

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Intrastromal Corneal Ring Segments (ICRS[®])

Device Trade Name: INTACS[®] Prescription Inserts for Keratoconus

Applicant's Name and Address: Addition Technology, Inc.
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Sunnyvale, CA 94089-1330

Humanitarian Device Exemption (HDE) Number: H040002

Date of Humanitarian Use Device Designation: Filed: March 30, 2004

Date(s) of Panel Recommendation: None

Date of Good Manufacturing Practice Inspection: July 29, 2003

Date of Notice of Approval to Applicant: July 26, 2004

II. INDICATIONS FOR USE

INTACS[®] prescription inserts are intended 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 subset 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.

III. CONTRAINDICATIONS

INTACS® prescription inserts for keratoconus are contraindicated:

- in patients who have abnormally thin corneas or who have corneal thickness of 449 microns or less at the proposed incision site;
- in patients with collagen vascular, autoimmune or immunodeficiency diseases;
- in pregnant or nursing women;
- in the presence of ocular conditions, such as recurrent corneal erosion syndrome or corneal dystrophy, that may predispose the patient to future complications; or
- in patients who are taking one or more of the following medications: isotretinoin (Accutane®¹) and amiodarone (Cordarone®²).

IV. WARNINGS AND PRECAUTIONS

Warnings

- Some patients with large dilated pupil diameters (≥ 7.0 mm) are predisposed to low light visual symptoms postoperatively and should be appropriately advised.
- The long-term safety of INTACS® prescription inserts on endothelial cell density has not been established. Central endothelial cell density loss for myopic eyes implanted with INTACS® inserts was $1.3\% \pm 3.2\%$ (n=94) during the first postoperative year and $2.0\% \pm 3.2\%$ (n=94) during the second postoperative year. Additional long term data are being collected in the U.S. myopia clinical trial.
- Under mesopic conditions, patients may experience some loss in contrast sensitivity at low spatial frequencies (1.5 cycles per degree).

Precautions

- Use of the vacuum centering guide subjects the eye to increased intraocular pressure. Continuous application of vacuum should be limited to 3 minutes or less and to no more than 750 mBar. If it is necessary to reapply the vacuum centering guide, wait 5 minutes to allow normal vascular perfusion of the eye to occur before re-establishing suction.
- INTACS® prescription inserts are not recommended in patients with systemic diseases likely to affect wound healing, such as insulin-dependent diabetes or severe atopic disease.

¹ Accutane® is a registered trademark of Roche Pharmaceuticals

² Cordarone® is a registered trademark of Wyeth-Ayerst Laboratories.

- It is recommended that the corneal thickness at the 6 mm to 9 mm optical zone be at least 350 microns to allow for an adequate amount of corneal tissue above the INTACS® inserts.
- INTACS® prescription inserts are not recommended in patients with a history of ophthalmic *Herpes simplex* or *Herpes zoster*.
- INTACS® prescription inserts are not recommended in patients who are taking sumatriptan (Imitrex³) for migraine headaches.
- A temporary decrease in central corneal sensation has been noted in some patients.
- The safety and effectiveness of alternative refractive procedures or a corneal transplant procedure following the removal of INTACS® prescription inserts have not been established.
- INTACS® prescription inserts are intended for single use only; do not reuse or resterilize. In the event that different thicknesses of INTACS® prescription inserts are used during a procedure, please return the unused segments to Addition Technology.
- The safety and probable benefit of INTACS® prescription inserts for keratoconus have not been established:
 - in patients with progressive myopia or astigmatism, nuclear sclerosis or other crystalline lens opacity, corneal abnormality, or previous corneal surgery or trauma;
 - for patients under 21 years of age;
 - for corneas with a central thickness less than 480 microns, or peripheral thickness less than 570 microns; or
 - in long-term use.

V. DEVICE DESCRIPTION

INTACS® Prescription Inserts

INTACS® prescription inserts are an ophthalmic medical device designed for the reduction or elimination of myopia and astigmatism in patients with keratoconus so that their functional vision may be restored and the need for a corneal transplant procedure can potentially be deferred. When placed in the corneal stroma, outside of the patient's central optical zone, the product reduces the cone by flattening the cornea and for non-central keratoconus, repositions the cone centrally. INTACS® prescription inserts are designed to be placed in the periphery of the cornea, at approximately two-thirds depth,

³ Imitrex® is a registered trademark of Glaxo Group Ltd.

and are surgically inserted through a small radial incision in the corneal stroma. The placement of the incision will typically be temporal. However, it may vary depending on the astigmatic axis and the amount of keratoconus present in the specific eye to be treated. The INTACS® inserts are to be placed equidistant on each side of the incision. The INTACS® product has been designed to allow removal or replacement, if desired.

INTACS® prescription inserts are composed of two clear segments, each having an arc length of 150° (see diagram below). They are manufactured from polymethylmethacrylate and are available in three thicknesses: 0.250 mm, 0.300 mm and 0.350 mm. In order to reduce the myopia and the irregular astigmatism induced by keratoconus, two INTACS® inserts ranging from 0.250 mm to 0.350 mm may be implanted depending on the orientation of the cone and the amount of myopia and astigmatism to be reduced. The product is designed with a fixed outer diameter and width. INTACS® prescription inserts have a positioning hole located in the superior end of each segment to aid in surgical manipulation.

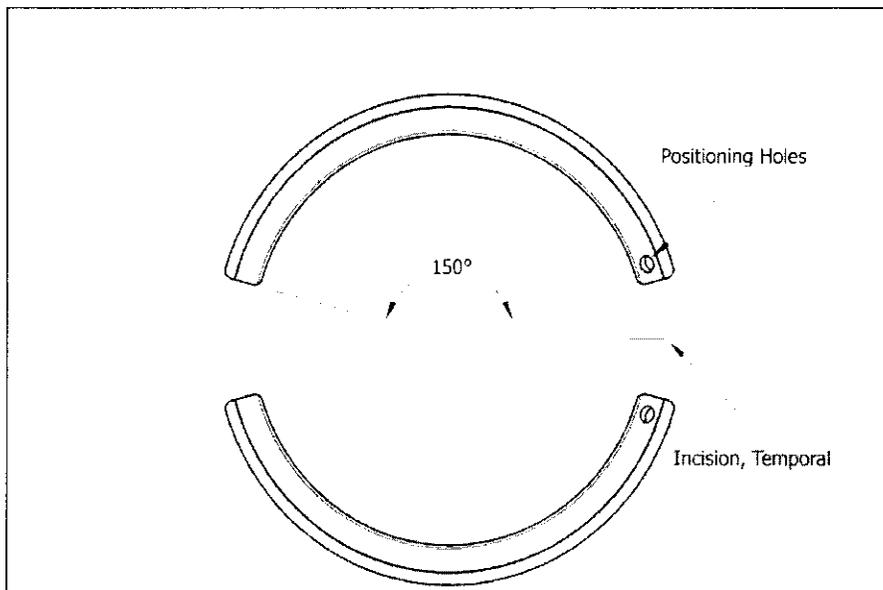


Diagram of INTACS® prescription inserts

Each keratoconic patient's eyes and disease state are unique; determination of the specific INTACS product placement and the thickness of the INTACS® inserts to be implanted will vary from patient to patient. The determination of which thicknesses of INTACS® prescription inserts to implant is dependent upon a number of variables (see physician's labeling for treatment nomogram), the most significant being the patient's preoperative manifest refraction spherical equivalent and the degree of asymmetric astigmatism.

Surgical Instruments

Addition Technology has a set of surgical instruments to be used in the INTACS® procedure. They include: corneal thickness gauges, glides, incision and placement marker, pocketing hook, pocketing lever, ring forceps, stromal spreader, vacuum centering guide with vacuum system and clockwise and counterclockwise dissectors. These instruments have been evaluated and cleared for marketing through the premarket notification (510(k)) process.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The specific subset of keratoconic patients proposed to be treated with INTACS® prescription inserts are those patients who have corneal transplantation as the only remaining option to improve their functional vision.

VII. MARKETING HISTORY

INTACS® prescription inserts for the treatment of keratoconus received the European Communities' CE mark on November 4, 2003 for the use of INTACS® in the treatment of keratoconus. The INTACS® insert for myopia has been marketed in the European Communities and other countries recognizing the CE mark since December 2, 1996 for the treatment of myopia. The INTACS® prescription inserts have also been marketed for the treatment of myopia in Canada since June 11, 1998 and the United States since February 10, 1999. INTACS® prescription inserts have not been withdrawn from any market for reasons relating to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The ocular complications/adverse events and clinical observations reported from the three keratoconus studies are representative of the clinical findings typically reported with INTACS® prescription inserts for the myopia indication approved under PMA P980031. The reported postoperative ocular complications/adverse event from the keratoconus studies include: lamellar channel deposits, incisional haze, visual symptoms, superficial placement, non-infectious lamellar keratitis, and neovascularization. The safety-related clinical findings reported from the use of INTACS® prescription inserts in keratoconic patients are similar to the clinical findings observed with the approved myopia indication for INTACS® inserts.

IX. SUMMARY OF PRECLINICAL STUDIES

Addition Technology referenced Premarket Approval (PMA) application P980031 for all preclinical studies. In the PMA, the applicant has performed testing in accordance with ANSI/AAMVISO 10993-1, "Biological Evaluation of Medical Devices," to establish the safety of the materials, processes and packaging components used in the manufacturing of the INTACS®. The results of these tests demonstrate that the INTACS® are nontoxic at the cellular, systemic, local and immunological levels.

Microbiological evaluations, including Limulus Amebocyte Lysate (LAL) and presterilization bioburden testing, were performed in accordance with the United States Pharmacopoeia (USP XXIII). The results of these tests were acceptable.

INTACS® were exposed to accelerated aging conditions to confirm that the packaging would continue to provide a sterile barrier 36 months after the date of manufacture. This testing was performed in accordance with ISO 11607: 1997, "Packaging for Terminally Sterilized Medical Devices." The results of this testing demonstrated that the package assembly seal strength and barrier properties are not adversely affected by normal manufacturing, handling and storage conditions for a time period equivalent to 36 months. The applicant is currently performing real-time aging to confirm the results of the accelerated aging.

Transit (or shipping) tests were conducted to determine if routine distribution and shipping activities would adversely affect the INTACS® and the packaging assembly. The transit tests were designed to simulate normal and expected transport conditions and were performed in accordance with ASTM D4169, "Performance Testing of Shipping Containers"; ASTM D642, "Test Methods for Compressive Resistance"; ASTM D999, "Test Methods for Loose Load Vibration"; ASTM D4728, "Test Methods for Random Vibrations"; and ASTM D5276, "Test Methods for Package Drop." The results of this testing demonstrated that the product and packaging were sufficient to withstand normal handling and transport conditions.

Validation studies were performed to demonstrate that the sterilization process would adequately sterilize the INTACS® within the package assembly. Sterilization was performed using 100% ethylene oxide (EO) gas. The validation studies were performed in accordance with ANSI/AAMI/ISO 11135: 1994, "Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization." The validation results demonstrated that the EO sterilization process is acceptable for sterilizing the INTACS® and does not adversely affect the functionality of the product and package assembly.

Additional validation studies were performed to demonstrate that the INTACS® could be successfully resterilized by the applicant. The purpose of the validation studies was to verify that a second sterilization cycle would not adversely affect or compromise biocompatibility, package integrity, visual and dimensional attributes, or product functionality. These studies demonstrated that the INTACS® could be resterilized by the applicant without adversely affecting the product or packaging.

An aeration process was validated for removing EO residuals from the packaged INTACS® product. The validation study was performed in accordance with ISO 10993-7: 1995, "Ethylene Oxide Sterilization Residuals" and the FDA-proposed residue limit for EO on intraocular lenses (Published in Federal Register 43, June 23, 1978). Based on the results of the validation study, the applicant concluded that the INTACS® and package assembly would not be adversely affected by the aeration process and that the process was capable of removing EO residuals from the INTACS® to acceptable limits. INTACS® were exposed to simulated aging conditions to determine whether exposure to ultraviolet (UV) radiation or hydrolysis would adversely affect the product's material strength or dimensional stability. Test results after simulated long-term exposure to UV radiation and hydrolysis demonstrated that the product was not adversely affected by these conditions; no material changes were observed.

X. SUMMARY OF CLINICAL INFORMATION

To support their HDE application, Addition Technology reported the findings from three keratoconus studies and referenced PMA P980031 (INTACS® insert for the treatment of myopia):

Study 1: Boxer-Wachler, B., N. Chandra, B. Chou, T. Korn, R. Nepomuceno, and J. Christie, "INTACS® for Keratoconus," *Ophthalmology*, Volume 110, Number 5, May 2003, pp. 1031-1040.

This was a retrospective, non-randomized comparative trial of 74 eyes of 50 keratoconic patients to evaluate the safety and efficacy of INTACS® prescription insert placement in keratoconic patients. The study utilized three PMA-approved INTACS® prescription insert thicknesses (0.25 mm, 0.30 mm and 0.35 mm) and the study results were used to establish the recommended INTACS® prescription insert treatment nomograms.

Of the 74 eyes implanted, 72% (53/74) experienced a gain of ≥ 2 lines in uncorrected visual acuity (UCVA), 19% (14/74) had no change in their UCVA after surgery, 9% (7/74) experienced a loss of ≥ 2 lines of UCVA, 45% (33/74) experienced a gain of ≥ 2 lines in best spectacle corrected visual acuity

(BSCVA), 51% (38/74) had effectively no change in BSCVA after surgery and 4% (3/74) experienced loss ≥ 2 lines of BSCVA.

The adverse events experienced during this clinical trial included secondary surgical reintervention (7%), loss of ≥ 2 lines UCVA and loss of ≥ 2 lines BSCVA (4%). Some of the surgical reinterventions were due to migration and externalization of the segments, foreign body sensation, inflammation and halos.

All subjects in this study were treated according to a new nomogram utilizing INTACS thicknesses that were approved in United States. Specifically, for eyes with preoperative SE < 3.00 D, 0.25 mm INTACS® were placed superiorly and 0.30 mm INTACS were placed inferiorly and for eyes with preoperative SE > 3.00 D, 0.25 mm INTACS® were placed superiorly and 0.35 mm INTACS were placed inferiorly. This nomogram is consistent with the nomogram pursued by Addition Technology in the HDE. Therefore, this article was considered most relevant to the evaluation of probable benefit. This article demonstrated: “Asymmetric INTACS® implantation can improve both uncorrected and best spectacle-corrected visual acuity and can reduce irregular astigmatism in corneas with and without corneal scarring.”

Study 2: Addition Technology sponsored clinical study for INTACS® Prescription Inserts.

A prospective clinical investigation was conducted at four European clinical sites to evaluate the safety and effectiveness of INTACS® prescription inserts for treatment of keratoconus. The study utilized the following PMA- and non-PMA approved INTACS® thicknesses: 0.25 mm, 0.30 mm, 0.35 mm, 0.40 mm and 0.45 mm. A total of 39 evaluable implant eyes diagnosed with keratoconus were followed for six months or greater postoperatively under protocol 01-99. Uncorrected and best corrected visual acuities manifest refraction, keratometry, intraocular pressure and pachymetry measurements were taken at scheduled postoperative exams.

Thirty-nine treated eyes were evaluated at 6 months and 62% (21/34) experienced a gain of ≥ 2 lines in BCVA, 32% (11/34) had no change in BCVA after surgery and 6% (2/34) experienced a loss of ≥ 2 lines of BCVA. Of the 32 treated eyes at 6 months (UCVA not performed preoperatively for two patients), 78% (25/32) experienced a gain of ≥ 2 lines in UCVA, 22% (7/32) had no change in their UCVA, 0% (0/32) experienced a loss of ≥ 2 lines of UCVA.

In addition to the loss of ≥ 2 lines BSCVA at 6 months (6%, 2/34), the adverse events experienced during this clinical trial included moderate or severe visual symptom consisting of: discomfort, itching, burning, photophobia, difficulty with night vision, glare and fluctuating vision (15.8%, 9/57; 18 eyes were from

another study was added to the 39 eyes in the original four European site). Dissatisfaction with visual symptoms was the reason for INTACS® prescription inserts removal from patients (12.3%, 7/57). A total of seven eyes had one or both INTACS® prescription inserts removed as a result of dissatisfaction with their outcome, primarily related to visual symptoms. After INTACS® prescription inserts removal, the eyes returned to their preoperative state, demonstrating that INTACS® prescription inserts can be removed from keratoconic eyes with no deleterious effect or permanent sequelae. These findings are consistent with INTACS® prescriptions inserts removals from myopic patients.

This study utilized three INTACS® thicknesses not available in the US. Therefore, this study had limitations with respect to the evaluation of the probable benefit of Addition Technology's proposed nomogram. However, this study supported safety evaluation of the HDE. This study demonstrated that in the majority of patients the INTACS® inserts restored the patient's functional vision and deferred the need for corneal transplantation.

Study 3: Siganos, C., G.D. Kymionis, N. Kartakis, M.A. Theodorakis, N. Astyrakakis, and I.G. Pallikaris. "Management of Keratoconus with INTACS®," *American Journal of Ophthalmology*, Volume 135, Number 1, January 2003, pp. 64-70.

This was a randomized clinical trial of 33 eyes of 26 keratoconic patients. The study utilized non-PMA approved 0.45mm INTACS® prescription insert thicknesses and the mean postoperative follow-up was 11.3 months. Of the 33 eyes implanted, 67% (22/33) experienced a gain of ≥ 2 lines in preoperative UCVA, 33% (11/33) eyes experienced no change and 0% (0/33) experienced a loss of ≥ 2 lines of UCVA, 45% (15/33) experienced an increase of ≥ 2 lines in preoperative BCVA, 52% (17/33) eyes experienced no change and 3% (1/33) experienced a loss of ≥ 2 lines in BCVA.

In the study, two patients had their INTACS® prescription inserts removed due to dissatisfaction. For one of these two patients, corneal transplant (penetrating keratoplasty procedure, PKP) was performed 3-month post- INTACS® prescription insert removal. The PKP was uneventful. A third patient was treated to a secondary surgical reintervention to remove the superior segment and reposition the inferior segment due topographical irregularity. The patient experienced subsequent improvement in UCVA and BCVA.

The authors of this article concluded after a mean postoperative follow-up of 11.3 months, that the INTACS prescription inserts seems to offer a minimally invasive alternate treatment before PKP for keratoconus patients with clear corneas and contact lens intolerance, especially in early stages of the disease with less topographic irregularities. Findings of this study provided supplemental safety information.

PMA P980031 – INTACS® for the treatment of myopia

The PMA P980031 information was also used to assess the INTACS® prescription inserts' safety. For the PMA, Addition Technology conducted two non-randomized, unmasked, multicenter U.S. clinical trials (Phase II and Phase III) to determine the safety and efficacy of INTACS® prescription inserts for the correction of myopia in a normal (non-keratoconus) population. The Phase II and Phase III trials were combined to form the PMA cohort used as the basis of FDA approval of the INTACS® prescription insert. Three INTACS® prescription insert thicknesses (0.25 mm, 0.30 mm and 0.35 mm) were evaluated with approximately the same number of eyes in each treatment. The patient's nonoperative fellow eye served as a control during the first six months postoperatively but, the fellow eye was eligible for INTACS® placement six months after the initial eye procedure. Complete follow-up data at the Month 12 exam were available for 97.6% (410/420) of the eligible initial implanted eyes.

Based upon the three articles and the PMA study, FDA determined that the INTACS® (0.25mm, 0.30mm and 0.35 mm) do not pose an unreasonable risk of injury in patients with keratoconus, who are no longer able to achieve adequate vision with their contact lenses or spectacles.

XI. RISK/PROBABLE BENEFIT ANALYSIS

Keratoconus is a non-inflammatory corneal disease that involves thinning of the corneal stroma. The advanced stages of keratoconus are typically characterized by progressive corneal thinning resulting in mixed myopic and irregular astigmatism. This progressive thinning results in a forward bulging of the cornea. As a keratoconic patient's disease progresses, the quality of their life continue to deteriorate due to the loss of visual acuity and the progressive development of a significant amount of irregular astigmatism. At this time, PKP is the only method available to restore functional vision to this subset of keratoconus patients.

This HDE is for INTACS® prescription inserts which are used 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 spectacle, so that their functional vision may be restored and the need for a corneal transplant procedure may potentially be deferred. There are several well-established risks associated with corneal transplant procedure. The major issue with corneal transplants is slow visual rehabilitation for up to 12 to 18 months following the procedure, graft rejection and graft astigmatism. Another important point is that corneal grafts have a limited life expectancy of approximately 10 to 15 years, which can be problematic for younger patients as they may require multiple corneal grafts during their lifetime.

The clinical data provided, although not adequate to demonstrate effectiveness, indicates that INTACS® prescription inserts provide a potential benefit of restoring some visual acuity in keratoconic patients while potentially deferring their need for a corneal transplant. Most patients implanted with INTACS® prescription inserts will still need to wear spectacles, soft toric or rigid gas permeable contact lenses.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

This HDE was not taken to an Ophthalmic Devices Panel (Panel) meeting because on January 12, 1999 the Panel reviewed the INTACS® PMA for its use in the treatment of myopia. At that meeting, the Panel recommended the PMA be approved subject to submission to and approval by the Center for Devices and Radiological Health (CDRH). On February 10, 1999, CDRH issued a letter advising that the INTACS® PMA was approvable subject to the submission of an amendment with changes as recommend by the Panel and required by FDA. The clinical issues raised by this HDE are sufficiently similar to those reviewed by the Panel in the PMA. Therefore, there were no new issues raised in the review of this HDE that required further Panel input.

XIII. CDRH DECISION

CDRH determined that, based on the data submitted in the HDE, that the INTACS® inserts for keratoconus (0.25 mm, 0.30 mm and 0.35mm thicknesses) will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health form using the device outweighs the risks of illness or injury, and issued an approval order on July 26, 2004.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

Boxer-Wachler, B., N. Chandra, B. Chou, T. Korn, R. Nepomuceno, and J. Christie, "INTACS® for Keratoconus," *Ophthalmology*, Volume 110, Number 5, May 2003, pp. 1031-1040.

Siganos, C., G.D. Kymionis, N. Kartakis, M.A. Theodorakis, N. Astyrakakis, and I.G. Pallikaris. "Management of Keratoconus with INTACS®," *American Journal of Ophthalmology*, Volume 135, Number 1, January 2003, pp. 64-70.