

# ZYDERM® COLLAGEN IMPLANT

## PHYSICIAN PACKAGE INSERT

### DESCRIPTION

Zyderm® collagen implant is a sterile device composed of highly purified bovine dermal collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine. ZYDERM collagen implant is available in two forms: ZYDERM 1 collagen implant and ZYDERM 2 collagen implant. ZYDERM 2 collagen implant contains almost twice the collagen concentration of ZYDERM 1 collagen implant.

### MODE OF ACTION

ZYDERM collagen implant is introduced into the dermis for correction of contour deficiencies of this soft tissue. After injection, the implant undergoes syneresis and, as the saline is lost, the suspended collagen condenses into a soft cohesive network of fibers. This network is responsible for restoring skin 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

ZYDERM collagen implant is indicated for the correction of contour deformities of the dermis in non-weight bearing areas. The etiology and distensibility of the lesion, tissue stress at the implant site, and the tissue plane of placement of the implant will affect the degree and duration of contour restoration. ZYDERM collagen implant should be injected into the superficial papillary dermis (see Directions for Use for complete instructions).

ZYDERM 1 and ZYDERM 2 collagen implant 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; rhinoplasty, skin graft or other surgically-induced irregularities; and other soft tissue defects. Severely indurated, sharply margined and very superficial lesions (e.g., ice-pick acne scars, viral poxmarks, and superficial rhytides such as some perioral lines) have proven 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. Deposits of even small amounts of ZYDERM collagen implant within a scar, however, often soften the tissue and allow for subsequent distension and correction.

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.

To decrease the total number of treatment visits required, it is recommended that the contour deficiency be overcorrected to compensate for the loss of saline in the suspension. Overcorrection to 1.5-2.0 times the initial depth of the lesion is recommended for ZYDERM 1 collagen implant. A lesser degree of overcorrection is required to achieve a given level of correction with ZYDERM 2 collagen implant. To date, no permanent overcorrection has been reported as a result of this technique.

Syneresis of the implant and the resulting absorption of the exuded saline result in a rapid (less than 24 hour) reduction of overcorrection, which is followed by a further, but more gradual (two or more weeks) reduction as the implant stabilizes. Approximately 25-30% of the ZYDERM 1 collagen implant and a higher percent of the ZYDERM 2 collagen implant volume remains, although this volume varies among individual patients. Therefore, two or more implant sessions at intervals of at least two weeks usually are required to achieve the desired effect.

Long-term follow-up data indicate that "touch-up" implantations at 6-18 month intervals are usually required to maintain maximum correction. The interval at which touch-up implantations are needed depends on the stresses that may exist at corrected sites. For example, ongoing mechanical stresses (such as smiling or frowning) will eventually cause these defects to recur. However, correction tends to persist longer in areas in which disease processes (such as acne) have been quiescent. Nevertheless, if a stable level of correction is desired, all patients should be counselled to anticipate supplemental implantations.

### CONTRAINDICATIONS

ZYDERM collagen implant therapy must not be initiated if the patient has an untoward response to the required test implantation (see Directions for Use for further details).

ZYDERM 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.

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

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

ZYDERM 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.

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

### WARNINGS

A test implantation must be administered and evaluated prior to soft tissue deficiency correction with ZYDERM collagen implant (see Directions for Use for further details). If the test implantation response is positive, the patient must not be treated with ZYDERM collagen implant. If the test implantation 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 (35, 36) 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). 29-34 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).

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.

ZYDERM collagen implant must not be implanted into blood vessels.

Collagen can initiate platelet aggregation, and implantation of ZYDERM 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 Zylplast® collagen implant 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.

Injectable bovine collagen should be used with caution in patients who are atopic or have a history of allergies. This class of patient has a greater potential of ultimately exhibiting an allergic reaction to bovine collagen than do other patients.

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

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

ZYDERM 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.

Overcorrection of lesions in the periorbital area, as well as around the vermilion border of the lip, has been slow to resolve due to minimal tissue stresses at these sites. Therefore, caution is advised when treating these areas. Special caution should be used when implanting ZYDERM 2 collagen implant in these sites, as the more concentrated material may lead to persistent overcorrection.

Clinical experience with injectable collagen implant 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

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. At times this has been accompanied by mild pruritus or minimal transient erythema. 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 ZYDERM collagen implant corrections, although they may persist throughout the life of the implant.

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.

Approximately 20% of patients treated with ZYDERM 2 collagen implant have reported temporary palpable lumpiness or visible white patches at injection sites. Both of these types of treatment-associated responses resolved spontaneously without sequelae, and are believed to reflect the fact that with ZYDERM 2 collagen implant, a higher concentration of collagen can be injected in a single treatment session.

### ADVERSE REACTIONS

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. Most of the remaining responses occurred in patients who became sensitized to ZYDERM collagen implant at some point during their course of treatment. Approximately 80% of these reactions occur within four weeks following the sensitizing dose.

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; oral, topical and intralesional steroids) have been tried, they usually 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, the hypersensitivity response has progressed to a cystic reaction which may drain purulent material. The incidence and severity of this type of hypersensitivity response reported to date has been greater with ZYPLAST collagen implant than with ZYDERM collagen implant. These reactions develop weeks to months following injection and may result in scar formation, rarely requiring medical revision to correct. This type of reaction can occur as multiple and/or recurrent sterile abscesses which tend to be persistent and resistant to drug therapy; careful incision and drainage has been a useful treatment.

Infections at implantation sites have occurred in fewer than one per thousand treated patients, and herpes simplex eruptions at sites which had been previously affected with herpes simplex have been reported in fewer than one per ten thousand patients. These responses resolved quickly and without sequelae.

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 ZYDERM collagen implant, a variety of systemic complaints have been reported. These reports have included flu-like symptoms (fever, myalgia, neuralgia, headache, nausea, malaise, or dizziness); pruritus; 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 with ZYDERM collagen implant, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

As with any injection into the head or neck, the injected material may be inadvertently implanted in a blood vessel. Localized necrosis and/or sloughing, which may result in a scar, has occurred following interruption of blood flow through blood vessel laceration or occlusion, or through tissue overdistention which compromised vascularity. The extent of necrosis has varied and has been reported more frequently in the glabellar region of the face than in other areas; nevertheless, the incidence is less than 1% of treated patients. Scar formation may also occur in conjunction with either infection and/or hypersensitivity responses. If implantation is followed by prolonged blanching or significant ecchymosis at the treatment site, gentle massage and close fol-

low-up are recommended.

In addition, forceful injection into superficial 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 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 superficial dermal implantation to avoid dermal blood vessels during implantation of ZYDERM collagen implant.

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

#### DIRECTIONS FOR USE

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

Prior to test implantation with ZYDERM collagen implant, the patient should be provided with a copy of the Patient Brochure. The patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment-associated reactions, adverse reactions, and method of administration of ZYDERM collagen implant. Patients also should be advised that supplemental "touch-up" implantations may be required to maintain maximum correction.

#### TEST IMPLANTATION

1. At the time of the initial evaluation, a complete medical history should be obtained to determine conditions that might influence the successful use of ZYDERM collagen implant.
2. After verifying that contraindications do not exist, a ZYDERM collagen implant test implantation is administered to ensure that the patient is not sensitive to ZYDERM collagen implant. After cleansing the site, 0.1cc of material from a ZYDERM collagen implant test syringe should be implanted intradermally into a volar forearm surface.
3. The results of the test implantation must be carefully evaluated for a four-week period prior to the initiation of treatment. Patients should be instructed to notify their physicians of any untoward test response observed within the four-week period. A positive test site response is defined as: erythema of any degree, induration, tenderness, or swelling at the test site, with or without pruritus, which persists for more than six hours or appears more than 24 hours following implantation. Patients with such responses are ineligible for treatment with ZYDERM collagen implant. In addition, the onset of rash, arthralgia or myalgia should be brought immediately to the attention of the treating physician in order that he might evaluate its possible relationship to the test dose. To date, approximately 3.0% of the patients tested have had one or more of the above-described reactions to the test implantation.
4. TREATMENT WITH ZYDERM COLLAGEN IMPLANT IS CONTRAINDICATED IN ANY PATIENT EXHIBITING AN UNTOWARD TEST RESPONSE DURING THE FOUR-WEEK EVALUATION PERIOD.

Occasionally, a normal skin test will exhibit a palpable bead of collagen in the absence of inflammation, swelling or pruritus. If the test implantation 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. The majority of retest responses will occur within 72 hours; however, the repeat test also should be observed for the full 4 weeks.

Clinical experience has shown that the screening of the test implant cannot be overemphasized. However, a negative skin test does not preclude the possibility of the patient subsequently developing a delayed hypersensitivity response to the implant material following additional exposures.

#### CORRECTIVE IMPLANTATION

(For those patients not exhibiting an untoward test response):

1. 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.
2. 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.
3. ZYDERM collagen implant is implanted intradermally through a fine-gauge needle into the plane(s) of apparent deformity. The needle should be placed as superficially as possible in the papillary dermis and the lesion should be deliberately overcorrected. When using ZYDERM 1 collagen implant, it is recommended that the lesion be overcorrected to 1.5-2.0 times the initial depth of deformity. A lesser degree of overcorrection is required to achieve a comparable level of correction when using the more concentrated ZYDERM 2 collagen implant. If blanching is not achieved, withdraw the needle immediately as it has probably been placed too deeply in the dermis. The rate and degree of subsidence of the implanted area is variable, but utilization of this technique has not resulted in any instances of permanent overcorrection. However, 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. Thus, these areas should be treated cautiously and small amounts of ZYDERM collagen implant should be implanted over several treatment sessions without overcorrection. Severely indurated lesions which initially resist distention often require several treatment sessions before desired correction is obtained. In such lesions it is preferable to implant within the scar rather than beneath it.  
Needles may become occluded or dull during a treatment session and replacement may be necessary.
4. Additional implantations at intervals of two or more weeks are usually necessary to achieve the desired level of correction.
5. 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 ZYDERM collagen implant use should also be promptly brought to the attention of the physician.
6. Discard any unused material and the syringe after a single treatment visit.

#### HOW SUPPLIED

ZYDERM collagen implant is supplied as ZYDERM 1 collagen implant and ZYDERM 2 collagen implant. Test and treatment syringes are packaged sterile with fine-gauge needles, ready for implantation.

ZYDERM Test syringes are appropriate for testing prior to treatment with either ZYDERM collagen implant or ZYPLAST collagen implant.

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

#### STORAGE DIRECTIONS

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

ZYDERM collagen implant has a whitish, opaque or semi-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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