CTA
Injectable HA Gel

CAUTION: Federal (U.S.) Law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

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.

INDICATION
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).

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.

WARNINGS
- CTA must not be implanted into blood vessels. Implantation of CTA into dermal vessels may cause vascular occlusion, infarction or embolic phenomena.
- Use of CTA at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes or hives) or infection is present should be deferred until the inflammatory process has been controlled.
- Injection site reactions to CTA have been observed consisting mainly of short-term inflammatory symptoms starting early after treatment and lasting ≤ 7 days duration. Refer to the adverse events section for details.

PRECAUTIONS
General
- STERILE CONTENTS. The pre-filled syringe is intended for single use only. The contents of the syringe should be used immediately after opening. Discard any unused CTA. Do not resterilize.
- Do not use CTA if the package has been opened or damaged or beyond the expiration date cited on the package.
- Based on preclinical studies, patients should be limited to 30 mL of CTA per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness of CTA for the treatment of dermal contour defects other than nasolabial folds (e.g., lips) has not been established.
- The long-term safety and effectiveness of CTA beyond one year have not been investigated.
- As with all transcutaneous procedures, CTA implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of CTA for use during pregnancy, in breastfeeding females and in patients under 18 years has not been established.

- The safety of CTA in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.
- CTA should be used with caution in patients on immunosuppressive therapy.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal regulations.
- CTA is a translucent gel without visible particulates. In the event that the contents of the syringe show signs of separation, do not use the syringe and notify Anika Therapeutics at 800-XXX-XXXX.
- Patients who are using substances that reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs, may, as with any injection, experience increased bruising or bleeding at injection sites.
- The patient should be informed that he or she should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather until any initial swelling and redness has resolved and puncture sites have healed.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with CTA, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if CTA is administered before the skin has healed completely after such a procedure.

ADVERSE EVENTS

In a randomized, controlled study to evaluate safety and effectiveness, 208 patients at 10 centers, were either injected with CTA in both nasolabial folds (NLF) (n=17) or CTA in one NLF and Cosmoplast® in the contralateral NLF (n=191). Symptoms reported in patient diaries during 14 days after treatment are listed in Tables 1 and 2. Symptom-related Adverse Events recorded by investigators at study visits are presented in Table 3.

Table 1: Maximum Intensity of Symptoms after Treatment, Patient Diary

	CTA Side N=208	COS Side N=191	CTA Side Intensity				COS 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%)

COS=Cosmoplast®

Table 2: Duration of Symptoms after Treatment, Patient Diary

	CTA Side (N=208) Number of Days				COS Side (N=191) Number of Days			
	<=3 N (%)	4-7 N (%)	8-13 N (%)	14+ N (%)	<=3	4-7	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 (19.9%)	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%)

COS=Cosmoplast®

Table 3: Adverse Events Occurring in >2% of Patients, CTA, Physician Reported

Description of Adverse Event (WHO Preferred Term)	**CTA Side** (N=208) N (%)	**Cosmoplast 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%)

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 and association of these events could not be identified.

Serious Adverse Events

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

Extension Study and Retreatment
185/191 subjects who completed the 6 month evaluation were eligible to continue in an extension phase of the study. No adverse events related to treatment were observed at the 9 and 12 month follow-up visits for the 101 subjects who were not retreated, but participated in the extension phase of the study.

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

CLINICAL TRIALS

A. I. U.S. Pivotal Study

A. 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. Subjects underwent treatment with CTA in one NLF and control implant (Cosmoplast human collagen) 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 a validated 6-point wrinkle severity scale (ranging from 0 = no wrinkles to 5= very deep wrinkle, redundant fold).

B. Study Endpoints

The primary effectiveness endpoint was the blinded evaluator's Lemperle Rating Scale (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.

C. Study Population

A total of 191 subjects (30 to 77 years of age) were randomized and treated and 185 (96.9%) completed the 6 month follow-up period. Demographics are outlined in Table 4.

Table 4: 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%)

D. 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 Cosmoplast® side (control). Forty-seven (47) CTA sides (24.6%) required one or more touch-ups, whereas 61 (31.9%) of Cosmoplast® sides required one or more touch-ups. No randomized CTA NLF and two control-treated NLFs required three touch ups.

E. Effectiveness Results

The primary effectiveness results for CTA based on the Blinded Evaluator assessment of NLF severity at 6 months are presented in Table 5.

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