



# BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

## Amniotic Membrane and Amniotic Fluid Injections

**Policy #** 00458

**Original Effective Date:** 08/19/2015

**Current Effective Date:** 08/17/2016

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers injection of micronized amniotic membrane to be **investigational\*** for all indications.

Based on review of available data, the Company considers injection of amniotic fluid to be **investigational\*** for all indications.

### **Background/Overview**

Several commercially available forms of human amniotic membrane (HAM) and amniotic fluid can be administered by injection. Amniotic membrane and amniotic fluid injections are being evaluated for the treatment of various conditions, including tendonitis, plantar fasciitis, and 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 numerous 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<sup>®†</sup> Injectable (MiMedx), Clarix<sup>®†</sup> Flo and Neox<sup>®†</sup> Flo (Amniox), AmnioMatrix<sup>®†</sup> (Derma Sciences), AmnioPro<sup>™†</sup> (Human Regenerative Technologies), and AmnioGen<sup>™†</sup> (US Biologix). Amniotic fluid products that are cryopreserved and contain living cells include AmnioVisc<sup>™</sup> (previously named AmnioClear<sup>®†</sup> LCT from Liventa Bioscience) and OrthoFlo<sup>™†</sup> (MiMedx). PalinGen<sup>®†</sup> Flow and Sport Flow<sup>™†</sup> (Amnio ReGen Solutions) contains cryopreserved amniotic fluid and cryo-fractured amniotic membrane. ReNu<sup>™†</sup> (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, antifibroblastic, and antimicrobial properties. Human amniotic membrane is considered to be nonimmunogenic 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.

Human amniotic membrane is an established treatment for corneal reconstruction and is being evaluated for the treatment of a variety of conditions, including skin wounds, burns, leg ulcers, and prevention of

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tissue adhesion in surgical procedures. Additional indications that have been studied in preclinical 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. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricin, cholesterol, and cytokines. Injection of amniotic fluid is being evaluated for the treatment of pain and stiffness in patients with osteoarthritis.

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 Policy 00258.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Human amniotic membrane and amniotic fluid are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### **Rationale/Source**

This policy was created in 2015 with a search of the MEDLINE database 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. Randomized controlled trials 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 (epub). 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



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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 HAM. One small (N=23) industry-sponsored double-blind study found similar improvements with injection of 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 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 8 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.

### Ongoing and Unpublished Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT02318511 <sup>a</sup>	An Investigation of ReNu Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	150	Mar 2017
NCT02427191 <sup>a</sup>	A Prospective, Single-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection as Compared to the Saline Placebo Injection in the Treatment of Plantar Fasciitis (AmnioFix Injectable)	146	Dec 2017
	Prospective Multicenter Registry of Amniotic Fluid Treatment for Osteoarthritis (AmnioClear LCT)	470	

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

### Summary of Evidence

The evidence on HAM in individuals who have osteoarthritis or plantar fasciitis includes a feasibility study and small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Literature on HAM injections is at a very early stage, with only 3 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 clinical trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of this treatment on plantar fasciitis pain and osteoarthritis. Also needed are RCTs in humans to evaluate the efficacy of amniotic membrane and amniotic fluid 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.



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### References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Amniotic Membrane and Amniotic Fluid Injections" 7.01.149, 12:2015.
2. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine? Regen Med. Mar 2009;4(2):275-291. PMID 19317646
3. Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. Oct 2013;10(5):493-500. PMID 23902526
4. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(1):167-177.
5. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. Dec 18 2015. PMID 26683979
6. Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. Foot Ankle Int. Feb 2015;36(2):151-158. PMID 25249320
7. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. Oct 2013;34(10):1332-1339. PMID 23945520

### Policy History

Original Effective Date: 08/19/2015  
 Current Effective Date: 08/17/2016  
 08/06/2015 Medical Policy Committee review  
 08/19/2015 Medical Policy Implementation Committee approval. New policy.  
 08/04/2016 Medical Policy Committee review  
 08/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.  
 Next Scheduled Review Date: 08/2017

### Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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*CPT is a registered trademark of the American Medical Association.*

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	20550, 20999, 96372



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HCPCS	Q4139, Q4100, Q4145, Q4155
ICD-9 Diagnosis	All related diagnoses
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

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