HYLAFORM PLUS - INSTRUCTIONS FOR USE - USA

Hylaform® Plus
(hylan B gel)

Caution: 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 Plus (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 Plus 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 Plus is contraindicated for patients with a history of known hypersensitivity to avian proteins.
- Hylaform Plus must not be injected into blood vessels. Introduction of Hylaform Plus into the vasculature may occlude the vessels and could cause infarction or embolization.

4. WARNINGS

- Use of Hylaform Plus 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 Plus for use in lip augmentation has not been established.
- Injection procedure reaction to Hylaform Plus 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 Plus 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 Plus 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 Plus 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 Plus beyond one year have not been investigated in clinical trials.
- As with all transcutaneous procedures, Hylaform Plus implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of Hylaform Plus for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- The safety of Hylaform Plus in patients with increased susceptibility to keloid formation, hypertrophic scarring and pigmentation disorders has not been studied. Hylaform Plus should not be used in patients with known susceptibility to keloid formation, hypertrophic scarring or pigmentation disorders.
- Hylaform Plus 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 Plus 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 Plus there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if Hylaform Plus is administered before the skin has healed completely after such a procedure.

6. ADVERSE EVENTS

A. Clinical Evaluation of Hylaform Plus

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of Hylaform Plus as a dermal filler for nasolabial folds, 96 patients 30 to 56 years of age who received Hylaform in the pivotal trial were randomized to receive the treatment (Hylaform Plus) and the control (Hylaform). In this Repeat Treatment Phase, each patient was injected with the respective dermal filler in the left or right nasolabial folds for wrinkle correction. Patients were followed for 12 weeks.

Treatment Phase

Adverse events reported during the 12 weeks following treatment were categorized according to the reported severity (see Table 1). Collection of adverse events during this Repeat Treatment Phase included the use of a patient diary.

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

Primary System Organ Class/Preferred Term	Hylaform Total	Hylaform Plus Total	Hylaform N = 96			Hylaform Plus N = 96		
			Mild	Mod*	Severe	Mild	Mod*	Severe
At least 1 adverse event	87 (91)	92 (96)	85 (89)	2 (2)	0 (0)	90 (94)	1 (1)	1 (1)
General disorders and administration site conditions	87 (91)	92 (96)	85 (89)	2 (2)	0 (0)	90 (94)	1 (1)	1 (1)
Injection site erythema	73 (76)	71 (74)	72 (75)	1 (1)	0 (0)	70 (73)	1 (1)	0 (0)
Injection site swelling	50 (52)	51 (53)	50 (52)	0 (0)	0 (0)	51 (53)	0 (0)	0 (0)
Injection site pain	46 (48)	51 (53)	45 (47)	1 (1)	0 (0)	50 (52)	1 (1)	0 (0)
Injection site bruising	34 (35)	42 (44)	34 (35)	0 (0)	0 (0)	41 (43)	0 (0)	1 (1)
Injection site nodule (lumps/bumps)	21 (22)	25 (26)	20 (21)	1 (1)	0 (0)	25 (26)	0 (0)	0 (0)
Injection site tenderness	17 (18)	19 (20)	17 (18)	0 (0)	0 (0)	19 (20)	0 (0)	0 (0)
Injection site pruritus	11 (12)	10 (10)	11 (12)	0 (0)	0 (0)	10 (10)	0 (0)	0 (0)
Injection site discoloration	7 (7)	7 (7)	7 (7)	0 (0)	0 (0)	7 (7)	0 (0)	0 (0)

* Mod = Moderate

Table 2 – Repeat Treatment Phase
Duration of Procedure or Device Related Events Occurring in > 5% of Patients
[Number (%) of Patients]

Primary System Organ Class/Preferred Term	Hylaform N = 96					Hylaform Plus N = 96				
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	55 (57)	16 (17)	0 (0)	2 (2)	73 (76)	54 (56)	14 (15)	1 (1)	2 (2)	71 (74)
Injection site swelling	44 (46)	6 (6)	0 (0)	0 (0)	50 (52)	42 (44)	8 (8)	1 (1)	0 (0)	51 (53)
Injection site pain	41 (43)	5 (5)	0 (0)	0 (0)	46 (48)	45 (47)	6 (6)	0 (0)	0 (0)	51 (53)
Injection site bruising	17 (18)	14 (15)	3 (3)	0 (0)	34 (35)	20 (21)	16 (17)	5 (5)	1 (1)	42 (44)
Injection site nodule (lumps/bumps)	10 (10)	2 (2)	4 (4)	6 (6)	22 (23)	12 (13)	4 (4)	5 (5)	4 (4)	25 (26)
Injection site tenderness	16 (17)	1 (1)	0 (0)	0 (0)	17 (18)	18 (19)	1 (1)	0 (0)	0 (0)	19 (20)
Injection site pruritus	10 (10)	1 (1)	0 (0)	0 (0)	11 (12)	9 (9)	1 (1)	0 (0)	0 (0)	10 (10)
Injection site discoloration	5 (5)	1 (1)	1 (1)	0 (0)	7 (7)	6 (6)	1 (1)	0 (0)	0 (0)	7 (7)

*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 (a total of 5 events) and all were of mild intensity. One patient (1%) on the Hylaform Plus side experienced involuntary muscle contractions; 1 patient (1%) on the Hylaform side experienced an injection site nodule; 1 patient (1%) experienced a sterile abscess on both the Hylaform Plus side and the Hylaform side (two events), and one patient (1%) experienced dizziness (non-NLF).

Clinical trial adverse events unrelated to either the device or the injection procedure and occurring in greater than 1% of patients (n=96) were contusion 3 (3.1%), back pain 2 (2.1%), dermatitis not otherwise specified 2 (2.1%), excoriation 2 (2.1%), herpes simplex 2 (2.1%), influenza 2 (2.1%), lip blister 2 (2.1%), and postoperative bruise 2 (2.1%).

During the Repeat Treatment Phase, hylan B IgG antibody titers were measured at baseline and throughout treatment. No patient exhibited a positive antibody response after treatment with Hylaform or Hylaform Plus.

B. Surveillance outside the US
Post market safety surveillance of the Hylaform product family 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 (Repeat Treatment Phase)

A prospective, double blind, randomized, multi-center clinical study was conducted to evaluate the safety and effectiveness of Hylaform Plus when used as a dermal filler in the nasolabial folds. Patients were randomized to receive Hylaform Plus on one side and a control material, Hylaform gel on the opposite side and were injected only once with enough material to achieve desired correction of each nasolabial fold. Touch-up treatments were not allowed as a part of the study design.

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 3 – Repeat Treatment Phase
Demographics and Pretreatment Characteristics of Total Patient Population, N=96
[Number (%) of Patients]

Gender		**Tobacco use**	
Male	**6 (6.3)**	**Non-smoking**	**55 (57.3)**
Female	**90 (93.8)**	**Smokers**	**41 (42.7)**
Ethnicity		**Sun Exposure (mean)**	**1.2 hrs/day**
Caucasian	**77 (80.2)**		
African American	**2 (2.1)**	**Patients With Prior Dermal Treatments**	**10 (10.4)**
Asian	**5 (5.2)**		
Hispanic	**11 (11.5)**		
Other	**1 (1.0)**		

B. Treatment Material Delivered

The mean total volume injected per nasolabial fold was 1.1 ml for patients in the treatment group (Hylaform Plus) and the control group (Hylaform gel). The mean volume injected was the same for left and right nasolabial folds.

C. Hylaform Plus Efficacy

Per the study design, Hylaform Plus was found to be comparable to the control material (Hylaform gel) in the correction of nasolabial folds at 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 Plus	2.4	2.3
Hylaform	2.3	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

Peak treatment effect with only one injection of Hylaform Plus 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 Plus and Hylaform at 12 weeks after one injection.

Mean Score Based on 6-Point Grading Scale

	Investigator Live Assessment	
	Pretreatment	**12 weeks after treatment**
Hylaform Plus	3.1	2.2
Hylaform	3.1	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

Based on investigator live assessment, 21% of Hylaform Plus patients returned to pretreatment levels at 12 weeks after one injection.

8. INDIVIDUALIZATION OF TREATMENT

Severely indurated, sharply marginated and very superficial wrinkles may be difficult to distend and, therefore, are difficult to correct. If a defect cannot be distended because of extensive scarring or non-elastic tissue, the course of correction will be prolonged, if correction is achievable.

Touch-up implantations may be required in areas with greater motion or mechanical stress (e.g., nasolabial folds). All patients should be counseled to anticipate supplemental implantations to achieve and maintain optimal correction.

9. HOW SUPPLIED

Hylaform Plus is supplied in individual treatment syringes with needles, and is packaged for single patient use, ready for injection (implantation). The contents of the syringe are sterile and non-pyrogenic. The volume markings on the syringe are for reference only.

TO ATTACH NEEDLE TO SYRINGE

Peel sealed cover off the needle guard.

Remove tip cap from syringe.

Attach needle to syringe and twist to secure. To assure proper needle attachment, use the needles provided or 27-gauge needles with similar needle guards. Fully seat hub of needle in syringe. Do not over tighten, as this may break the needle and/or dislodge the syringe.

Pull off the needle guard to expose needle.

PROCEDURE TO CHANGE NEEDLE

Peel sealed cover off new needle guard.

Twist used needle to disconnect it from the syringe.

Attach new needle to syringe and twist to secure.

Pull off the needle guard to expose needle.

To place an order, contact INAMED Corporation at (800) 624-4261.

INSTRUCTIONS FOR USE

1. Hylaform Plus is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). Prior to treatment with Hylaform Plus, the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain maximum correction.

2. A complete medical history, including allergies, should be obtained to determine whether the patient is an appropriate candidate for Hylaform Plus treatment.

3. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Depending on the type of skin, best results are obtained when the defect is readily distensible and correction can be visualized by manual manipulation (stretching) of the skin. Pretreatment photographs are recommended.

4. Topical or injectable anesthesia may be used to manage pain during and after injection.

5. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic. Prior to injecting Hylaform Plus, depress the plunger rod until the product flows out of the needle.

6. Hylaform Plus is administered using a thin gauge needle (27G x ½"). The injection technique with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary. A linear threading technique, serial puncture injections, or a combination of the two have been used to achieve optimal results. Subdermal application should be avoided because such application may not provide optimal correction. If Hylaform Plus is injected too deep, the duration of the effect will be shorter. If Hylaform Plus is injected too superficially this may result in visible lumps and/or discoloration.

7. Inject Hylaform Plus 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

the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.

8. Only correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique. Markedly indurated defects may be difficult to correct.

9. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color.

10. When injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an over correction has occurred, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.

11. If the wrinkle needs further treatment, the same procedure should be repeated until a satisfactory result is obtained. With patients who have localized swelling the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient to a touch-up session after 1-2 weeks.

12. Patients may have mild to moderate injection site reactions, which typically resolve in a few days. If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period.

13. After the initial treatment (from 1 to 2 weeks later), an additional treatment of Hylaform Plus may be necessary to achieve the desired level of correction. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as wrinkle severity, skin elasticity and dermal thickness at the treatment site.

14. The physician should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of Hylaform Plus.

PATIENT INSTRUCTIONS

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

- To report an adverse reaction, phone the Product Support Department, INAMED Corporation, **(800) 624-4261.**

- Within the first 24 hours, patients should avoid:
  - Strenuous exercise
  - Extensive sun or heat exposure
  - Alcoholic beverages

  Exposure to any of the above may cause temporary redness, 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 and infection).

STORAGE

Hylaform Plus should be stored at room temperature, 2°-30°C (36°-86°F). DO NOT FREEZE.

Hylaform Plus has a clear appearance. In the event that a syringe contains material that is not clear do not use the syringe and notify INAMED Corporation immediately at (800) 624-4261.

STERILITY

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

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