial reports worse outcomes with Procuren. The available evidence does not allow any conclusion about the effects of Procuren on non-healing cutaneous wounds.</td>
<td>The use of platelet derived growth factors for the treatment of non-healing cutaneous wounds is approved by the FDA and therefore GHC Criteria 1 is met. There is insufficient scientific evidence that Procuren is medically effective and therefore <strong>GHC Medical Technology Assessment Criteria 2-5</strong> are not met. In the absence of adequate, well designed studies of effectiveness, the medical appropriateness of this technology (GHC Criteria 6) cannot be determined.</td>
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| 06/04/08   | Wound Healing (Procuren) The reviewer’s conclusion in the previous MTAC report of 1999 was, “The published evidence on the effect of Procuren™ for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren™ as compared to placebo, and the other trial reports worse outcomes with Procuren™. The available evidence does not allow any conclusion about the effects of Procuren™ on non-healing cutaneous wounds.”  
The literature search for the current review did not reveal any additional evidence that would determine the efficacy and safety of platelet derived growth factor for the treatment of non-healing cutaneous wounds.  
Bone Fracture Healing (GEM 21STM) There insufficient published evidence to determine the efficacy and safety of autologous platelet derived wound healing factors for the treatment of non-healing fractures. | The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Wounds does not meet the **Group Health Medical Technology Assessment Criteria.**  
The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Fractures does not meet the **Group Health Medical Technology Assessment Criteria.** |
| 2/14/2011  | Achilles tendinopathy  
A recent double-blind, placebo-controlled RCT evaluated the effects of adding a platelet rich plasma (PRP) injection to an eccentric exercise program in 54 patients with chronic midportion Achilles tendinopathy. The primary outcome measures were pain and activity level, | The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the **Group Health Medical Technology Assessment Criteria.**  |
measured using the Victorian Institute of Sports Assessment-Achilles (VISA-A). In both groups, VISA-A scores improved significantly after 24 week; however, there was no significant difference in VISA-A score between the two groups. With regard to safety, no microbial growth was found in the collected PRP samples, and no complications (infections, hematomas, or ruptures) were reported after the treatment (de Vos 2010).

Lateral epicondylitis (tennis elbow)
A double-blind RCT that included 100 subjects compared the efficacy of a platelet rich plasma injection to a corticosteroid injection for the treatment of lateral epicondylitis in patients who had failed non-operative treatment. In addition to a platelet rich plasma injection or a corticosteroid injection subjects also participated in an eccentric exercise program. The primary outcome measures were pain, measured using the visual analog scale (VAS), and disability, measured using the disability of the arm, shoulder, hand (DASH) outcome measure. Successful treatment was defined as more than a 25% reduction in VAS or DASH without a re-intervention after 1 year. According to the VAS, treatment was successful for 73% of subjects in the platelet rich plasma group and 49% in the corticosteroid group ($P<0.001$). When using the DASH, treatment was successful for 73% of subjects in the platelet rich plasma group and 51% in the corticosteroid group ($P=0.005$). This trial did not address safety. Results from this study should be interpreted with caution as there are several methodological limitations (Peerbooms 2010).

Conclusion:
There is insufficient evidence to support the use of platelet rich plasma injection for the treatment of Achilles tendinopathy. There is evidence from one small RCT that supports the use of this technology for patients with lateral epicondylitis; however, because of methodological limitations results from this trial are insufficient to determine the safety and efficacy of this procedure. Several trials are currently underway to determine the safety and efficacy of platelet rich plasma injections for the treatment of tendinopathy.

### Evidence/ Source Documents

<table>
<thead>
<tr>
<th>Date of Literature Search</th>
<th>Articles</th>
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<tr>
<td>6/4/2008</td>
<td>Wound Healing</td>
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<td></td>
<td>The search yielded around 100 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies, randomized or non-randomized controlled studies, published after the last review, were identified.</td>
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<tr>
<td></td>
<td>Bone Fracture Healing</td>
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<td>The literature search did not reveal any empirical studies on the use of PDGF for bone</td>
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fractures. The published studies were all related to the use of PDGF for dental implants, periodontal wounds, defects, or bone turnover during periodontal repair. None was selected for critical appraisal.

2/14/2011

Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of platelet rich plasma injections for the treatment of tendinopathy. Studies were excluded if they lacked a valid comparison group. Two RCTs were selected for review.

The following studies were critically appraised:

de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. JAMA 2010; 303:144-149. See Evidence Table