Implantation of Intrastromal Corneal Ring Segments

Policy # 00164
Original Effective Date: 05/23/2005
Current Effective Date: 06/18/2014

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.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider implantation of intrastromal corneal ring segments (ICRS) as a treatment of keratoconus to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for implantation of intrastromal corneal ring segments (ICRS) as a treatment of keratoconus will be considered when all of the following criteria are met:

- Patients have experienced a progressive deterioration in their vision, such that they can no longer achieve adequate functional vision on a daily basis with their contact lenses or spectacles; and
- Patients are 21 years of age or older; and
- Patients have clear central corneas; and
- Patients have a corneal thickness of 450 microns or greater at the proposed incision site; and
- Patients who have corneal transplantation as the only other remaining option to improve their functional vision.

When Services Are Considered Investigational
Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers implantation of intrastromal corneal ring segments (ICRS) when criteria are not met to be investigational.*

Based on review of available data, the Company considers implantation of intrastromal corneal ring segments (ICRS) for all other conditions to be investigational.*

Note: The correction of refractive errors of the eye is considered an exclusion in most member contracts.

Background/Overview
Intrastromal corneal ring segments consist of micro-thin soft plastic inserts of variable thickness that are placed in the periphery of the cornea. ICRS have been investigated as a means of improving vision in diseases such as keratoconus and pellucid marginal degeneration, and for refractive surgery to correct mild myopia.
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Intrastromal corneal ring segments are flexible, crescent-shaped rings of polymethylmethacrylate that are placed in the periphery of the cornea. An incision is made in the cornea, and channels are created in it by rotating a lamellar dissector or by using a femtosecond laser. One or two corneal implant segments are introduced to each channel, and various implants with a range of implant thicknesses are available for different degrees of correction. They affect refraction in the eye by physically changing the shape of the cornea (flattening the front of the eye), thereby correcting the irregular corneal shape. If required, the implants can be removed at a later date.

Keratoconus is a progressive bilateral dystrophy that is characterized by paracentral steepening and stromal thinning that impairs visual acuity. Initial treatment often consists of hard contact lenses. A penetrating keratoplasty (i.e., corneal grafting) is the next line of treatment in patients who develop intolerance to contact lenses. While visual acuity is typically improved with keratoplasty, perioperative complications are an associated risk; long-term topical steroid use is required; and endothelial cell loss occurs over time, which is a particular concern in younger patients. As an alternative, a variety of keratorefractive procedures have been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or laser in situ keratomileusis (LASIK), but in general, results of these techniques have been poor. In deep anterior lamellar keratoplasty, pathologic corneal stromal tissue is selectively removed to the level of the Descemet membrane; followed by transplantation of a donor graft. Implantation of intrastromal corneal ring segments represents an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for a penetrating keratoplasty.

Pellucid marginal degeneration is a noninflammatory progressive degenerative disease, typically characterized by bilateral peripheral thinning (ectasia) of the inferior cornea. Deterioration of visual function results from the irregular astigmatism induced by asymmetric distortion of the cornea, and visual acuity typically cannot be restored by using spherocylindrical lenses. Rigid gas permeable contact lenses may be used to treat pellucid marginal degeneration. Intracorneal ring segment implantation, crescentic lamellar keratoplasty, penetrating keratoplasty, and corneal wedge excision have also been proposed.

In myopia, intrastromal inserts correct myopia by flattening the center of the cornea and represent an alternative to LASIK and other refractive surgeries. The proposed advantages of the intrastromal corneal rings are that their insertion does not affect the central cornea, and thus, their effect is not related to the healing process in the cornea. No corneal tissue is removed, and the implants are reversible.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
INTACS® represents an intrastromal corneal ring that has received approval by the U.S. FDA for two indications.

In 1999, INTACS inserts were approved through a premarket approval process (PMA) for the following labeled indication:
“The KeraVision Intacs are intended for the reduction or elimination of mild myopia (-1.00 to -3.00 diopters spherical equivalent at the spectacle plane) in patients:
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- Who are 21 years of age or older;
- With documented stability of refraction as demonstrated by a change of less than or equal to 0.50 diopter for at least 12 months prior to the preoperative examination; and
- Where the astigmatic component is +1.00 diopter or less."

In 2004, INTACS received an additional approval by the FDA through the humanitarian device exemption (HDE) process for the following indication:

“This device is indicated for the reduction or elimination of myopia and astigmatism in patients with keratoconus, who are no longer able to achieve adequate vision with their contact lenses or spectacles, so that their functional vision may be restored and the need for a corneal transplant procedure may potentially be deferred. The specific set of keratoconic patients proposed to be treated with INTACS prescription inserts are those patients:

- Who have experienced a progressive deterioration in their vision, such that they can no longer achieve adequate functional vision on a daily basis with their contact lenses or spectacles;
- Who are 21 years of age or older;
- Who have clear central corneas;
- Who have a corneal thickness of 450 microns or greater at the proposed incision site; AND
- Who have corneal transplantation as the only remaining option to improve their functional vision.”

Note: HDE does not require the manufacturer to provide data confirming the efficacy of the device but rather data supporting its “probable” benefit. The HDE process is available for devices treating conditions that affect fewer than 4,000 Americans per year.

Intrastromal corneal ring devices available outside of the U.S. include:

- INTACS SK
- Ferrara ICRS
- Keraring ICRS
- MyoRing intracorneal continuous ring (ICCR)

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source
Myopia
Approval by the U.S. FDA for the INTACS device was based on the results of a multi-institutional study involving 361 subjects with mild myopia. Subsequently, the 2-year results of this study were published in the peer-reviewed literature. These data suggested that the intrastromal rings predictably and effectively reduced or eliminated mild myopia (-1.00 to -3.00 diopter) and that the refractive effect was stable over time. However, mild myopia is effectively treated with either spectacles or contact lenses. In addition, as noted in the Benefits Applications section, many Plan benefits or contracts contain a specific exclusion for refractive eye surgeries.
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Keratoconus

The published data regarding INTACS for keratoconus consists primarily of single institution case series. These case series indicate that a substantial proportion of patients with keratoconus treated with this system have improved vision at up to 5-year follow-up. Most studies have reported improvements (in uncorrected or corrected visual acuity) in 75% to 80% of patients in whom changes in 2–3 lines of corrected or uncorrected visual acuity were considered success. Approximately 10% of patients required a second procedure because of an unsatisfactory initial result.

For example, in 2007 Colin and Malet reported 2-year follow-up from a prospective, single-center European study in 100 eyes with keratoconus (82 consecutive patients) and INTACS implantation. Patients had been referred for a penetrating keratoplasty procedure due to contact lens intolerance for correction of myopia and irregular astigmatism. INTACS inserts were removed from 4 eyes (4%) due to poor visual outcome or extrusion, and 14 eyes were lost to follow-up. Of the 82 remaining eyes (68 patients), both corrected and uncorrected visual acuity remained relatively stable between 1- and 2-years’ follow-up.

Several retrospective studies have reported stable vision at up to 5 years after INTACS implantation. Bedi et al. evaluated the risk of keratoconus progression in a study of 105 consecutive eyes (85 patients) that had undergone INTACS implantation. At 1-year follow-up, 1 eye had extrusion, and 12 (11.4%) had undergone removal of INTACS because of unsatisfactory results; these eyes were managed by penetrating or deep lamellar keratoplasty. Of the 105 eyes, 80% retained the INTACS implant and showed no keratoconus progression over 5 years of follow-up. Vega-Estrada et al. reported that in a series of 51 eyes, the improvement in vision obtained at 6 months after INTACS implantation was maintained out to 5 years postoperatively, although this study only included cases without significant changes in corneal topography over the 12 months before surgery.

Kymionis et al. reported 5-year follow-up on 28 patients (36 eyes) who had initially participated in a clinical trial for safety and efficacy of INTACS implantation in patients with keratoconus. In 5 patients (7 eyes), the INTACS segments were removed due to patient dissatisfaction. Five-year follow-up was reported for 17 eyes (59%). Refractive stability was obtained at the 6-month follow-up (spherical equivalent error at baseline -5.54 to -2.68 at 6 months) and remained stable throughout the 5-year follow-up (-3.02).

One retrospective study compared outcomes between intrastromal corneal ring segments (Keraring, n=30) and deep anterior lamellar keratoplasty (DALK, n=36) in patients with advanced keratoconus. One eye in the DALK group was converted to penetrating keratoplasty and was not included in the analysis. At 24 months’ follow-up, compared to preoperatively, the DALK group had significantly greater improvement in uncorrected and corrected distance visual acuity and significantly greater reduction in spherical equivalent, manifest cylinder, and K values. The uncorrected distance visual acuity improved by at least 1 line in all eyes in the DALK group. In the intrastromal corneal ring segment group, uncorrected distance visual acuity improved in 24 (80%) eyes, remained unchanged in 3 (10%) eyes, and decreased in 3 (10%) eyes.

Ongoing randomized clinical trials are evaluating combined treatment with INTACS and corneal collagen cross-linking to slow the progression of keratoconus.
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Astigmatism after Penetrating Keratoplasty

Several case series from Europe and South America have been identified in which intrastromal ring segments have been implanted for the correction of residual astigmatism after penetrating keratoplasty. In one of the studies, 9 patients received intrastromal ring segments (Kerarings) for high astigmatism (greater than 4 diopters) after penetrating keratoplasty. Mean keratometry decreased 4.17 diopters (from 46.28 to 42.11). Of the 9 patients, 1 reported night halos, and 2 had the implant removed due to compulsive eye rubbing and vascularization in the stromal tunnel. The authors noted that in patients with a corneal transplant with a diameter of 7.5 mm or smaller, INTACS intrastromal ring segments should not be used because the segments would be close to the graft-host junction.

Pellucid Marginal Degeneration

In 2009, Pinero and colleagues published a European multicenter retrospective analysis of 21 consecutive eyes in 15 patients with intrastromal corneal ring implantation (3 INTACS and 18 Kerarings) for pellucid marginal degeneration who had reduced best-corrected visual acuity and/or contact lens intolerance or dissatisfaction. At 6 months after surgery, uncorrected visual acuity had not changed; 17% of eyes lost lines of best-corrected visual acuity, and 44% of eyes gained 2 lines or greater of best-corrected visual acuity. Ring explantation was performed in 4 eyes (19%) due to visual deterioration during the follow-up. Mean keratometry decreased 1.76 diopters, from 44.95 diopters to 43.19 diopters at 6-months postoperatively.

A 2010 publication from Europe reported a retrospective analysis of intrastromal ring segment implantation (210-degree arc length Keraring) in 16 consecutive eyes of 10 patients with pellucid marginal degeneration who had reduced best-corrected visual acuity and dissatisfaction with spectacle and contact lens-corrected vision. At 12 months after implantation, uncorrected visual acuity improved from 1.69 logMAR to 0.83 logMAR. At the 36 month follow-up, patients (n=11) had gained a mean of 2.4 lines uncorrected visual acuity and 3.3 lines of spectacle-corrected visual acuity. There was a statistically significant reduction in manifest spherical refraction from -2.43 diopters to -0.72 diopters. For the 11 patients who completed 36-month follow-up, there was no significant change in outcome measures between 12 and 36 months. No intraoperative or postoperative complications were noted aside from white deposits around the segments in 1 patient.

Adverse events

Updated literature searches have identified a number of case reports of adverse events following implantation of ICRS, including persistent pain, extrusion, traumatic shattering, bacterial keratitis, fungal keratitis, corneal edema, deep corneal vascularization, Descemet membrane’s detachment, and alterations of extracellular matrix components and proteinases. In a multicenter series of 251 ICRS implantations, 58 eyes of 47 patients had the devices explanted. The main cause was found to be extrusion (48%), followed by poor refractive outcome (38%), keratitis (7%), and corneal melting and perforation (7%). The time from implantation to explantation ranged from 0.1 to 82 months.

In another study, 6 of 20 eyes had “significant” postoperative problems with regards to thinning and ring exposure, and a dense corneal infiltrate developed in 1 patient at 7 months. Histopathologic examination of 8 eyes that underwent penetrating keratoplasty after removal of INTACS inserts revealed keratocyte
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apoptosis. Further study long-term is needed to determine whether INTACS reduce or accelerate corneal thinning and progression of keratoconus.

Ongoing Clinical Trials
A search of online site ClinicalTrials.gov in August 2013 identified 2 large randomized trials on the treatment of keratoconus with combined use of ICRS and collagen cross-linking. A Phase II/III randomized trial (NCT01081561) will compare corneal collagen cross-linking in eyes with INTACS compared to eyes without INTACS. The study has an estimated enrollment of 400 subjects with estimated completion in 2015. Another Phase III trial (NCT01112072) will randomly assign subjects to receive collagen cross-linking immediately after, or 3 months after, INTACS implantation. Estimated enrollment is 160 subjects, with an estimated completion date of December 2014.

Summary
Clinical input strongly supports the use of ICRS in a select group of patients with advanced keratoconus whose only other option for restoration of visual function is the more invasive penetrating keratoplasty. Although questions remain regarding the impact of this procedure on long-term health outcomes, the risk of adverse events is decreased in comparison with the existing alternative (corneal transplant), and there is a potential (as yet unproven) to delay the need for the more invasive procedure. Therefore, use of ICRS may be considered medically necessary in patients who meet the FDA- HDE criteria for use of this device.

There is insufficient evidence to evaluate health outcomes in patients with pellucid marginal deterioration. Therefore, ICRS in this population are considered investigational.

References

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

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Policy History
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04/05/2005 Medical Director review
04/27/2005 Medical Policy Committee review
05/23/2005 Managed Care Advisory Council approval
02/01/2006 Medical Director review
02/15/2006 Medical Policy Committee review. Coverage changed from investigational to eligible with criteria.
02/23/2006 Quality Care Advisory Council approval
07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
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04/04/2007  Medical Director review
04/18/2007  Medical Policy Committee approval
06/13/2007  Medical Director review
06/20/2007  Medical Policy Committee approval. When services are considered not medically necessary section was deleted. Myopia was deleted from the statement “BCBS considers ICRS as a treatment of any other condition except keratoconus and myopia to be investigational”.
06/13/2007  Medical Director review
06/20/2007  Medical Policy Committee approval
07/02/2008  Medical Director review
07/16/2008  Medical Policy Committee approval. No change to coverage eligibility.
06/04/2009  Medical Director review
06/17/2009  Medical Policy Committee approval. No change to coverage eligibility.
06/03/2010  Medical Policy Committee review
06/16/2010  Medical Policy Implementation Committee approval. Title changed to “Implantation of Intrastromal Corneal Ring Segments.”
06/02/2011  Medical Policy Committee review
06/15/2011  Medical Policy Implementation Committee approval. No change to coverage.
06/14/2012  Medical Policy Committee review
06/20/2012  Medical Policy Implementation Committee approval. No change to coverage.
06/06/2013  Medical Policy Committee review
06/25/2013  Medical Policy Implementation Committee approval. No change to coverage.
06/05/2014  Medical Policy Committee review
06/18/2014  Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date:  06/2015

*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.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.
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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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