Name of Policy:
Amniotic Membrane and Amniotic Fluid Injections

Policy #: 597
Latest Review Date: February 2016
Category: Surgery
Policy Grade: D

Background/Definitions:
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.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**
There are several commercially available forms of human amniotic membrane (HAM) that can be administered by injection. Amniotic membrane injections are being evaluated for the treatment of a variety of conditions, including tendonitis, plantar fasciitis, and cartilage damage. Injection of an amniotic fluid product is being evaluated for alleviation of pain and stiffness in patients with osteoarthritis.

Amniotic membrane forms the amniotic sac and the innermost lining of the placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. There are several commercially available forms of human amniotic tissue that are available in a micronized form that can be suspended in liquid and administered by injection. These include AmnioFix® Injectable (MiMedx), Clarix® Flo and Neox® Flo (Amniox), AmnioMatrix® (Derma Sciences), AmnioPro™ (Human Regenerative Technologies), and AmnioGen™ (US Biologix). Amniotic fluid products that are cryopreserved and contain living cells include AmnioVisc™ (previously named AmnioClear® LCT from Liventa Bioscience) and OrthoFlow™ (MiMedx). PalinGen® Flow and Sport Flow™ (Amnio ReGen Solutions) contained cryopreserved amniotic fluid and cryo-fractured amniotic membrane. ReNu™ (NuTech Medical) is composed of a human amniotic membrane suspension along with amniotic fluid derived cells.

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. There is evidence that the tissue has anti-inflammatory, anti-fibroblastic, and antimicrobial properties. HAM is considered to be non-immunogenic and has not been observed to cause substantial immune response. It is believed that these properties are retained in cryopreserved HAM (C-HAM) and dehydrated HAM (D-HAM) products, resulting in a readily available tissue with regenerative potential. In support, one D-HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells both in vitro and in vivo.

HAM is an established treatment for corneal reconstruction ([refer to medical policy #616 Amniotic Membrane Transplantation for the Ocular Surface](#)) and is being evaluated for the treatment of a variety of conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures ([refer to medical policy #527, Bio-Engineered Skin and Soft Tissue Substitutes](#)). Additional indications that have been studied in pre-clinical models include tendonitis, tendon repair, nerve repair, and cartilage repair. The ready availability of an injectable preparation of amniotic membrane opens the possibility of regenerative medicine for a wide variety of conditions.

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea. The fluid contains proteins, carbohydrates, proteins and peptides, fats, amino acids, enzymes, hormones, pigments and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927. Amniotic fluid has been compared with synovial fluid, containing hyaluronan,
lubricant, cholesterol, and cytokines. Injection of amniotic fluid is being evaluated for the treatment of pain and stiffness in patients with osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as a source of pluripotent stem cells. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. The use of stem cells in orthopedic applications is addressed separately in medical policy #430 Orthopedic Applications of Stem Cell Therapy.

**Policy:**
Injection of human amniotic membrane and/or amniotic fluid for all indications does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

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 member's 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:**
The most recent literature update was performed through December 14, 2015.

For conditions in which pain and/or other subjective, patient-reported measures are the primary outcomes, randomized controlled trials (RCTs) are particularly important due to the expected placebo effect and the variable natural history. RCTs are also important because there may be numerous confounders of outcomes, and nonrandomized comparisons are prone to selection bias. Because of these factors, RCTs are essential to demonstrate the clinical effectiveness of amniotic membrane injections compared with alternatives such as continued medical management. Therefore, evidence reviewed for this policy focuses on RCTs.

**Osteoarthritis**
A feasibility study (N=6) of cryopreserved human amniotic membrane (C-HAM) suspension with amniotic fluid-derived cells (ReNu™) for the treatment of knee osteoarthritis was reported in 2015. A single intra-articular injection of the suspension was used, with follow-up of the patients at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analysis was not performed for this small sample. No adverse effects aside from a transient increase in pain were noted. An RCT is in progress.
**Plantar Fasciitis**

Two randomized pilot studies were identified on the treatment of plantar fasciitis with injection of micronized human amniotic membrane (HAM). One small (N=23) industry-sponsored double-blind study found similar improvements with injection of cryopreserved HAM (C-HAM; Clarix® Flo) compared with corticosteroid injection. Another industry-sponsored patient-blinded study (N=45) compared injection of saline versus 0.5 cc or 1.25 cc of dehydrated HAM (D-HAM; Amniofix®) in patients with symptoms recalcitrant to conservative treatment. In the two D-HAM groups in this study, scores on the American Orthopaedic Foot and Ankle Society Hindfoot Scale improved by about 50 points over the eight weeks of the study compared with 10 points for controls (p<0.001). FACES pain scores decreased from 8.7 of 10 at baseline to 0.8 at 8 weeks with D-HAM, compared with a decrease from 8.0 to 4.6 for controls (p<0.001). Longer follow-up is ongoing.

**Summary**

The evidence on human amniotic membrane (HAM) in individuals who have osteoarthritis or plantar fasciitis includes a feasibility study and small randomized controlled trials (RCTs). Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Literature on human amniotic membrane injection for regenerative medicine is at a very early stage, with only two pilot studies identified to date. These pilot studies show promising results for the treatment of plantar fasciitis with micronized amniotic membrane, and there is a feasibility study for a larger RCT of HAM injection for knee osteoarthritis. Additional studies with larger sample sizes and longer follow-up are needed to permit conclusions regarding the effect of this treatment on plantar fasciitis pain and osteoarthritis. Also needed are randomized controlled trials in humans to evaluate the efficacy of amniotic membrane injections for the treatment of other conditions, including but not limited to tendonitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statement**

No guidelines or statements were identified

**U.S. Preventive Services task Force Recommendations**

Not applicable

**Key Words:**


**Approved by Governing Bodies:**

HAM and amniotic fluid are considered to be minimally processed and not significantly changed in structure from the natural material. U.S. Food and Drug Administration (FDA) classify HAM material as banked human tissue and therefore, it does not require FDA approval. These tissues are regulated by the American Association of Tissue Banks.
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT Codes:
There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injections (e.g., 20550), the unlisted general musculoskeletal system code (20999) or if subcutaneous or intramuscular the therapeutic injection code (96372).

HCPCS Codes
- **Q4139** AmnioMAtrix or BioDMatrix, injectable, 1 cc
- **Q4155** NeoxFlo or Clarifix, 1 mg
- **Q4162** Amniopro flow, bioskin flow, biorenew flow, woundex flow, amniogen-a, amniogen-c, 0.5cc (Effective 01/01/16)
- **Q4163** Amniopro, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per square centimeter (Effective 01/01/2016)

There is no specific code for Amniofix. It is possible that it might be reported using the code for another MiMedx product, **Q4145**- Epifix, injectable, 1 mg, or the not otherwise specified code **Q4100**.

There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (e.g., 20550), the unlisted general musculoskeletal system code (20999) or the subcutaneous or intramuscular therapeutic injection code (96372).

**References:**


Policy History:
Medical Policy Panel, April 2015
Medical Policy Group, May 2015 (3): New policy adopted for this injection procedure – products already considered investigational (Q4139, Q4155, Q4145)
Medical Policy Administration Committee, June 2015
Available for comment June 1 through July 15, 2015
Medical Policy Group, November 2015: 2016 Annual Coding Update. Added new HCPCS code Q4162 and Q4163 to current coding
Medical Policy Panel, February 2016
Medical Policy Group, February 2016 (3): 2016 Updates to Description, Key Points, Key Words & References; no change in policy statement

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 plan contracts.