# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

Device Generic Name: Dermal Collagen Implants for Aesthetic Use

Device Trade Name: CosmoDerm™ 1 Human-Based Collagen
CosmoDerm™ 2 Human-Based Collagen
CosmoPlast™ Human-Based Collagen

Applicant: Inamed Corporation
5400 Ekwill Street
Santa Barbara, California 93111

PMA Number: P800022

Supplement Number: S50

Date of Good Manufacturing Practice Inspection: April 14, 2000 and April 2, 2001

Date of Notice of Approval to Applicant: March 11, 2003

## II. INDICATIONS FOR USE

- CosmoDerm™ 1 Human-Based Collagen and CosmoDerm™ 2 Human-Based Collagen are injected into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

- CosmoPlast™ Human-Based Collagen is injected into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

## III. DEVICE DESCRIPTION

CosmoDerm and CosmoPlast Human-Based Collagen implants are sterile devices composed of highly purified human-based collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine. CosmoDerm Human-Based Collagen implants are available in two forms: CosmoDerm™ 1 Human-Based Collagen and CosmoDerm™ 2 Human-Based Collagen. CosmoDerm™ 2 Human-Based Collagen implant contains almost twice the collagen concentration of CosmoDerm™ 1 Human-Based Collagen. CosmoPlast™ Human-Based Collagen is a sterile device composed of highly purified human-based collagen that is crosslinked with glutaraldehyde, and dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine.

CosmoDerm and CosmoPlast Human-Based Collagen implants contain collagen purified from human fibroblast cell culture. The cell line used for collagen production is qualified by extensive testing for viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity. Prior to release each lot of human collagen is tested for protein concentration, purity, pH, lidocaine content, residue on ignition, differential scanning calorimetry, extrusion, appearance, sterility and pyrogenicity.

CosmoDerm and CosmoPlast Human-Based Collagen implants are sterile and supplied in individual treatment syringes packed with sterile needles, ready for use. CosmoDerm and CosmoPlast Human-Based Collagen implants are single use devices.

## IV. CONTRAINDICATIONS

- CosmoDerm and CosmoPlast Human-Based Collagens must not be used in patients with severe allergies manifested by a history of anaphylaxis.

- CosmoDerm and CosmoPlast Human-Based Collagens contain lidocaine and must not be used in patients with known lidocaine hypersensitivity.

- CosmoDerm and CosmoPlast Human-Based Collagens are contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

## V. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen labeling.

## VI. ALTERNATIVES

Alternate therapies for dermal soft tissue augmentation include bovine-based dermal fillers (Zyderm® and Zyplast® collagen implants), 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 includes chemical peels, laser skin resurfacing, dermabrasion and surgical intervention.

## VII. POTENTIAL ADVERSE EFFECTS

Information about the adverse events observed in the use of Zyderm and Zyplast (i.e., bovine collagen) may be found in the product labeling for these products.

In a study to evaluate sensitization to CosmoDerm and CosmoPlast Human-Based Collagen implants, 428 patients were injected intradermally with CosmoDerm™ 1 Human-Based Collagen into the volar forearm and followed for 2 months. All reported adverse events with

two or more occurrences in this study, are listed in Table 1 in descending order according to frequency.

**Table 1 – Adverse Events with Two of More Occurrences in the Sensitization Study**

| Description of Adverse Event | Number | % Frequency |
|---|---|---|
| Cold Symptoms | 17 | 4.1 |
| Flu-Like Symptoms | 8 | 2.0 |
| Urinary Tract Infection | 4 | 1.0 |
| Bronchitis | 3 | 0.7 |
| Strep Throat | 3 | 0.7 |
| Sinus Infection | 3 | 0.7 |
| Acid Dyspepsia or Reflux | 2 | 0.5 |
| Back Ache, Pain, Spasm | 2 | 0.5 |
| Ear Infection | 2 | 0.5 |
| Fever and Slight Fever | 2 | 0.5 |
| High Blood Pressure | 2 | 0.5 |
| Insomnia | 2 | 0.5 |
| Sore Throat | 2 | 0.5 |

### Local Treatment Site Reactions

One subject reported redness and pain (moderate severity) at one week after the first injection. This was confirmed by the investigator as redness, tenderness, induration and swelling at the injection site. These symptoms spontaneously resolved after 10 days without treatment or sequelae. The absence of an antibody response against CosmoDerm™ 1 Human-Based Collagen and histopathological examination of a biopsy of the injection site suggested that the injection site reaction was not immunologically-related to CosmoDerm™ 1 Human-Based Collagen injection.

## VIII. MARKETING HISTORY

The human collagen products CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen do not have established market history. The equivalent bovine collagen products ZYDERM® I, ZYDERM® II and ZYPLAST® were approved in the United States in 1981, 1983 and 1985, respectively and have since also been available for commercial distribution in select international markets.

## IX. SUMMARY OF PRECLINICAL STUDIES

### Preclinical Testing:

The testing presented in the original PMA application and its supplements was adequate to document the safety and effectiveness of the bovine collagen devices (Zyderm and Zyplast) for the correction of contour deficiencies of soft tissues. The following table summarizes the additional testing submitted in Supplement 50 to support of the use of CosmoDerm and CosmoPlast Human-Based Collagen implants. These studies focused on examinations of the biophysical and biochemical properties of samples from 3 production lots of Zyderm, Zyplast, CosmoDerm™ 1 Human-Based Collagen and CosmoPlast™ Human-Based Collagen. These analyses demonstrated the similarity of the composition, purity and structure of the approved bovine collagen devices (i.e., Zyderm and Zyplast) and CosmoDerm and CosmoPlast Human-Based Collagen implants. These study results demonstrate that bovine and human collagen products, manufactured by similar methods, should display equivalent clinical performance.

**CosmoDerm™ 1 Human-Based Collagen and CosmoPlast™ Human-Based Collagen Preclinical Studies**

| STUDY | RESULTS/CONCLUSIONS |
|---|---|
| **Biochemical Identity and Purity** | |
| Amino Acid Composition | Amino acid analyses verified that the composition of the human collagen implants (Gly~33%, Pro~12%, Hypro~10%, Tyr ~0.2%, Cys<0.1%) are consistent with the published literature and similar to the composition of the bovine collagen devices Zyderm and Zyplast. |
| SDS-PAGE Analysis | Polyacrylamide gel electrophoresis demonstrated that the protein banding patterns were similar for human (i.e., 99% within α, β and γ bands) and bovine (i.e., 97% within α, β and γ bands) collagen products. No contaminating proteins were observed. |
| Type I Collagen Western Blot | Type I collagen was detected as the major component of bovine and human collagen products with a Western Blot analysis. |
| Type III Collagen Western Blot | Type III collagen was detected as a minor component of the human collagen in a Western Blot assay specific for human Type III collagen. |
| Type Collagen – Interrupted Electrophoresis | Interrupted gel electrophoresis was used to assess the amount of type III collagen (*BBRC*, **72** (4) 1472 – 80 (1976)). Concentrations in human (7.0 %) and bovine (4.0 %) collagen were similar. |
| Type IV Collagen Western Blot | Type IV collagen was not detected in human collagen using a Western Blot assay specific for human Type IV collagen. |
| Pepsin Determination | A sandwich ELISA demonstrated that pepsin was not detectable in the bovine or human collagen products. |
| Trypsin Digestion | Triple helical structure of interstitial collagen is resistant to trypsin digestion while non-collagenous proteins and denatured collagens are readily degraded. The lack of degradation observed with both human and bovine collagen products indicates a similar structure and purity for both products. |

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|---|---|
| Collagenase Digestion | Purified collagenase was used for specific digestion of triple helical collagen. Analyses demonstrated the absence of non-collagenous proteins in both human and bovine products. |
| Vascular Endothelial Growth Factor (VEGF) Determination | Sandwich ELISA results demonstrated that VEGF was not detectable in CosmoDerm. |
| Bovine Serum Albumin Determination | A sandwich ELISA confirmed the absence of bovine serum albumin in the bovine or human collagen products. |
| Lipid Content | Analyses demonstrated that the lipid content of human (0.03%) and bovine (0.01%) collagens were similar. |
| Carbohydrate Content | Analyses demonstrated that the carbohydrate content of human (7.0 ug/mg) and bovine (4 ug/mg) collagens were similar. |
| Aldehyde Concentration | The aldehyde concentrations in solutions of glutaraldehyde cross-linked Zyplast and CosmoDerm were similar for the human (2.3 ppm) and bovine (0.90 ppm) products. |
| USP Heavy Metals | CosmoDerm and CosmoPlast implants passed the USP heavy metal test. |
| pH Measurement | The pH of final human (7.1) and bovine (7.2) products were similar. |
| Residue on Ignition Test | The residue on ignition of the final human (1.0%) and bovine (1.0%) collagen products were similar. |
| Determination of % Soluble and Denatured Protein - | Percent soluble and denaturated protein for the bovine (6%) and human (7%) collagen products were similar. |
| Determination of Lidocaine | Spectroscopic analyses demonstrated that the lidocaine concentration was similar for the final human (3.1 mg/ml) and bovine (3.0 mg/ml) products. |
| Sterility and Pyrogen Levels | Both the human and bovine final products were found to be sterile and non-pyrogenic. |
| **Structure** | |
| Differential Scanning Calorimetry (DSC) | DSC confirmed that the triple helix structure of native and crosslinked human and bovine collagens were similar. |
| Opacity of 35mg/ml Collagen Homogenate | The opacities of human (1.5 O.D) and bovine (1.7 O.D) collagen products at 410 nm suggest that the products from different sources are similar with respect to over-glycosylation and fiber diameter. |
| Extrusion Test | The force to extrude the devices through a 30 gauge needle was found to be similar for human (12 N) and bovine (15 N) products |

**Virus inactivation study**

The human collagen manufacturing processes were evaluated for the ability of specific purification procedures to remove/inactivate the following model viruses: bovine viral diarrhea virus (BVDV – enveloped –RNA virus), hepatitis A virus (HAV – non-enveloped –RNA virus), HIV-1 (enveloped RNA virus), porcine parvovirus (PPV – non-enveloped virus DNA virus) and pseudorabies virus (PrV – enveloped DNA virus). The 4 steps in the manufacturing process tested were pH 2 pepsin digestion, Cell Debris Remover treatment, diatomaceous earth

filtration and 0.25 N NaOH inactivation. The total inactivation potential for these 4 processing steps are:

| Virus | $Log_{10}$ Reduction | Virus type |
|---|---|---|
| BVDV | 15.7 | enveloped –RNA virus |
| HAV | 4.9 | non-enveloped –RNA virus |
| HIV | 18.2 | enveloped RNA virus |
| PPV | 5.4 | non-enveloped DNA virus |
| PrV | 17.0 | enveloped DNA virus |

## X. SUMMARY OF THE RESULTS OF THE CLINICAL INVESTIGATION

The clinical data provided in the original application and its supplements were sufficient to demonstrate the safety and effectiveness bovine collagen injection for the correction of contour deformities of the dermis. This section describes the new clinical data submitted in Supplement 50. In specific, Study # 01-711, "Inamed Human Collagen Immunogenicity Clinical Study" examined the incidence of patients displaying an immune response (i.e., a humoral or clinically detectable skin reaction) against CosmoDerm™ 1 Human-Based Collagen.

Study Design:
A prospective, open label clinical study was conducted to evaluate patient immune system responses to CosmoDerm™ 1 Human-Based Collagen. Male and female subjects who were 18 years of age or older were enrolled. Exclusion criteria were: pregnant and/or nursing, treated with chemotherapy agents or corticosteroids within the past 3 months, allergic to lidocaine, or currently receiving treatment with immunosuppressive drugs. Patients were also excluded if they had a history of an autoimmune disorder, severe allergies manifested by a history of anaphylaxis, or a current disease state that could affect an immune response (e.g., flu, cancer, HIV).

A pre-treatment blood sample was taken followed by a 0.1 ml intradermal injection of CosmoDerm™ 1 Human-Based Collagen into the volar forearm. The test site was monitored daily by the subject for signs of systemic and local reactions (e.g., erythema, pain, and swelling). Each subject returned to the clinic at approximately 72 hours after the first CosmoDerm™ 1 Human-Based Collagen injection to have any observations recorded. After a 30-day observation period, subjects returned to the clinic for a second CosmoDerm injection, and the same procedures of test site observation by the subject and a 72-hour visit with the clinical staff took place. Thirty days after the second CosmoDerm™ 1 Human-Based Collagen injection, subjects returned for a final clinic visit, which included a post-treatment blood draw.

Subject accounting and lost-to-follow-up:

Four hundred and forty-seven 447 subjects were entered into the screening phase of the study. Because nineteen patients did not meet the inclusion/exclusion criteria, 428 subjects (257 females and 171 males ages 18-74) were enrolled into the study and received a first injection. Seventeen subjects dropped from the study after the first injection and before the second injection one month later. Four hundred and six of the four hundred and eleven subjects that received a second injection of CosmoDerm completed the two month study.

Study Withdrawals:

Sixteen subjects were lost to follow-up and one subject withdrew consent due to personal reasons unrelated to the study. One subject was dropped from the study at visit 3 (72 hours after the first injection) for violating the exclusion criteria (i.e., receiving a cortisone shot for shoulder pain). One additional subject withdrew consent for personal reasons unrelated to the study after visit 3 and before visit 4. An additional subject was lost to follow up at visit 4 and was therefore dropped from the study. One subject received the 1st and 2nd injection, but did not return for visit 6 (28 days post-second injection) and was lost to follow-up, because the subject unexpectedly moved out of state.

**Lost to follow-up:**

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| Patient status | Number of subjects |
|---|---|
| Total subjects screened | 447 |
| Total subjects enrolled | 428 |
| Total no. of subjects at visit 1 | 428 |
| Total no. of subjects at visit 2 (1st injection) | 411 |
| Total No. of subjects at visit 3 (72 hr evaluation) | 411 |
| No. of subjects at visit 4 (28 day eval. & 2nd injection) | 407 |
| No. of subjects at visit 5 (72 hour evaluation) | 407 |
| No. of subjects at visit 6 (28 eval. & final blood draw) | 407 |
| No. of subjects discontinuing the study | 22 |

*CosmoDerm Immune Response*

Serum samples obtained before CosmoDerm™ 1 Human-Based Collagen exposure and 30 days after the second CosmoDerm injection were assessed with an ELISA capable of detecting IgG, IgM and IgA antibodies against Type I human collagen. No positive responses against human Type I collagen were observed. Equivocal titers (titers of 40-80), were found in four samples. Two of these four samples were from the same subject who displayed a pretreatment titer of 40 and post-treatment titer of 80. Of the remaining two equivocal samples, one subject's sample (with a titer of 40) was pre-treatment, and a negative result was observed post-treatment. The other equivocal response (with a titer of 40) was from a post-treatment sample of a different subject. None of the equivocal response serum samples cross-reacted

with bovine collagen.

Based on the observation that no patient displayed a positive response against CosmoDerm™ 1 Human-Based Collagen (i.e., 0/407 subjects), a single sided 95% upper confidence limit of 0.7% was calculated for the risk of experiencing a hypersensitivity response against human collagen after two CosmoDerm injections. Because a single patient did display a reaction at the test site 1 week after CosmoDerm injection, a second calculation based on an incidence of 1 in 407 (0.2%) subjects was used to calculate a single sided 95% upper confidence limit of 1.2% for the risk of developing a clinically detectable immune response against human collagen after two CosmoDerm™ 1 Human-Based Collagen injections.

Previous publications suggest that the incidence of positive skin test reactions to a Zyderm (i.e., bovine collagen) skin test are 3.0%[1] to 3.1%[2]. In the patients that showed no response to a single Zyderm skin test, the reported incidence of subsequent immunology-related adverse reactions was reported as 1.3%[1] to 1.5%[2]. The results of the CosmoDerm™ 1 Human-Based Collagen the skin test study suggests that the risk of experiencing hypersensitivity reaction against CosmoDerm is no greater than the risk of a patient experiencing a hypersensitivity reaction against a Zyderm or Zyplast treatment after failing to show a reaction to a single Zyderm skin test. For this reason the labeling for CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen do not require skin testing prior to use of the products.

## XI. CONCLUSIONS DRAWN FROM THE STUDY

The results of the Inamed Human Collagen Immunogenicity Clinical Study demonstrate that the 95% upper confidence interval for experiencing a hypersensitivity reaction against CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen will be less than 1.3%. This incidence is less then the reported incidence of immunologically related adverse events reported in Zyderm/Zyplast-treated patients who initially displayed a negative skin test. Consequently CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen may be used without a screening skin test prior to injection.

## XII. PANEL RECOMMENDATION

CosmoDerm/CosmoPlast were not discussed at a meeting of the General and Plastic Surgery Devices Advisory Panel. However, a Panel Member performed an evaluation of the biophysical and biochemical data presented in Supplement 50 as a homework assignment. This review concluded:

1) There were no significant differences observed in the biophysical and biochemical properties of bovine and human collagens that would result in a clinically significant difference in the safety or effectiveness of Zyderm/Zyplast and CosmoDerm/ CosmoPlast.

2) The current biophysical and biochemical analyses are sufficiently sensitive to allow one to predict that Zyderm/Zyplast and CosmoDerm/CosmoPlast which appear similar in *in vitro* studies, will also perform similarly in the clinical setting.

## XIII. CDRH DECISION

The FDA agreed with the conclusions of the member of the General and Plastic Surgery Devices Advisory Panel stated above.

The clinical data provided in the original application and its supplements were sufficient to support the safety and effectiveness of the bovine collagen device for use in the correction of contour deformities of the dermis, in non-weight bearing areas. The data previously collected on the bovine collagen device also supports the safety and effectiveness of the human collagen device.

The results of the skin test study suggest that the 95% upper confidence limit for the incidence of developing a clinically detectable immune response against human collagen after two injections is 1.2%. For this reason skin testing prior to use of CosmoDerm™ 1 Human-Based Collagen, CosmoDerm™ 2 Human-Based Collagen and CosmoPlast™ Human-Based Collagen is not required.

Inspection of the sponsor's manufacturing facilities was conducted on April 14, 2000 and April 2, 2001 and was found to be in compliance with the device Good Manufacturing Practice regulations.

## XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

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

Postapproval Requirements and Restrictions: See approval order.

## XV. References

1. Cooperman, L.V., et. al., *Aesth. Plastic. Surg*. **9**, 145 – 151 (1985).
2. Castrow, F.F. and Krull, E.A., *J. Amer. Acad. Dermatol*: **9**: 889 – 893 (1983).