HYLAFORM - INSTRUCTIONS FOR USE - USA

Hylaform®
(hylan B gel)

Federal (USA) law restricts this device to sale by or on the order of a licensed physician, or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

Hylaform (hylan B gel) is a sterile, nonpyrogenic, viscoelastic, clear, colorless gel implant composed of cross-linked molecules of hyaluronan. Hyaluronan is a naturally occurring polysaccharide of the extra-cellular matrix in human tissues, including skin.

2. INTENDED USE/ INDICATIONS

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

3. CONTRAINDICATIONS

- Hylaform gel is contraindicated for use in breast augmentation, or for implantation into bone, tendon, ligament, or muscle.
- Hylaform gel is contraindicated for patients with a history of known hypersensitivity to avian proteins.
- Hylaform gel must not be injected into blood vessels. Introduction of Hylaform gel into the vasculature may occlude the vessels and could cause infarction or embolization.

4. WARNINGS

- Use of Hylaform gel 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 underlying process has been controlled.
- The safety and efficacy of Hylaform gel for use in lip augmentation has not been established.
- Injection procedure reaction to Hylaform gel has been observed as consisting mainly of short-term inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the CLINICAL STUDIES section for details.

5. PRECAUTIONS

- Hylaform gel is packaged for single patient use ready for use. Do not resterilize. Do not use if package is opened or damaged.

- Based on preclinical studies, patients should be limited to 20 mL of Hylaform gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of Hylaform gel for the treatment of anatomic regions other than nasolabial folds has not been established in controlled clinical studies.
- Long-term safety and effectiveness of Hylaform gel beyond one year have not been investigated in clinical trials.
- As with all transcutaneous procedures, Hylaform gel implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of Hylaform gel for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- The safety of Hylaform gel in patients with increased susceptibility to keloid formation, hypertrophic scarring and pigmentation disorders has not been studied. Hylaform gel should not be used in patients with known susceptibility to keloid formation, hypertrophic scarring or pigmentation disorders. Genzyme is conducting a post approval study to determine the likelihood of keloid formation and pigmentation disorders in patients with Fitzpatrick Scale Skin types IV - VI receiving Hylaform injections
- Hylaform gel should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding, such as aspirin, non-steroidal anti-inflammatory drugs and warfarin may, as with any injection, experience increased bruising or bleeding at injection sites.
- 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 requirements.
- Hylaform gel is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe and notify INAMED Corporation at (800) 624-4261.
- The patient should be informed that he or she should minimize exposure of the treated area to excessive sun and UV lamp exposure and extreme cold weather until any initial swelling and redness has resolved.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with Hylaform gel there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if Hylaform gel is administered before the skin has healed completely after such a procedure.

6. ADVERSE EVENTS

A. Clinical Evaluation of Hylaform Gel

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of Hylaform gel as a dermal filler for nasolabial folds, 261 patients 30 to 55 years of age were randomized between the treatment (Hylaform) and the control (Zyplast) implant. During the initial phase of the study, each patient was injected with the respective dermal filler in the nasolabial folds for wrinkle correction. Patients were followed for 12 weeks. Following completion of the initial phase, each of the patients who initially received Hylaform gel treatment was offered repeat treatment with Hylaform products in both nasolabial folds and evaluated for safety for an additional 4 weeks.

Initial Treatment Phase

Adverse events reported during the 12 weeks following treatment were categorized according to the reported severity (see Table 1).

Table 1 – Injection Procedure Related Adverse Events by Maximum Severity Occurring in >5% of Patients [Number (%) of Patients]

Primary System Organ Class/Preferred Term	Hylaform Total	Zyplast Total	Hylaform N = 133			Zyplast N = 128		
			Mild	Mod*	Severe	Mild	Mod*	Severe
At least 1 adverse event	111 (84)	109 (85)	105 (79)	6 (5)	0 (0)	105 (82)	2 (2)	2 (2)
General disorders and administration site conditions	111 (84)	109 (85)	105 (79)	6 (5)	0 (0)	105 (82)	2 (2)	2 (2)
Injection site erythema	84 (63)	86 (67)	83 (62)	1 (1)	0 (0)	85 (66)	1 (1)	0 (0)
Injection site bruising	54 (41)	39 (30)	52 (39)	2 (2)	0 (0)	37 (29)	2 (2)	0 (0)
Injection site swelling	47 (35)	53 (41)	45 (34)	2 (2)	0 (0)	52 (41)	1 (1)	0 (0)
Injection site pain	42 (32)	29 (23)	40 (30)	2 (2)	0 (0)	26 (20)	1 (1)	2 (2)
Injection site pruritus	10 (8)	11 (9)	10 (8)	0 (0)	0 (0)	11 (9)	0 (0)	0 (0)
Injection site desquamation	3 (2)	7 (6)	3 (2)	0 (0)	0 (0)	7 (6)	0 (0)	0 (0)

* Mod = Moderate

Table 2: Duration of Procedure or Device Related Events Occurring in Greater than 5% of Patients

Primary System Organ Class/Preferred Term	Hylaform gel n = 133 n (%)					Zyplast n = 128 n (%)				
Duration*	≤ 3 days	4 - 7 days	8 – 14 days	> 14 days	Total	≤ 3 days	4 -7 days	8 – 14 days	> 14 days	Total
Injection site erythema	53 (40)	16 (12)	13 (10)	2 (2)	84 (63)	59 (46)	11 (9)	5 (4)	11 (9)	86 (67)
Injection site bruising	19 (14)	23 (17)	10 (8)	2 (2)	54 (41)	10 (8)	21 (16)	5 (4)	3 (2)	39 (31)
Injection site swelling	31 (23)	12 (9)	4 (3)	0 0	47 (35)	38 (30)	12 (9)	0 0	3 (2)	53 (41)
Injection site pain	39 (29)	2 (2)	1 (1)	0 0	42 (32)	22 (17)	5 (4)	1 (1)	1 (1)	29 (23)
Injection site pruritus	8 (6)	0 0	1 (1)	2 (2)	11 (8)	7 (6)	2 (2)	2 (2)	0 0	11 (9)
Injection site desquamation	1 (1)	1 (1)	1 (1)	0 0	3 (2)	3 (2)	3 (2)	1 (1)	0 0	7 (6)

*Duration refers to number of days irrespective of onset of Adverse Event to the date of the study device implantation

Device related adverse events occurred infrequently in both groups and were primarily of mild intensity; 2 patients (2%) experienced 3 events in the Hylaform group, and 9 patients (7%) experienced 14 events in the Zyplast group. The Hylaform device related adverse events were erythema, induration and pruritus.

Clinical trial adverse events unrelated to the injection procedure reported in the Hylaform treatment group occurring in greater than 1% of patients (n=133) were nasopharyngitis (5.3%), headache (4.5%), influenza (3.8%), rash (3%), conjunctivitis (1.5%), and sinusitis (1.5%).

Repeat Treatment Phase

During the initial and repeat treatment phases of the study, hylan B IgG antibody titers were measured at baseline and throughout treatment. Only one patient exhibited a positive antibody response after treatment with hylan B. This patient experienced adverse events of injection site bruising and headache lasting 11 days and 2 days after initial treatment, respectively. These adverse events were not reported as device-related and were not considered to be associated with the increased antibody titer level. None of the other study patients developed similar increases in antibody titer levels during the initial or repeat study phases.

Of the 133 patients treated with Hylaform gel during the initial phase, 96 underwent repeat treatment with Hylaform products and were followed for up to 4 weeks for safety. The types of adverse events seen after repeat treatment with Hylaform products were similar to those seen during the initial clinical evaluation. The most frequently reported adverse events included injection site erythema, bruising, swelling, pain, nodules, pruritus and tenderness. Device-related adverse events were reported in 3 patients during repeat treatment with Hylaform gel and included involuntary muscle contraction described as eye fasciculations in one patient and dizziness in another. A third patient experienced bilateral aseptic abscess formation at the site of injection, but did not develop increased hylan B antibody titers throughout either the initial or repeat phase of the study.

B. Surveillance outside the US

Hylaform post market safety surveillance in countries outside of the United States indicates that the most frequently reported adverse events include: injection site erythema, nodule, swelling, and induration. These adverse events are similar in frequency and duration to what has been noted during clinical trials.

7. CLINICAL STUDIES

A. Study Design

A prospective, double blind, randomized, multi-center clinical study was conducted to evaluate the safety and effectiveness of Hylaform gel when used as a dermal filler in the nasolabial folds. Patients were randomized between Hylaform gel and a commercially available control material, Zyplast implant (derived from bovine collagen) and were injected with enough material to achieve desired correction of each nasolabial fold. (Patients enrolled into the study underwent double bovine collagen skin testing.) At 2 weeks touch-up treatment with additional material was allowed, only if patients showed less than a 1-point improvement on the 6-point grading scale (see description below).

The primary efficacy endpoint for the study was the ability to correct nasolabial folds at 12 weeks in comparison to the control material. Correction of nasolabial folds was determined by an independent panel of blinded dermatologists through photographic assessment. Photographs of nasolabial folds were taken prior to treatment and at 3 days, 2, 4, 8, and 12 weeks following treatment. A 6-point grading scale was used to rank wrinkle severity for each photograph in a random, blinded fashion. Additional analyses included the investigator's visual assessment of each patient's nasolabial folds using the 6-point grading scale, and a qualitative assessment of the level of correction by the investigator and by the patient.

Table 2 Demographics and Pretreatment Characteristics of Total Patient Population, N=261 [Number (%) of Patients]

Gender		**Tobacco use**	
Male	**16 (6.1)**	**Non-smoking**	**216 (82.7)**
Female	**245 (93.9)**	**Smokers**	**45 (17.2)**
Ethnicity		**Sun Exposure (mean)**	**1.6 hrs/day**
Caucasian	**208 (79.7)**		
African American	**5 (1.9)**	**Patients With Prior Dermal Treatments**	**157 (60.1)**
Asian	**9 (3.4)**		
Hispanic	**34 (13.0)**		
Other	**5 (1.9)**		

B. Treatment Material Delivered

The mean total volume injected per nasolabial fold was 0.8 mL for patients in the treatment group (Hylaform gel) and 1.1 mL for patients in the control group (Zyplast implant). The mean volume injected was the same for left and right nasolabial folds and was approximately equivalent to the total volume supplied in one syringe of Hylaform gel (0.75 mL) and of Zyplast implant (1.0 mL) for the clinical study.

Twenty-two (16.5%) of 133 Hylaform patients and 9 (7.1%) of the 128 Zyplast patients required a touch-up treatment. The mean volume injected for touch-up per nasolabial fold was 0.3 mL for Hylaform patients and 0.5 mL for Zyplast patients.

C. Hylaform Gel Efficacy

Hylaform gel was found to be equivalent to the control material (Zyplast implant) in the correction of nasolabial folds after 12 weeks using the independent review of photographs.

Mean Score Based on 6-Point Grading Scale

	Blinded Photographic Assessment	
	Pretreatment	**12 Weeks after Treatment**
Hylaform	2.2	2.3
Zyplast	2.3	2.2

Grading scale: 0=No wrinkles, 1=Just perceptible wrinkle, 2=Shallow wrinkles, 3=Moderately deep wrinkle, 4=Deep wrinkle, well-defined edges, 5=Very deep wrinkle, redundant fold

Peak treatment effect with one injection of Hylaform gel was observed during the first 2 weeks after treatment. Photographic assessment showed that, on average, patients had returned to baseline in both groups at 12 weeks. However, the secondary endpoints of investigator's visual assessment and a qualitative assessment of correction by the investigator and by the masked patient during the controlled clinical study support the effectiveness of Hylaform and Zyplast at 12 weeks.

Mean Score Based on 6-Point Grading Scale

	Investigator Live Assessment	
	Pretreatment	**12 weeks after treatment**
Hylaform	3.5	2.4
Zyplast	3.5	2.3

Grading scale: 0=No wrinkles, 1=Just perceptible wrinkle, 2=Shallow wrinkles, 3=Moderately deep wrinkle, 4=Deep wrinkle, well-defined edges, 5=Very deep wrinkle, redundant fold

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