

**CONFIDENTIAL**

CTA Commercial U.S. Package Insert  
Revision Date: 10/12/06

**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  $\leq 7$  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			
			Unknown N (%)	Mild N (%)	Moderate N (%)	Severe N (%)	Unknown N (%)	Mild N (%)	Moderate 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 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%)

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.

**Table 5: Mean Blinded Evaluator LRS Scores**

Timepoint	N	CTA	Cosmoplast®	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.

The blinded evaluator LRS scores demonstrated non-inferiority of CTA to Cosmoplast.

**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(33%) 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.

**HOW SUPPLIED**

CTA® is supplied in a single-use glass syringe with a luer-lock fitting. The product is presented as a sterile, non-pyrogenic gel in a 1.0 mL syringe. Fill volume varies by presentation and is stated on the syringe label and carton. A rubber cap is provided on the syringe tip to prevent leakage and protect sterility of the product. The CTA syringe components contain no latex. One 30 G. x ½” sterile needle is co-packaged with each syringe of CTA. Two patient record labels are provided.

**DIRECTIONS FOR USE**

**Assembly of Needle to Syringe**

For safe use of CTA, it is important that the needle is properly assembled onto the syringe. Use the 30 G. x ½” needle provided.

1. Carefully unscrew the syringe tip cap while securely holding the syringe Luer adapter.
2. With a loose grip on the narrow part of the needle shield, mount the needle on the luer-syringe lock by screwing clockwise until counterpressure is felt.
3. With a firm grip on the wider part of the needle shield, press and turn the needle further until secure (approximately a quarter turn).
4. Remove the needle shield by pulling the shield straight away from the syringe, ensuring not to twist the shield during removal.

**Injection of CTA**

1. Prior to injection, counsel the patient regarding the appropriate indications, risks, benefits and expected responses to CTA treatment. Advise the patient of necessary precautions and that touch-ups may be required to achieve and maintain optimal correction.
2. Assess the patient’s need for pain management and provide anesthetic per standard of care.
3. Clean the area to be treated with suitable antiseptic solution.

4. Before injecting the patient, depress the syringe plunger until a droplet of CTA is visible at the tip of the needle.
5. Insert the needle at an angle of approximately 30° parallel to the length of the wrinkle or fold. The bevel of the needle should face upwards, and CTA should be injected into the mid to deep dermis. This can be ascertained by observing a subtle elevation of the defect without any blanching following injection. If CTA is injected too deep or intramuscularly, the duration of effect may be shorter.
6. Inject CTA applying even pressure on the plunger rod while slowly pulling the needle backwards. The wrinkle should be lifted and eliminated by the end of the injection. It is important that injection be stopped just before the needle bevel is pulled out of the skin to prevent material from leaking out or being placed too superficially in the skin.
7. The defect should not be overcorrected but filled such that the contour depression is at the level of the surrounding skin (i.e., almost 100% correction). Do not overcorrect. With dermal contour deformities, the best results are obtained if the defect can be manually stretched to the point where the deformity is eliminated. The degree and duration of correction depend on the character of the defect treated, tissue stress at the implant site, depth of the implant in the tissue and injection technique. Markedly indurated defects may be difficult to correct.
8. Specific injection technique with regard to depth of injection and administered quantity of CTA may vary. The linear threading technique, serial puncture technique and a combination of the two have been used with success.
9. When injection is completed, the treated site may be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against underlying superficial bone to obtain optimal results. Excessive massage is not recommended.
10. If “blanching” is observed on injection (i.e., the overlying skin turns a whitish color), injection should be stopped immediately and the area massaged until it returns to a normal color.
11. If the wrinkle or fold needs further treatment, the same procedure should be repeated with several punctures of the skin until a satisfactory result is obtained. Additional treatment with CTA may be necessary to achieve desired correction. In patients who have localized swelling after injection, the degree of correction may be difficult to judge immediately after treatment. In this case, touch-up injections at 1-2 weeks after the initial treatment may be indicated.
12. Typical material usage for each treatment session is less than 1.5 mL per treatment site.
13. Patients should be advised to apply ice intermittently to the treated sites for 24 hours after injection to minimize swelling.
14. Patients may have mild to moderate injection site reactions, which typically resolve in a few days.

**CAUTION:** Do not reshield needles. Recapping by hand is a hazardous practice and should be avoided. Discard used syringes and needles in approved sharps containers.

#### **PATIENT INSTRUCTIONS**

It is recommended that the following information be shared with patients:

- To report an adverse reaction, phone Anika Therapeutics at 800-XXX-XXXX.
- Within the first 24 hours after injection, patients should avoid strenuous exercise, extensive sun or heat exposure or alcoholic beverages. Exposure to any of these

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conditions may cause temporary redness or darkening of needle puncture sites, swelling and/or itching at the injection sites.

- Make-up may be applied a few hours post-treatment if no complications are present (e.g., open wounds, bleeding or infection).

**STORAGE**

- CTA should be stored refrigerated or at room temperature (2-25°C, 36-77°F). Do not freeze.
- CTA is a 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 XXX-XXX-XXXX.

**Manufactured and distributed by:**  
Anika Therapeutics, Inc.  
236 West Cummings Park  
Woburn, Massachusetts USA 01801

U.S. Patent 6,537,979 B1. U.S. Patent Pending US10/743,557.

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**CTA Product (Cosmetic Tissue Augmentation)  
Patient Information**

*Review this brochure carefully before beginning your CTA treatment.*

*The information in this brochure is not meant to replace information provided by your physician or healthcare provider. You should always ask your physician or healthcare provider about your actual diagnosis, treatment and care.*

**What is CTA?**

CTA is new type of dermal filler that is used to correct facial wrinkles and folds. It is a gel of modified hyaluronic acid (HA). The HA in CTA is made from a fermented source. It is injectable and compatible with the skin. CTA is formulated with lidocaine, a local anesthetic, to provide pain relief at the injection site. Skin testing is not required. CTA is slowly absorbed by the body.

**What is CTA used for?**

CTA is use for correction of moderate to severe facial wrinkles and folds (such as the folds occurring around the mouth) by injection into the mid to deep dermis.

**Do the injections hurt?**

CTA contains lidocaine to reduce injection site pain. Lidocaine is similar to the anesthetics used in dental procedures. Your physician may also use other kinds of anesthesia. In general, patients may experience varying levels of discomfort. The majority of patients report that the discomfort is mild to moderate and goes away within a few hours or days.

**How does it work?**

Your physician will cleanse the area appropriately and inject CTA just below the skin surface using a very thin needle. CTA will remain where is injected and add volume to correct the wrinkle or fold.

**What is involved in CTA treatment?**

If you feel you are a candidate for this treatment, talk with your physician. He or she will help you decide if you are a candidate for CTA treatment. Your physician will determine the appropriate course of injections and any periodic touch ups in order to achieve and maintain your satisfaction with the result.

**Who should not use CTA?**

- Patients with severe allergies or history or presence of multiple severe allergies should not use CTA.
- 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.
- The safety of CTA for use during pregnancy, in patients who are breastfeeding and in patients under the age of 18 years has not been studied.

- The safety of CTA has not been studied in patients with an increased chance of developing keloid formations and hypertrophic scarring.
- CTA should be used with caution in patients on immunosuppressive therapy.
- Patients taking medicines that can prolong bleeding, such as aspirin and non steroidal anti-inflammatory drugs, may experience increased bruising or bleeding at injection sites.

**What else should I know about CTA?**

- The safety and effectiveness of CTA for areas other than the nasolabial folds (the folds extending from the nose to the corners of the mouth) or for time periods longer than one year has not been established.
- As with all injections, the injection of CTA carries a chance of infection.
- Minimize exposure of the area to excessive sun, tanning lamps and extreme cold weather until any initial swelling and redness have resolved.
- If laser treatment, chemical peeling or a similar procedure is considered before or after treatment with CTA, there is a possible chance of an inflammatory reaction at the injection site.

**How will I feel immediately after treatment?**

You may notice temporary redness, swelling, bumps, slight bruising and tenderness around the treatment sites. These are normal after hyaluronic acid injections.

Most patients could return to non-strenuous activity following treatment. Avoid strenuous exercise, extensive sun or heat exposure and alcoholic beverages for the first 24 hours after injection. These could cause temporary redness, swelling and itching.

**Is the product safe?**

Yes, for most people. CTA is highly purified and is not derived from animal or human tissues so it is free of animal proteins. This reduces the risk from any animal-based transmitted disease. People with certain conditions or allergies should not use the product (please see **Who should not use CTA?**). Your physician can help you determine if you are a good candidate.

**Were side effects reported during the initial treatment clinical trial?**

CTA was studied in 208 patients who were injected with CTA on one side of the mouth and collagen on the other. Swelling, redness, bumps, bruising and tenderness were the most common side effects noted by patients after injection of CTA. Most of these side effects went away on their own within a few days or a week. See Table 1 for the side effects as reported by the patients.

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

	CTA Side N=208	Cosmoplast® Side N=191
	Total reporting symptoms N (%)	Total reporting symptoms N (%)
Bruising	131 (63.0%)	94 (49.2%)
Redness	151 (72.6%)	124 (64.9%)
Swelling	181 (87.0%)	129 (67.5%)
Pain	108 (51.9%)	63 (33.0%)
Tenderness	145 (69.7%)	101 (52.9%)
Itching	83 (39.9%)	49 (25.7%)
Nodule formation	129 (62.0%)	112 (58.6%)

**What are the potential concerns when using CTA?**

Complications such as prolonged redness or swelling, an open wound, hard lumps, abscess, bleeding or infection could occur.

**When should I notify my physician?**

Any side effects that last longer than a week should be reported to your physician. Call your physician if you are concerned about the side effects or think you have a complication.

**What should I do after treatment?**

Apply ice to the site for up to 15 minutes every hour or two for 24 hours after injection to minimize swelling and redness. You may need touch-ups to achieve and maintain optimal correction. Discuss pain management with your physician before the injections are performed.

**When may I apply make-up?**

You can apply make-up a few hours after treatment if there are no complications such as open wounds, bleeding or infection.

**How long does the correction last?**

After six months, 56% of the patients maintained benefit compared to their original appearance. However, the correction is temporary, and repeat injections are usually needed to maintain correction. Your results will depend upon your aging process, the extent of the wrinkle and even your physician.

**How often will I require treatment?**

CTA is absorbed into your body naturally over time. The correction will likely disappear as this happens. That is why you may need additional treatments but the amount and how many times will depend upon each individual. Typically patients may require treatment every 6-12 months.

**What are the risks of retreatment?**

The same complications such as prolonged redness or swelling, an open wound, hard lumps, abscess, bleeding or infection could occur with retreatment as with initial treatment. There are no known additional risks associated with retreatment with CTA.

**Without touch-ups, how will my skin look?**

Without any additional touch ups, your skin will eventually look like it did before treatment, because the CTA will be absorbed into your body over time.

**What are my other options for treatment?**

There are a variety of dermal fillers available in the US. Prices, safety and effectiveness vary. Consult with your physician to determine which one is right for you.

**For more information, write or call:**

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

Toll-Free: 800-XXX-XXXX

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