

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Names: Injectable Dermal Filler

Device Trade Name: Cosmetic Tissue Augmentation product (CTA)

Applicant: Anika Therapeutics, Inc.
236 West Cummings Park
Woburn, MA 01801

Premarket Approval (PMA) Application Number: P050033

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: December 20, 2006

II. INDICATIONS FOR USE

CTA is indicated for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

III. CONTRAINDICATIONS

- CTA is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- CTA is composed of hyaluronic acid, lidocaine and may contain trace amounts of gram positive bacterial proteins. CTA is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the CTA physician's labeling.

V. DEVICE DESCRIPTION

CTA is a sterile, nonpyrogenic gel implant, composed of hyaluronan produced by *Streptococcus equi* (bacterial fermentation) that is crosslinked and suspended in a buffer solution at a concentration of 28 mg/mL. CTA contains 0.3% lidocaine HCl. The finished product is provided in a pre-filled glass syringe at a volume of 1 mL, co-packaged with two 30 G. x ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES & PROCEDURES

Alternative therapies for cosmetic tissue augmentation include bovine collagen dermal fillers, human collagen dermal fillers, other hyaluronic acid-based dermal fillers, and autologous fat transfer. Other treatment options for the treatment of photo-damaged skin with its associated wrinkling and changes in texture and pigmentation include topical creams (containing e.g. retinoids), chemical peeling procedures or laser resurfacing. Deep wrinkles, folds, scars, and other depressed lesions are often treated with surgery (e.g. rhytidectomy).

VII. MARKETING HISTORY

CTA is a new product that has not yet been commercialized.

VIII. POTENTIAL ADVERSE EFFECTS ON HEALTH

In a study of 208 patients at 10 centers, symptoms reported in patient diaries during 14 days after initial treatment are listed in Table 1 by intensity of symptoms and Table 2 by duration of symptoms. Patients in the study were either injected with CTA in both nasolabial folds (NLF) (n=17) or CTA in one NLF and a human collagen dermal filler (Control) in the contralateral NLF (n=191). Eighty-eight percent (88%) of patients reported symptoms on both sides of the face following treatment. In most cases, symptoms (bruising, redness, swelling, pain, tenderness, itching, nodule formation) were of mild to moderate intensity and resolved in 7 days or less. Adverse events were reported on the physician case report form. Events occurring in > 2% of the 191 randomized patients are listed in Table 3. Many of these adverse events represent physician reporting of the same data reported by patients in Table 1. Local adverse events are reported in Table 3 by side of face; because of the “split-face” study design, causality of systemic adverse events cannot be assigned.

Table 1. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary

	CTA Side N=208	Control Side N=191	CTA Side Intensity				Control Side Intensity			
	Total reporting symptoms N (%)	Total reporting symptoms N (%)	Unknown N (%)	Mild N (%)	Mode- rate N (%)	Severe N (%)	Unknown N (%)	Mild N (%)	Mode- rate N (%)	Severe N (%)
Bruising	131 (63.0%)	94 (49.2%)	7 (3.3%)	45 (21.6%)	49 (23.6%)	30 (14.4%)	4 (2.1%)	58 (30.4%)	26 (13.6%)	6 (3.1%)
Redness	151 (72.6%)	124 (64.9%)	6 (2.9%)	45 (21.6%)	76 (35.5%)	24 (11.5%)	6 (3.1%)	71 (37.2%)	42 (22.0%)	5 (2.6%)
Swelling	181 (87.0%)	129 (67.5%)	11 (5.3%)	31 (14.9%)	78 (37.5%)	61 (29.3%)	7 (3.7%)	86 (45.0%)	34 (17.8%)	2 (1.0%)
Pain	108 (51.9%)	63 (33.0%)	6 (2.9%)	52 (25.0%)	40 (19.2%)	14 (6.7%)	2 (1.0%)	51 (26.7%)	9 (4.7%)	1 (0.5%)
Tenderness	145 (69.7%)	101 (52.9%)	11 (5.3%)	57 (27.4%)	57 (27.4%)	20 (9.6%)	6 (3.1%)	71 (37.2%)	20 (10.5%)	4 (2.1%)
Itching	83 (39.9%)	49 (25.7%)	7 (3.4%)	63 (30.3%)	10 (4.8%)	3 (1.4%)	2 (1.0%)	43 (22.5%)	4 (2.1%)	0 (0.0%)
Nodule formation	129 (62.0%)	112 (58.6%)	11 (5.3%)	39 (18.8%)	61 (29.3%)	18 (8.7%)	9 (4.7%)	69 (36.1%)	32 (16.8%)	2 (1.0%)

Table 2. Duration of Symptoms after Initial Treatment, Patient Diary

	CTA Side (N=208)				Control Side (N=191)			
	Number of Days				Number of Days			
	<=3 N (%)	4-7 N (%)	8-13 N (%)	14+ N (%)	<=3 N (%)	4-7 N (%)	8-13 N (%)	14+ N (%)
Bruising	56 (26.9%)	51 (24.5%)	17 (8.2%)	7 (3.7%)	47 (24.6%)	25 (13.1%)	16 (8.4%)	6 (3.1%)
Redness	79 (38.0%)	49 (23.6%)	14 (6.7%)	9 (4.7%)	78 (40.8%)	28 (14.7%)	13 (6.8%)	5 (2.6%)
Swelling	81 (38.9%)	77 (37.0%)	19 (9.9%)	4 (2.1%)	87 (45.5%)	28 (14.7%)	11 (5.8%)	3 (1.6%)
Pain	87 (41.8%)	15 (7.2%)	3 (1.6%)	3 (1.6%)	52 (27.2%)	5 (2.6%)	3 (1.6%)	3 (1.6%)
Tenderness	83 (39.9%)	52 (25.0%)	5 (2.4%)	5 (2.6%)	61 (31.9%)	31 (16.2%)	7 (3.7%)	2 (1.0%)
Itching	61 (29.3%)	13 (6.3%)	5 (2.6%)	4 (2.1%)	35 (18.3%)	7 (3.7%)	4 (2.1%)	3 (1.6%)
Nodule formation	27 (13.0%)	28 (13.5%)	48 (23.1%)	26 (12.5%)	24 (12.6%)	24 (12.6%)	46 (24.1%)	18 (9.4%)

Table 3. Adverse Events Occurring in >2% of Patients, Physician Case Report Form

Description of Adverse Event (WHO Preferred Term)	CTA Side (N=208) N (%)	Control Side (N=191) N (%)
Any Adverse Event	59 (27.7%)	37 (19.4%)
Injection Site Bruising	5 (2.1%)	1 (0.5%)
Injection Site Discoloration	3 (1.6%)	4 (2.1%)
Injection Site Erythema	4 (1.0%)	6 (3.1%)
Injection Site Edema	5 (2.6%)	0 (0.0%)
Nodule	17 (8.4%)	15 (7.9%)
Swelling	14 (6.8%)	5 (2.6%)
Contusion	15 (7.3%)	4 (2.1%)
Erythema	2 (1.0%)	4 (2.1%)
Swelling Face	7 (3.7%)	1 (0.5%)

No adverse events related to treatment were observed at the 9 and 12 month follow-up visits in the 101 subjects who participated in the extension phase of the study

Local adverse events

Local adverse events were observed by the physician in 59/208 subjects treated with CTA in the randomized study. Injection site reactions included bruising and edema. Additional non-injection site reactions of nodule formation, swelling, contusion and facial swelling account for the majority of adverse events observed. In most cases, symptoms (bruising, redness, swelling, pain, tenderness, itching, nodule formation) were of mild to moderate intensity and resolved in 7 days or less.

Non-local adverse events

Non-local adverse events occurred in 34/191 (17.8%) of the study subjects. Since each patient received both CTA treatment and control, the causality of these events could not be identified. Non local adverse events occurring in >2% of the subjects included Infections and Infestations occurring in 12 subjects (5.8%) (bronchitis, cystitis, diverticulitis, folliculitis, herpes zoster, influenza, onychomycosis, sinusitis, suture line infection and upper respiratory infection); Musculoskeletal disorders (2.4%) (arthralgia, back pain, osteoporosis, extremity pain); and Nervous System disorders (2.4%) (dizziness, headache and sinus headache).

Serious Adverse Events

Six subjects experienced serious adverse events. One event (i.e., injection site cellulitis) was judged definitely related to study treatment. The remaining serious adverse events (i.e., difficulty breathing, dizziness and chest pain) were not considered related to study treatment.

Retreatment Phase

90 patients enrolled in an open label retreatment extension study 6 months after their final treatment to achieve optimal correction. The safety profile observed during the 1 and 3 month follow-up was similar to that described above in the pivotal study.

IX. NONCLINICAL STUDIES

The clinical trial of CTA was conducted using CTA formulated with HA from an avian source. Commercial CTA will be formulated with HA from a bacterial fermentation source. Nonclinical studies demonstrated that the CTA formulated with avian sourced HA was safe to be evaluated in clinical studies, and that CTA formulated with fermented sourced HA is equivalent to CTA used in the clinical trial.

Biocompatibility Testing

Both the avian- and fermentation-derived CTA devices were tested in accordance with ISO 10993 "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" for devices in contact with tissue and bone for durations of greater than 30 days and in compliance with FDA GLP regulations. Test results are summarized in Table 5.

Table 5. Summary of Anika CTA Biocompatibility Test Results

Test	ISO Reference	Test Results
Genotoxicity-Bacterial Reverse Mutation	ISO 10993-3	Test article was nonmutagenic
Genotoxicity- <i>In Vitro</i> Chromosomal Aberration	ISO 10993-3	No evidence of genotoxicity
Genotoxicity-Mouse Bone Marrow Micronucleus	ISO 10993-3	No evidence of genotoxicity No evidence of cellular toxicity
Cytotoxicity-Agarose Overlay Method	ISO 10993-5	No evidence of cell lysis or toxicity
ISO Maximization Sensitization	ISO 10993-10	No evidence of delayed contact sensitization
Systemic Toxicity	ISO 10993-11	No evidence of systemic toxicity
Rat Chronic Toxicity-13 week, subcutaneous implant	ISO 10993-11	Slight irritant following subcutaneous implantation; no evidence of systemic toxicity, no changes in histopathology, hematology values, or clinical chemistry of biological significance or related to treatment.
Implantation Test-Intradermal Injection in Guinea Pig	ISO 10993-6	Slight irritant following intradermal injection; present at the injection sites up to 24 weeks post-injection

Design Verification Testing

Design verification testing was conducted to compare the avian and fermented HA raw materials and finished products and to demonstrate that the two raw materials are equivalent, that the change in raw material source did not affect the finished product, and that design outputs meet design inputs. The results of the raw material comparison testing (Table 6) demonstrated that the HA from the avian source is comparable to the HA produced by bacterial fermentation. The design verification testing of finished CTA product (Table 7) demonstrated that CTA made from the two HA raw materials (avian and fermented) is comparable and that all design outputs for the fermented CTA product met design inputs.

Table 6. Comparability Studies for Avian and Bacterial HA

Test	Result / Conclusion
Molecular Weight (MW)	The average MW for three lots of avian (797.8 kD) and fermented (930.3 kD) HA were comparable
Infrared (IR) spectroscopy	The IR Spectra for avian and bacterial HA are comparable
Nuclear magnetic resonance (NMR) spectroscopy	The NMR Spectra for avian and bacteria HA are identical
Endotoxin	All values observed with avian (n=3) and fermented (n=3) lots were below the specification of 0.03 EU/mg
Bioburden	All avian (n=3) and fermented (n=3) lots had < 10 cfu/g with regard to bacteria and yeast and no detectable pathogens
Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)	The protein concentrations observed in the SDS-PAGE of avian and bacterial HA are equivalent
Ultraviolet (UV) absorbance	The average A_{260nm} for avian lots (n=3) 0.069 were similar to, but less than the average absorbance observed with bacterial HA (i.e., 0.125)
Iron Content	All values observed with avian (n=3) and fermented (n=3) lots were less than 80 ppm
Heavy Metals	All values observed with avian (n=3) and fermented (n=3) lots were less than 20 ppm

Table 7. Comparison of CTA Final Products Prepared from Avian HA (n=3 lots) and Bacterial HA (n=3 lots)

Test	Result / Conclusion
Appearance	Avian and bacterial-derived CTA were both clear and colorless
Sterility	All avian and bacterial CTA lots were sterile
Endotoxin	All avian and bacterial CTA lots had endotoxin values < 0.08 Endotoxin Units/ml
Residual solvents	All lots of avian and bacterial CTA met the specifications for residual levels of dimethyl sulfoxide, ethanol, acetone and methanol
Residual Mercury	All lots of avian and bacterial CTA had values < 0.005 ppm
pH	All lots of avian and bacterial CTA met the specification of 6.2 – 7.6
Osmolality	The average value observed with 3 lots of bacterial CTA (i.e., 300 mOsm) met the specification of 280 – 340 mOsm
Crosslinked HA Concentration	All lots of avian and bacterial CTA were within the 21 – 29 mg/ml specification
Low Molecular Weight Hyaluronic Acid Fragments	The average fragments concentrations were 0.04% for bacterial CTA and 0.06% for avian CTA
Crosslinker Concentration	The Abs _{250nm} for avian and bacterial CTA were similar
Durability	The average values for resistance to hyaluronidase were similar for bacterial (i.e., 86.2%) and avian CTA (71.2%)
Extrusion Force	Forces between 3-5 lbs were measured for all lots of bacterial and avian CTA

The following additional tests were performed to further characterize the final CTA device.

Table 8. Other Preclinical Studies with the Final CTA Product

Test	Results / Conclusions
Lidocaine Bio-Availability	<i>In vitro</i> testing demonstrated that over 90% of the lidocaine elutes from CTA within 2 minutes.
Shelf-life via tests for: Sterility, Visual appearance, Endotoxin, Viscoelastic Properties of Crosslinked Gel (i.e., Storage Modulus G' and Decrease in G' as a Function of Time Due to Enzyme Digestion), UV Absorbance of the Crosslinked HA, pH, Osmolality, HA Concentration (Gravimetric), Extrusion Force, HA fragments and Lidocaine concentration	Stability studies support an expiration date of 15 months

X. CLINICAL STUDIES

The following is a summary of the pivotal study (i.e., “A Randomized, Controlled, Paired Double-Blind, Multicenter, and Pivotal Study of Cross-Linked Hyaluronic Acid in the Treatment of Dermal Contour Deformities”, Study CTA0302). Following this discussion is a summary of the re-treatment study “Study CTA0302-1 “An Extension to the Randomized, Controlled, Paired, Double-Blind Multicenter, Pivotal Study of Cross-Linked Hyaluronic Acid (Anika CTA) in the Treatment of Dermal Contour Deformities.”

Study Design:

The safety and effectiveness of CTA for the treatment of facial wrinkles and folds was evaluated in a prospective, randomized, controlled, paired, double-blinded, multi-center, pivotal clinical study. Randomized subjects underwent treatment with CTA in one NLF and control implant (a human collagen dermal filler) in the contralateral (NLF).

Up to three bilateral treatments (i.e., initial treatment and up to 2 touch-up treatments), approximately 2 weeks apart, were allowed. At 2 and 4 weeks after each treatment, a Blinded Evaluator assessed the level of correction. If correction was less than optimal after the first or second treatment, the Investigator re-treated the under-corrected NLFs using the same respective treatment materials as in the initial treatment. The blinded evaluator and subject remained blinded to the randomized treatment assignment.

Routine follow-up visits for safety and effectiveness occurred at 2 weeks after each treatment and at 1, 4, 6, 9 and 12 months after the last treatment. The blinded reviewer and subject independently evaluated the severity of the subjects NLF using the Lemperle Rating Scale (LRS), (i.e., a validated 6-point wrinkle severity scale ranging from 0 = no wrinkles to 5= very deep wrinkle, redundant fold).

Study Endpoints

- *Effectiveness*

The primary effectiveness endpoint was the blinded evaluator’s LRS score at 6-months following the last touch-up (at which optimal correction was achieved). Secondary effectiveness endpoints included: blinded evaluator LRS at 1- and 4-months; subject LRS at 1-, 4- and 6-months; proportion of nasolabial folds returning to baseline at 6-months; number of treatment sessions and volume of material to obtain optimal correction. The primary endpoint, the LRS score, is a 6-point scale. A change in LRS of 1 was considered to be clinically significant. Optimal correction was defined to be the best possible cosmetically pleasing result and 100% correction; unlimited touch-ups were permitted to achieve optimal correction.

- *Safety*

Adverse outcomes were evaluated by comparing the incidence and severity of clinical events reported in patient diaries during the 14 days after treatment and the adverse events assessed during study visits by investigator.

Patient Enrollment

The study enrolled subjects with bilateral NLF with a 3 or 4 LRS score. Patients were excluded if they had: an allergy to avian products, sensitivity to lidocaine, previous exposure to soft tissue augmentation in any area of the face, aesthetic or dermatologic procedures in the target area of the face in the past 6 months, (i.e., medium depth or deep chemical peel, facial wrinkle therapies (e.g., Accutane and Renova), facial silicone injections, facial surgery (facelift), or facial dermabrasion). Laser resurfacing of the face in the last 56 months was also an exclusion criterion. In addition, subjects were excluded if they had: HIV/AIDS, Hepatitis C, active facial acne lesions or severe acne scarring that might affect NLF assessment, active skin diseases or inflammation on or near the NLF (e.g., psoriasis, herpes zoster, infection and discoid lupus), or if they received immunosuppressive therapy, anticoagulant therapy, chemotherapy or systemic corticosteroids within the last 3 months or a history of bleeding disorders or connective tissue disease. Patients were also excluded if they were involved in any research with an investigational product or new application of an approved product within 30 days of screening. Finally, patient enrollment also required cessation of anti-platelet therapy for 7-10 days prior to each treatment and a commitment to forgo dermabrasion, laser resurfacing, facial wrinkle therapies, all aesthetic facial surgeries and all other soft tissue augmentation for the study duration.

- *Patient Accounting*

A total of 208 patients were treated at 10 centers, including 17 “roll-in” patients implanted with CTA in both NLF and 191 subjects treated with CTA in one NLF and Control in the contralateral NLF (n=191). Accounting of these patients is presented below in Table 9.

Table 9. Patient Accounting

	All subjects N=208	Randomized N=191	Roll-in N=17
Eligible/randomized	208	191	17
Withdrew prior to month 6	9 (4.3%)	6 (3.1%)	3 (17.6%)
Completed 6 months	199 (95.7%)	185 (96.9%)	14 (82.4%)
Eligible for re-treatment	151 (72.6%)	140 (73.3%)	11 (64.7%)
Participated in re-treatment*	90 (43.3%)	84 (44.0%)	6 (35.3%)
Eligible for extended follow-up study (not retreated)	101 (48.6%)		
Subjects at 9 month visit (not retreated)	90 (43.3%)		
Subjects at 12 month visit (not retreated)	84 (40.4%)		

*For accounting of retreatment patients, see below

- *Baseline Demographics*

The randomized study population (n=191) was composed of 16 men and 175 women between the ages of 30 and 77 years of age. The baseline demographics are displayed in Table 10.

Table 10. Study Population Demographics

Demographic	N (%)
Total study enrollment (randomized)	191 (100%)
Age (mean ± standard deviation)	52.6 ± 8.5
Gender	
Male	16 (8.4%)
Female	175 (91.6%)
Race	
Caucasian	172 (90.1%)
Black or African-American	7 (3.7%)
Asian	4 (2.1%)
Other	8 (4.2%)
Ethnicity	
Hispanic or Latino	18 (9.4%)
Not Hispanic or Latino	173 (90.6%)
Cigarette Use (Pre-treatment)	
Non-Smoker	90 (47.1%)
Current Smoker	37 (19.4%)
Former Smoker	64 (33.5%)
Sun Exposure (Pre treatment)	
To Natural Sunlight	
Minimal	59 (30.9%)
Moderate	99 (51.8%)
High	33 (13.3%)
To Artificial Sunlight	
None	127 (66.5%)
Minimal	54 (28.3%)
Moderate	10 (5.2%)
High	0 (0.0%)

- *Ethnic Representation*

The majority of patients enrolled in the study were Caucasian (90.1 %). Minority populations comprised 9.9 percent of the study population. While the study did not directly record Fitzpatrick skin type as part of the case report forms, on retrospective analysis they believe that between 16-18 subjects had skin types between 4-6 on the Fitzpatrick scale, (i.e., 7 African Americans, 4 Asian, 1 Native American, 4 Hispanic and 2 Non-Hispanic subjects).

- *Treatment Material Delivered*

The mean total volume injected per nasolabial fold for all treatment sessions (initial and touch-ups) was 1.2 mL for the CTA side and 1.9 mL for the control. Forty-seven (47) CTA sides (24.6%) required one or more touch-ups, whereas 61 (31.9%) of control sides required one or more touch-ups. No randomized CTA NLF and two control-treated NLFs required three touch ups.

Effectiveness Results

The primary effectiveness results for CTA based on the Blinded Evaluator assessment of NLF severity at 6 months are presented in Table 11. The blinded evaluator LRS scores demonstrated non-inferiority of CTA to Control.

Table 11. Mean Blinded Evaluator LRS Scores

Timepoint	N	CTA	Control	P-Value
Pretreatment	191	3.5	3.5	0.8733
Optimal Correction	188	1.1	1.1	0.2586
4-Months	175	2.2	2.7	<0.0001*
6-Months	182	2.7	3.0	0.0001*

* p-values are from a paired comparison using McNemar's test.

Safety Results

- *Adverse Events*

The reported adverse events are presented in section VIII.

- *Antibody Testing*

A pre-existing antibody response against CTA was observed in 5/208 (2.4%) subjects and 18/208 (8.7%) subjects developed a response after CTA injection. 6/18 subjects with elevated anti-CTA titers post-treatment experienced adverse events at the injection site that were judged related to device administration. This proportion of adverse events is similar to that observed in the entire CTA population 59/208 (27.7%). While most reactions were mild in severity, one severe case of swelling and one severe case of inflammation were reported.

Other Clinical Studies with CTA

- *Extension Study and Retreatment*

185/191 subjects who completed the 6 month evaluation were eligible to continue in an extension phase of the study. All subjects who had a blinded LRS evaluation which

worsened by 2 or more points were eligible for CTA retreatment (which was a total of 140 subjects). 84 of these subjects, plus an additional 6 patients from the “roll-in” phase of the study underwent retreatment. These subjects were followed for safety for 3 months following treatment. Please refer to Section VIII (Adverse Events) for a discussion of study outcomes.

101 Subjects who opted not to undergo retreatment as well as those who were ineligible for retreatment participated in the extended follow-up evaluation through 9 and 12 months. 90 subjects were followed through 9 months and 84 subjects through 12 months. Please refer to Section VIII (Adverse Events) for a discussion of study outcomes.

XI. CONCLUSIONS DRAWN FROM STUDIES

Based on both blinded evaluator and subject assessments during the CTA0302 clinical study, CTA was shown to be effective and non-inferior to an approved human collagen dermal filler. Reasonable assurance of safety has also been demonstrated by the short duration and generally mild/moderate severity of adverse events observed.

The *in vitro* and *in vivo* studies performed to test CTA demonstrate that: 1) CTA is biocompatible; 2) fermented HA is comparable to avian-derived HA in all tested specifications and characteristics; 3) CTA produced using fermented HA is comparable to CTA made with avian-derived HA; and 4) the finished CTA product, when manufactured in accordance with the approved design outputs, meets all user requirements and design inputs.

Therefore it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risks of illness or injury when used as indicated in accordance with the direction for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515c(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. FDA DECISION

FDA issued an approval order on December 20, 2006.

The applicant’s manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

To better understand the safety of the device in patient populations that were underrepresented in the clinical study, the sponsor was requested to perform an open-

label, longitudinal, uncontrolled, Post Approval study in a minimum of 100 patients with Fitzpatrick Skin Types 4, 5 or 6 at 10 or more U.S. centers. These patients will have elected to undergo nasolabial fold treatment with intradermal injection of CTA and will be followed for a minimum of 24 weeks to assess pain, tenderness, redness, ecchymosis, swelling, itching, mass (nodule / cyst / abscess) formation, dermal pigmentation and keloid changes at the site of injection.

XIV. APPROVAL SPECIFICATIONS

Direction for use: See the 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