

ZYPLAST® COLLAGEN IMPLANT

PHYSICIAN PACKAGE INSERT

DESCRIPTION

Zyplast® collagen implant is a sterile device composed of highly purified bovine dermal collagen that is lightly crosslinked with glutaraldehyde and dispersed in a phosphate-buffered physiological saline containing 0.3% lidocaine.

MODE OF ACTION

ZYPLAST collagen implant is introduced into mid to deep dermal tissues for correction of contour deficiencies. After injection, the suspended collagen forms a soft cohesive network of fibers, which is responsible for restoring contour. Over a period of months the implant is colonized by host connective tissue cells; once established, the implant takes on the texture and appearance of normal host tissue and is subject to the same stresses and aging processes.

INDICATIONS AND USAGE

ZYPLAST collagen implant is indicated for the correction of contour deficiencies of soft tissue. The etiology and distensibility of the defect, tissue stress at the implant site, and plane of placement of the implant will affect the degree and duration of contour restoration. Results of *in vitro* and *in vivo* studies suggest that ZYPLAST collagen implant, because it is crosslinked, may persist in tissue to a greater extent than non-crosslinked Zyderm® collagen implant; therefore, it is recommended that during treatment, correction should be limited to no more than 100% of the defect. Two or more implant sessions at intervals of at least two weeks may be required to achieve the desired effect.

Collagen implants have been employed successfully in many areas of the body to correct distensible acne scars, atrophy from disease or trauma, glabellar frown lines, nasolabial folds, or defects secondary to rhinoplasty, skin graft or other surgery, and other soft tissue defects. Severely indurated, sharply marginated and very superficial lesions (e.g., ice-pick acne scars, viral pockmarks, and superficial rhytides such as some perioral lines) have proved difficult to distend and, therefore, are difficult to correct. If a defect cannot be distended because of extensive scarring or nonelastic tissue, the course of correction will be prolonged, if correction is achievable.

Touch-up implantations at 6-18 month intervals will be required to maintain maximum correction. The interval at which touch-up implantations are needed depends on the nature of the lesion, the amount of implant introduced, the plane of placement and the stresses that may exist at corrected sites. For example, ongoing mechanical stresses eventually cause these defects to recur. Correction tends to persist longer in areas in which disease processes have become quiescent. Nevertheless, if a stable level of correction is desired, all patients should be counselled to anticipate supplemental implantations.

CONTRAINDICATIONS

ZYPLAST collagen implant therapy must not be initiated if the patient has a positive response to the required Collagen Test Implant. Refer to Collagen Test Implant Physician Package Insert for complete instructions for administration and evaluation of the test implant.

ZYPLAST collagen implant must not be used in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.

ZYPLAST collagen implant contains lidocaine and must not be used in patients with known lidocaine hypersensitivity.

ZYPLAST collagen implant must not be used in patients with a history of allergies to any bovine collagen products, including but not limited to collagen injectables, collagen implants, hemostatic sponges and collagen-based sutures, because these patients are likely to have hypersensitivity to ZYPLAST collagen implant.

ZYPLAST collagen implant must not be used in patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.

ZYPLAST collagen implant is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

WARNINGS

A Collagen Test Implant must be administered and evaluated prior to soft tissue deficiency correction using ZYPLAST collagen implant. (Refer to Collagen Test Implant Physician Package Insert.) Note: The Collagen Test Implant is non-crosslinked collagen, while ZYPLAST collagen implant is crosslinked collagen. If the Collagen Test Implant response is equivocal, it is recommended that a second test implantation be administered in the opposite arm and evaluated prior to the initiation of treatment.

Some physicians have reported the occurrence of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), and dermatomyositis (DM) subsequent to collagen injections in patients with no previous history of these disorders. Conflicting studies have been published (27, 28) in peer reviewed journals regarding the association between PM/DM and injectable collagen. A causal relationship between collagen injections and the onset of PM/DM, or the other connective tissue diseases listed, has not been established.

Also, an increased incidence of cell-mediated and humoral immunity to various collagens have been found in systemic connective tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). 19-24 Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. Therefore, caution should be used when treating these patients including consideration for multiple skin testing (see Skin Test Package Insert).

Local necrosis is a rare event which has been observed following collagen implantation. Most necroses reported through post-marketing surveillance have occurred in the glabella. It is thought to result from the injury, obstruction, or compromise of blood vessels. ZYPLAST collagen implant is more often injected deeper into the dermis closer to the local vascular supply than is ZYDERM collagen implant. Additionally, ZYPLAST collagen implant does not undergo syneresis after injection. Therefore, interruption of the local blood supply may more likely occur with ZYPLAST collagen implant. It is recommended that corrections in the glabellar region be performed using ZYDERM collagen implant rather than ZYPLAST collagen implant.

Patients with a history of dietary beef allergy should be carefully evaluated before injectable bovine collagen therapy, since it is possible that the collagen component of the beef may be causing the allergy. More

than one skin test is highly recommended prior to treating these patients.

ZYPLAST collagen implant must not be implanted into blood vessels. Collagen can initiate platelet aggregation, and implantation of ZYPLAST collagen implant into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

PRECAUTIONS

Use of ZYDERM 1 collagen implant in an individual patient should be limited to 30 cc over a one-year period. Use of ZYDERM 2 collagen implant in an individual patient should be limited to 15 cc over a one-year period. The combination of these products or of ZYDERM in conjunction with ZYPLAST in an individual patient should be limited to 30 cc over a one-year period. The safety of injecting greater amounts on an annual basis has not been established.

ZYPLAST collagen implant should be used with caution in patients with histories of allergic reactions to other substances, as injectable collagen use has been associated with allergic hypersensitivity responses, especially in patients with such histories.

The injection of ZYPLAST collagen implant carries an inherent, yet minimal, risk of infection, as does any transcutaneous procedure.

Use of ZYPLAST collagen implant 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 of ZYPLAST collagen implant for use during pregnancy or in infants has not been established.

ZYPLAST collagen implant should be used with caution in patients on immunosuppressive therapy.

Patients who are using substances which reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.

ZYPLAST collagen implant is not recommended for use in the periorbital area. Overcorrection of the vermilion border of the lip has been slow to resolve due to minimal tissue stresses at this site. Therefore, caution is advised for ZYPLAST collagen implant use in this area.

Clinical experience with injectable collagen implants was not available prior to 1976; the safety of this product for a longer duration is not known.

Since it has been reported that host collagen may be deposited at the site of collagen implantation, the patient should be informed that part or all of the correction may last for 2 years or more.

TREATMENT RESPONSES

Transient or minimal swelling, mild redness, and discomfort will probably occur at the implant site immediately following implantation. Increasing discomfort or swelling, or spreading redness should be brought immediately to the physician's attention.

Transient pain and tenderness at injection sites has been associated with the injection of the collagen implants.

On occasion, transient painless bruising or discoloration has been noted to develop at one or more of the implantation sites. Resolution has always been spontaneous.

Fewer than 1% of patients receiving ZYDERM collagen implant have at some time reported an intermittent swelling response, involving moderate induration at the implant site and edema within the surrounding tissues. In some cases, these responses have been found to be associated with antibodies to bovine collagen. At times this has been accompanied by mild pruritis or minimal erythema which may persist for a period up to several months. These reactions may last only a few hours and are usually associated with causes of peripheral vasodilatation, such as consumption of alcohol, prolonged exposure to sun and/or heat, exercise, and flare-ups of hay fever and other causes of nasal and sinus congestion. To date, these reactions have been self-limiting and have not been shown to affect adversely the long-term success of collagen implant correction, although they may persist throughout the life of the implant.

Infections at collagen implant sites have occurred in fewer than one per thousand treated patients, and reactivation of a pre-existing herpes simplex infection at implantation sites has been reported in fewer than one per ten thousand patients. These responses resolved quickly and without sequelae.

As with any injection into the head or neck, the injected material may be inadvertently implanted into a blood vessel. Forceful injection into dermal arterial branches of the face and scalp could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Such a complication, although unlikely, has been reported with the use of ZYDERM collagen implant in one patient, and resulted in the sudden and permanent loss of vision in one eye. Similar complications have been associated with other injectable preparations, including corticosteroids, local anesthetics, and angiographic agents. These findings emphasize the importance of avoiding implantation into blood vessels.

ADVERSE REACTIONS

Patients treated intradermally with ZYPLAST collagen implant have reported temporary palpable lumpiness or visible material (milia-like yellow or white papules) at injection sites. Both of these types of treatment responses resolved spontaneously without sequelae, and are believed to reflect reduced shrinkage of crosslinked implants due to water resorption, compared with non-crosslinked collagen implants.

Sensitization reactions to injectable collagen implants have occurred in 1-2% of treated patients. Most reactions have been of a hypersensitivity nature and have consisted of erythema, swelling, induration and/or urticaria at implantation sites. Often these reactions have occurred following an unrecognized or unreported positive collagen skin test.

Typically, allergic reactions persist between one and nine months, with an average duration of four months. These reactions may be intermittent or continuous in nature. In rare instances, reactions have resolved in one or two weeks, or have persisted for more than one year. Although several forms of therapy (antihistamines, NSAIDS, oral, topical and intralesional steroids) have been tried, usually they resulted in only temporary improvement. In most cases, time has proved to be the determining factor in the resolution of these reactions. In rare instances, patients have been left with residual firmness at the site of a resolved adverse reaction.

On rare occasions, abscess formation has occurred at implantation sites. In some cases this reaction has been associated with elevated titers of anti-bovine collagen antibodies, and can be multiple or recurrent. These

reactions develop weeks to months following injections and may result in induration and/or scar formation. Most of the remaining responses occurred in patients who became sensitized to collagen implants at some point during their course of treatment.

The antigenic specificity of ZYPLAST collagen implant has been determined to be identical to that of ZYDERM collagen implant. During clinical trials and post-marketing surveillance, the incidence of hypersensitivity responses to ZYPLAST collagen implant has been significantly lower than to ZYDERM collagen implant; however, because of the potential for prolonged local availability of antigen, it is possible that the long-term rate of response to ZYPLAST collagen implant may exceed the low rate experienced to date.

Systemic complaints have been reported by fewer than 0.5% of collagen implant patients. During clinical testing and subsequent monitoring of patient complaints following exposure to ZYPLAST collagen implant, a variety of systemic complaints have been reported. These reports have included flu-like symptoms (fever, headache, myalgia, neuralgia, nausea, malaise, or dizziness); pruritis; rash; transient visual disturbances including blurred vision; tingling and numbness; transient polyarthralgia; and various systemic diseases including immune-mediated diseases. Rare anaphylactoid responses have been reported, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

Localized necrosis and/or sloughing, resulting in a scab and/or a scar, has occurred following interruption of blood flow such as through blood vessel laceration or occlusion. The extent of necrosis has varied and is in the pattern of the tissue served by the vessel involved. This phenomenon has been reported more frequently in the glabellar region of the face than in other areas; nevertheless, the incidence of this scab or scar formation is less than 1%, and may occur in conjunction with either infection and/or hypersensitivity response. In these patients, implantation can be followed by prolonged blanching or development of ecchymosis at the treatment site. It is possible that overdilatation of tissue in areas of compromised vascularity may lead to similar complications, caused by interruption of blood supply to an injection site.

To report an adverse reaction, phone the Medical Monitoring Department, McGhan Medical Corporation, toll-free: (800) 722-2007.

DIRECTIONS FOR USE

NOTE: ZYPLAST collagen implant should be stored at standard refrigerator temperatures. DO NOT FREEZE.

1. Prior to a Collagen Test Implant, the patient should be provided with a copy of the Patient Brochure.
2. Prior to treatment with ZYPLAST collagen implant, the results of the test implantation must be carefully evaluated; the patient must not have a response to the required Collagen Test Implant. For a complete discussion of the Collagen Test Implant, refer to the Collagen Test Implant Physician Package Insert supplied with test syringes.
3. Prior to treatment with ZYPLAST collagen implant, 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 will be required to maintain maximum correction.
4. A complete medical history should be obtained to determine whether the patient is an appropriate candidate for treatment with ZYPLAST collagen implant.
5. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pretreatment photographs are recommended.
6. 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.
7. ZYPLAST collagen implant is implanted through a fine-gauge needle. The needle should be placed into the plane(s) of apparent deformity and the defect should not be overcorrected. Best results with ZYPLAST collagen implant are achieved in defects requiring mid to deep dermal implant placement. The rate and degree of subsidence of correction in the implanted area varies with patient, treatment site, and plane of implant placement. Correction should be conservative during initial treatment. Clinical experience has shown that overcorrection has been slow to resolve in the periorbital area and in treatment sites around the vermilion border of the lip. Therefore, caution is advised for ZYPLAST collagen implant use in these areas. Severely indurated defects such as scars, which initially resist distention, may require several treatment sessions before desired correction is obtained.

Needles may become occluded or dull during a treatment session, and replacement may be necessary.
8. Vigorous massage of the treated areas is recommended following implantation.
9. Successive implantations at intervals of two or more weeks may be necessary to achieve the desired level of correction.
10. The physician should instruct the patient to report to her/him any evidence of adverse texture change in the surrounding implantation site. Other problems possibly associated with the use of ZYPLAST collagen implant should be promptly brought to the attention of the physician.
11. The syringe and any unused material should be discarded after a single treatment visit.

HOW SUPPLIED

ZYPLAST collagen implant is sterile and supplied in individual treatment syringes packaged with fine-gauge needles, ready for use.

To place an order, phone toll-free: (800) 624-4261.

STORAGE DIRECTIONS

ZYPLAST collagen implant should be stored at standard refrigerator temperatures. DO NOT FREEZE.

ZYPLAST collagen implant has an off-white opaque appearance. In the event that a syringe contains material that is clear (like water), do not use the syringe and notify McGhan Medical Corporation immediately at (800) 624-4261.

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE, DISTRIBUTION, OR USE BY, OR ON THE LAWFUL ORDER OF A LICENSED PHYSICIAN OR AN ORAL AND MAXILLOFACIAL SURGEON.

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A complete bibliography on Injectable Collagen Implant may be requested from McGhan Medical Corporation.

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