

**SUMMARY OF SAFETY AND
EFFECTIVENESS DATA (SSED)**

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I. GENERAL INFORMATION

Device Generic Name:	Injectable dermal filler
Device Trade Name:	Hylaform [®] (hylan B gel)
Applicant's Name and Address:	Genzyme Corporation 500 Kendall Street Cambridge, MA 01242
Premarket Approval Application (PMA) Number:	P030032
Date of Panel Recommendation:	November 21, 2003
Date of GMP Inspection:	December 9, 2003
Date of Notice of Approval To the Applicant:	April 22, 2004

II. INDICATIONS FOR USE

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).

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Hylaform gel professional labeling.

V. DEVICE DESCRIPTION

Hylaform (hylan B) 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.

Hylaform gel is injected into the dermal tissue to provide a space-occupying viscoelastic supplement for the extra-cellular matrix of the connective tissue. This viscosupplementation or augmentation of the dermal tissue can result in the temporary correction of skin contour deficiencies caused by wrinkles and folds.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternate therapies for dermal soft tissue augmentation include bovine collagen based dermal fillers (Zyderm[®] and Zyplast[®] collagen implants), human collagen based dermal fillers (CosmoDerm[®] and CosmoPlast[®] collagen implants), hyaluronic acid based dermal filler (Hylaform[®] gel), autologous fat transfer, and cadaveric-based products. Aside from the use of these dermal fillers, additional options for the correction of fine lines and wrinkles include chemical peels, laser skin resurfacing, dermabrasion, botulinum toxin injections, and surgical intervention (i.e. facelift).

VII. MARKETING HISTORY

Hylaform gel was first approved for marketing and sale in November 1995 in the European Union including the EEA and EFTA. In 1997 registration was obtained in Canada, Chile and Israel. In 1998 the product was registered in Argentina and Brazil. In 1999 the product was registered in Australia, China and Turkey. In 2000 the product was registered in Hong Kong and New Zealand. During 2002 approval was obtained in Lebanon, Romania and Singapore.

Hylaform gel has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of Hylaform gel as a dermal filler for nasolabial folds, 261 patients 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 duration and the relationship to the treatment device and/or the procedure (see Tables 1 and 2).

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 N = 133			Zyplast N = 128		
	Hylaform Total	Zyplast Total	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 (%)				
	≤ 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 NOS (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 (pretreatment) 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.

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.

IX. SUMMARY OF PRECLINICAL STUDIES

Hylaform (hylan B gel) was studied in non-clinical studies to characterize biological properties and ensure safety. In all toxicity studies of hylan B gel, the concentrations (masses) of the polymers used were comparable to or exceeded the anticipated clinical use. Concentrations (masses) higher than those intended for clinical use were used in some studies to enhance any potential toxicity. The short- and long-term biological testing conducted on Hylaform gel was consistent with testing recommended under ANSI/AAMI ISO 10993-1:1994 (Biological Evaluation of Medical Devices –PART 1: Guidance on selection of tests) and FDA guidance document, G95-1 for a tissue implant with a contact duration of greater than 30 days. These testing results are summarized below (see Table 3):

Table 3 - Summary of Non-Clinical Studies: ISO 10993 Biocompatibility Studies

Study	Results/Conclusions
Short-Term Biological Tests	
Irritation <ul style="list-style-type: none"> Intracutaneous – rabbit 24-72 Hr Subcutaneous – rabbit 2 days 	Negative (well tolerated) Negative (well tolerated)
Sensitization <ul style="list-style-type: none"> Immunization, subchronic intramuscular rabbit 13 weeks Dermal – Maximization method Delayed contact - Maximization 	Negative (well tolerated) Negative (well tolerated) Negative (well tolerated)
Cytotoxicity – MEM elution and Agarose Overlay	Negative (no cell lysis)
System Toxicity (Acute) – systemic (intravenous/intraperitoneal)	Negative (no toxic effect by intraperitoneal)
Hemocompatibility – In Vitro direct contact	Non-hemolytic
Pyrogenicity – USP Rabbit	Non pyrogenic
Implantation <ul style="list-style-type: none"> USP muscle 7D rabbit USP muscle 30D rabbit 	Well tolerated, slight irritant Well tolerated, non-irritant
Genotoxicity <ul style="list-style-type: none"> Ames mutagenicity Chemical induction 	Non-mutagenic No chromosomal aberrations
Long-Term Biological Tests	
Sub-Chronic Toxicity <ul style="list-style-type: none"> Intramuscular 12 weeks in rabbits in rabbits 30x dose Intraperitoneal 2 mg/mL clinical dose 2 weeks 	Negative (well tolerated) negative (well tolerated)
Chronic Toxicity & Carcinogenicity – 1 year in rats	Negative (well tolerated)
Reproductive Development – colony life span of owl monkeys	Negative (well tolerated)
Pharmacokinetics Intradermal Injection of [³ H]-Hylan B 4 weeks	Negative (well tolerated)

Hylaform gel passed all the biocompatibility tests. The preclinical testing indicated that Hylaform gel was safe to be evaluated in clinical studies.

X. SUMMARY OF CLINICAL STUDIES

Initial Phase of the Controlled, Randomized Trial

The clinical basis for approval for this pre-marketing application is the outcome of a prospective Pivotal Clinical Study performed in the United States.

The Hylaform clinical trial included an initial treatment phase with 12-week follow-up for efficacy and safety in the treatment of nasolabial folds. This initial treatment phase allowed for a touch-up treatment as appropriate within two weeks of initial treatment.

Devices

The investigational device used in the study was the present formulation of Hylaform gel. The gel was delivered during study as 0.75 mL of sterile, clear hylan B gel in a 0.9 mL glass syringe and a 30 gauge x 1/2" needle.

The control device was a marketed, cross-linked collagen implant composed of purified bovine dermal collagen cross linked with glutaraldehyde, dispersed in phosphate buffered saline and 0.3% lidocaine (Zyplast). This collagen implant is indicated for the correction of contour deficiencies of soft tissue. This implant was delivered during the study via 1.0 cc syringe and fine gauge needle.

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.) Blood samples were drawn prior to treatment and at 4 and 12 weeks to evaluate any hypersensitivity developed to hylan B gel. 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. Effectiveness was studied with 12 week follow-up from baseline. Safety was studied from initial treatment and touch-up through 12 weeks post-baseline follow-up.

Primary Objectives

The primary objective was to evaluate the safety and effectiveness of Hylaform compared to Control in patients seeking augmentation correction of bilateral nasolabial folds that met study criteria.

- Efficacy (non-inferiority) of Hylaform gel for the correction of nasolabial folds (NLFs), as compared with Zyplast collagen implant. Assessment of wrinkle correction was performed using serial photographic documentation and blinded Independent Panel

Review (IPR) photographic evaluation. Efficacy was based on the blinded IPR Wrinkle Assessment Scores of the Week 12 or 14 photographs (12 weeks following the last device implantation).

- Safety of Hylaform gel as compared with Zyplast:
Safety was determined by the incidences of adverse experiences (AEs) associated with the use of each product. Patients were observed for a total of 12 weeks following the last implantation of the device.

Secondary Objectives

The secondary objective of the initial treatment phase was to:

- Evaluate the clinical utility of Hylaform gel with respect to physician assessment and patient self-assessment

Patient Enrollment

A total of 261 subjects were injected with either Hylaform gel (133 subjects) or with Zyplast implant (128 subjects) at 10 dermatology centers in the U.S. Follow-up periods for both safety and efficacy were at 3 days, 2 weeks, 4 weeks, 8 weeks, and 12 weeks.

Selected Study Population Criteria

- Men or women, 30 years or older but less than or equal to 55 years of age
- Negative skin test to Collagen Test Implant
- Two fixed facial sites, fully visible bilateral nasolabial folds, which were both candidates for correction by the procedure described in the protocol
- Wrinkle severity score of 3 or 4 on the 6-point grading scale at the areas to be treated
- If female and of childbearing potential, had a negative urine pregnancy test, agreed to use oral contraceptives for at least 1 month prior to treatment and for the duration of the study, or agreed to use 2 forms of contraception (eg, condoms plus spermicide), or was surgically sterile, or postmenopausal for at least 1 year
- Ability to understand and comply with the requirements of the study
- Willingness and ability to provide written informed consent prior to performance of any study-related procedures
- Agreed to refrain from seeking other treatment for this condition without first notifying the investigator.

Effectiveness Assessments

Treatment effectiveness was assessed at each follow-up visit. Photographs were taken at the time of pre-treatment evaluation and at each post-treatment evaluation. From the photographs, IPR scored each fold according to the 6-point Genzyme grading scale, a scale that was created and validated for this study. Standardized reference photographs were used by the blinded reviewers for comparison. For evaluation of secondary objectives, investigators rated success of treatment using the Genzyme grading scale while observing the patient, and both the investigators and the patients indicated satisfaction ratings using a qualitative scale.

<u>6-point Genzyme grading scale</u>		<u>Investigator and patient satisfaction rating scale</u>	
0	No wrinkle	-2	Much worse
1	Just perceptible wrinkle	-1	Worse
2	Shallow wrinkles	0	No change
3	Moderately deep wrinkle	1	Better
4	Deep wrinkle, well-defined edges	2	Much better
5	Very deep wrinkle, redundant fold		

This 6-point grading system was validated based upon a review of 30 non-study photos by Evaluating Investigators. Based on this photo review, a change of 1-point was considered to be clinically significant.

Study Outcomes

Demographic Data

The majority of the patients in each treatment group were Caucasian and female. The mean age of all patients was 46.6 years and the mean weight was 63.6 kilograms. Table 5 presents patient demographics for the intent to treat (ITT) population.

Over 50% of patients in each treatment group never smoked. The number of current and former smokers was comparable for the treatment groups; however, current smokers smoked more cigarettes per day in the Zyplast group (11.5/day) than in the Hylaform group (6.5/day). The number of hours per day of sun exposure was similar between the treatment groups.

**Table 5 - Demographics and Pretreatment Characteristics of Total Patient Population, N=261
[Number (%) 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%)	Patients With Prior Dermal Treatments	157 (60.1%)
African American	5 (1.9%)		
Asian	9 (3.4%)		
Hispanic	34 (13.0%)		
Other	5 (1.9%)		

Treatment Exposure

Time on study during the initial phase of the study was similar between the two treatment groups. The mean time on study was 89.1 days (range: 46 to 140 days) for Hylaform patients and 87.2 days (range: 21 to 149 days) for Zyplast patients. All touch-up patients (22 Hylaform patients and 9 Zyplast patients) completed the study. Six patients (3 Hylaform patients, 3 Zyplast patients) discontinued after initial treatment but before completion of the 12-week visit.

Blinding

At the final (12 week) visit patients were asked to assess which treatment they believed they received. Over 50% of the patients in each treatment group did not know what treatment they received. In the Hylaform group, 36 (27.1%) believed they received Hylaform gel; 18 (13.5%) believed they received Zyplast implant, and 76 (57.1%) did not know. In the Zyplast group, 31 (24.2%) believed they received Zyplast implant, 25 (19.2%) believed they received Hylaform gel, and 69 (53.9%) did not know.

Clinical Trial, Initial Phase: Effectiveness Conclusions

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 blinded 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

Based on investigator live assessment, 15% of Hylaform patients and 10% of Zyplast patients returned to pretreatment levels at 12 weeks.

In addition, 22 (16.5%) of 133 Hylaform patients and 9 (7.0%) of 128 Zyplast patients required a touch-up treatment which was performed approximately 2 weeks after the initial 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.

Clinical Trial, Initial Phase: Safety Conclusions

The reported Adverse Events are the compilation of the safety data presented in the PMA (see Tables 1 and 2).

Repeat Treatment Phase of the Controlled, Randomized Trial

In order to study the effects of repeat treatment with Hylaform gel, the protocol was amended to offer repeat treatment with Hylaform products to each of the 133 patients initially randomized to Hylaform gel.

Objectives

The primary objectives of the repeat treatment phase were as follows:

- Evaluate the safety of repeat treatment with hylan B viscoelastic gel products. Safety was determined through 4 weeks after treatment by rates of adverse events associated with repeat treatment with Hylaform gel and Hylaform Plus gel and by the presence or absence of a potential immune response to hylan B gel as measured by the development of hylan B IgG antibody titers after repeat device implantation.

Patient Enrollment

Of the 133 patients who received Hylaform gel for initial treatment, 96 re-enrolled for repeat treatment. As previously indicated, adverse events in the repeat treatment phase were similar to those observed in the pivotal study.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Based on the live investigator assessments, masked patient assessments, and the photographic assessments, efficacy has been shown for the device. Safety has been demonstrated by the lack of severe adverse events, and by the short duration of the events observed.

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

XII. SKIN TYPE AND GENDER BIAS

The majority of patients enrolled in the pivotal clinical study were Caucasian (81%), who most commonly represent Fitzpatrick skin types I – III. Minority populations, who more commonly represent Fitzpatrick skin types IV – VI comprised 19% of the study group. This proportion may not be reflective of the general U.S. population that may seek treatment with Hylaform gel.

Women made up a majority of the patients in the U.S. trial (95%). Gender was represented as may be expected in the US market.

XIII. PANEL RECOMMENDATION

This PMA was referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation on November 21, 2003. The panel recommended that the PMA be Approvable with Conditions. The panel recommended the following conditions:

- The sponsor should conduct a postapproval study to collect safety and effectiveness data on persons of color.
- A statement should be placed on the labeling stating "Limited controlled clinical study data are available regarding the use of Hylaform gel in patients with skin types V and VI on the Fitzpatrick scale and people of color."
- The sponsor should provide confirmation of physician education prior to use of the device.
- The FDA will determine the best method for assessment of potential hypersensitivity reactions to avian products.
- A statement should be placed in the labeling that limited controlled clinical data are available for safety and efficacy of multiple use of the device.
- A statement should be placed in the labeling that safety and efficacy for use in lip augmentation has not been established in controlled clinical trials.

XIV. CDRH DECISION

CDRH agreed with and accepted all of the Panel's recommendations with slight modifications, as follows:

- The sponsor will conduct a post-approval study on persons with Fitzpatrick skin types IV - VI. The FDA believes that this range of skin types would encompass persons of color.
- To emphasize the lack of data in patients with Fitzpatrick skin types V and VI, the following precaution has been added to the labeling, "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."

- The sponsor is developing educational material that will be provided to the physicians prior to the procedure to address the Panel's physician education recommendation.

Based on the preclinical and clinical data in the PMA, CDRH determined the data provide reasonable assurance that the device is safe and effective when used in accordance with the labeling.

The applicant's manufacturing facility was inspected on December 9, 2003, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on April 22, 2004.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling.

Postapproval Requirement and Restrictions: See the approval order.