SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable dermal filler
Device Trade Name:	Hylaform® Plus (hylan B gel)
Applicant's Name and Address:	Genzyme Corporation 500 Kendall Street Cambridge, MA 01242
Premarket Approval Application (PMA) Number:	P030032/S001
Date of Notice of Approval To the Applicant:	October 13, 2004

II. INDICATIONS FOR USE

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).

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warning and precautions can be found in the Hylaform Plus professional labeling.

V. DEVICE DESCRIPTION

Hylaform Plus (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. Hyaluronan is chemically, physically and biologically similar in the tissues of all species.

Hylaform Plus 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, Restylane® injectable 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 Plus was first approved for marketing and sale in August 2001 in the Czech Republic, Switzerland, European Union including the EEA and EFTA. In 2002 registration was obtained in Australia, Canada, Israel, Lebanon, Romania and Singapore. During 2003 the product was registered in Peru.

Hylaform Plus 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

A clinical study was conducted at 10 centers in the United States in two phases. These two phases included:

1. An initial treatment phase evaluating safety and efficacy over a 12-week follow-up period and
2. A repeat treatment phase to evaluate repeat treatment with Hylaform over a period of four (4) weeks. This study was extended to 12 weeks to allow an additional eight week follow-up period to study the safety and efficacy of Hylaform Plus compared to Hylaform.

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.

Adverse events reported during the 12 weeks following treatment were categorized according to the relationship to the treatment device and/or the procedure and reported

duration (see Tables 1 and 2). 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

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treatment with Hylaform or Hylaform Plus.

Surveillance outside the US
Post market safety surveillance of the Hylaform product family (made up of: Hylaform, Hylaform Plus and Hylaform Fineline) 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

The non-clinical investigations, including stability and sterilization and packaging validations, described in P030032 volumes 2 and 3 apply to the Hylaform Plus device because the material formulation, manufacturing process, container/closure and packaging configuration are the same. The only differences between Hylaform and Hylaform Plus include a slightly higher median particle size (700 microns vs 500 microns) and a larger needle gauge (27 G vs. 30G) that do not affect the non-clinical testing and results. The studies characterized the chemical, physical and biological properties of Hylaform (hylan B gel). These studies include a large number of nonclinical laboratory studies to examine biological safety properties. Under the conditions of the *in vitro* and *in vivo* biological tests, Hylaform was found to be a non-irritant, non-pyrogenic, non-immunogenic, non-carcinogenic, non-hemolytic and non-cytotoxic.

X. SUMMARY OF CLINICAL STUDIES

Repeat 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/Hylaform Plus clinical trial included a 12-week follow-up for efficacy and safety in the treatment of nasolabial folds. This repeat treatment phase did not allow for a touch-up treatment.

Devices
The investigational device used in the study was the present formulation of Hylaform Plus. 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 27 gauge x 1/2" needle.

The control device was a Hylaform gel. Hylaform is indicated for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). This implant was delivered during the study as 0.75 ml of sterile, clear Hylan B gel in 0.9 ml glass syringe and a 30 gauge x 1/2" needle.

Study Design

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. Blood samples were drawn prior to treatment and at 4 and 12 weeks to evaluate any hypersensitivity developed to hylan B gel. Effectiveness and safety were studied with 12 week follow-up from injection.

Primary Objectives

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

- Efficacy (non-inferiority) of Hylaform Plus for the correction of nasolabial folds (NLFs), as compared with Hylaform viscoelastic gel. 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 photographs.
- Safety of Hylaform Plus as compared with Hylaform:
  Safety was determined through 12 weeks post treatment by the rates of adverse experiences (AEs) associated with repeat treatment with Hylaform and Hylaform Plus and by the presence or absence of a potential immune response to hylan B gel as measured by the development of anti-hylan B (IgG) antibody titers after repeat device implantation

Secondary Objectives

The secondary objective of the repeat treatment phase was to:

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

Patient Enrollment

A total of 96 subjects were injected with Hylaform Plus and Hylaform 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

- Received Hylaform treatment during initial phase of the study and completed 12 week follow-up visit for initial phase
- 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.

Efficacy 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.

	6-point Genzyme grading scale	**Investigator and patient satisfaction rating scale**	
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 47.5 years and the mean weight was 64.4 kilograms. Table 3 presents patient demographics for the intent to treat (ITT) population.

Over 50% of patients in each treatment group never smoked.

Table 3 - Demographics and Pretreatment Characteristics of Total Patient Population, N=96 [Number (%) 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)		

Treatment Exposure

The mean time on study during the repeat phase of the study was 86.7 days (range: 71 to 113 days). All patients completed the study.

Clinical Trial, Repeat Phase: Efficacy Conclusions

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.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Based on the live investigator assessments, masked patient assessment, 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 (80%), who most commonly represent Fitzpatrick skin types I – III. Minority populations, who more commonly represent Fitzpatrick skin types IV – VI comprised 20% of the study group. This proportion may not be reflective of the general U.S. population that may seek treatment with Hylaform Plus.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CDRH DECISION

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.

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.