

LABELING



OP-1 PUTTY PACKAGE INSERT

HUMANITARIAN DEVICE. OP-1 Putty is authorized by Federal law for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes. The effectiveness of OP-1 Putty for this use has not been demonstrated.

PRODUCT DESCRIPTION:

OP-1 Putty is an osteoinductive and osteoconductive bone graft material. OP-1 Putty consists of the recombinant human Osteogenic Protein (rhOP-1), Type 1 Bovine Bone Collagen Matrix (collagen matrix) and the Putty Additive carboxymethylcellulose sodium (CMC). OP-1 Putty is intended to be reconstituted with sterile saline (0.9%) solution.

OP-1 Putty is provided as two components:

- A large vial containing one gram sterile dry powder consisting of bovine collagen and OP-1.
- A small vial containing the Putty Additive (230 mg) consisting of a sterile dry powder comprised of carboxymethylcellulose (CMC).

Both components must be combined with sterile saline to produce the product.

STORAGE CONDITIONS:

Store OP-1 Putty at 2-8 °C.

SYMBOLS:



ATTENTION, SEE INSTRUCTIONS FOR USE



DO NOT REUSE



USE BY



CAUTION: Federal law restricts this device to sale by or on the order of a physician



CATALOGUE NUMBER



LOT NUMBER



STERILE BY IRRADIATION

INDICATIONS:

OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

CONTRAINDICATIONS:

- OP-1 Putty should not be used to treat patients who have a known hypersensitivity to any of the components of the product.
- OP-1 Putty should not be applied at or near the vicinity of a resected tumor or in patients with a history of malignancy.
- OP-1 Putty should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- OP-1 Putty should not be administered to pregnant women. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

WARNINGS:

- Women of childbearing potential should be advised that antibody formation to OP-1 and its influence on fetal development have not been assessed in recent studies. Antibodies to OP-1 were measured at pretreatment and 6 weeks and 6 months post treatment. Antibodies were detected in 23 out of 24 (96%) patients treated with OP-1 Putty. No antibodies were detected in patients treated with autograft. Neutralizing antibodies were detected in 7/24 (29%) patients treated with OP-1 Putty. For six out of the seven patients, neutralizing activity was detected at 6 weeks post treatment, but not at 6 months post treatment. For the seventh patient, neutralizing activity was detected only at 6 months post treatment. The clinical significance of these antibodies is not known. The effect of maternal antibodies to OP-1 on the unborn fetus is unknown, both when the antibodies are detected during the first year following treatment and later, when the antibodies may not be detectable. Studies in genetically altered mice indicate that OP-1 is critical for fetal development and that lack of OP-1 activity, as might be induced by antibody, may cause neonatal death or birth defects.
- Women of childbearing potential should be advised to avoid becoming pregnant for one year following treatment with OP-1 Putty.

- The maximum human dose should not exceed 2 vials.
- Localized ectopic or heterotopic bone formation may occur outside of the treatment site.
- OP-1 Putty has no biomechanical strength.

PRECAUTIONS:

- Clinical studies using OP-1 Putty were performed in patients requiring a primary spinal fusion. Except for an animal study evaluating the effect of OP-1 on revision spinal fusion surgery in the presence of nicotine, no data have been collected on the use of OP-1 Putty for revision spinal fusion surgery in compromised patients, i.e., those who are smokers or have diabetes or osteoporosis.
- The safety or probable benefit of OP-1 Putty in patients with autoimmune disease has not been demonstrated.
- The effect of radiation therapy, chemotherapy, immunosuppressive or steroid therapy on the probable benefit of OP-1 Putty is not known.
- There are no data on the excretion of OP-1 in the breast milk of female patients who are nursing.
- OP-1 is important in the development of the kidney. Studies have not been performed to examine the effect of neutralizing antibodies to OP-1 in patients with impaired renal function.
- IMMUNOGENICITY: As with all therapeutic proteins, there is a potential for immune responses to be generated against components of the OP-1 Putty. In the degenerative spondylolisthesis pilot study, antibodies to OP-1 were measured at pretreatment and 6 weeks and 6 months post treatment. Antibodies were detected in 23 out of 24 (96%) patients treated with OP-1 Putty. No antibodies were detected in patients treated with autograft. Neutralizing antibodies were detected in 7/24 (29%) patients treated with OP-1 Putty. For six out of the seven patients, neutralizing activity was detected at 6 weeks post treatment, but not at 6 months post treatment. For the seventh patient, neutralizing activity was detected only at 6 months post treatment. The clinical significance of these antibodies is not known. The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to OP-1 Putty with the incidence of antibodies to other products may be misleading
- A two year rat bioassay, in which approximately 17.5-70 times the equivalent maximum human dose of 2 vials of OP-1 Implant, a component of OP-1 Putty, was placed under the skin, produced more cancer growths at the site of implantation of the OP-1 compared to rats that had no OP-1. It is believed that this may be due to the Oppenheimer Solid State Tumor Effect, the formation of tumors at the site of implantation of inert objects under the skin in rats. This effect has not been reported in humans. Additional studies are ongoing to examine the effect of OP-1 on the growth of pre-existing tumors.
- Take care to ensure that OP-1 Putty will be contained by viable tissue. Obtain adequate hemostasis before implanting OP-1 Putty to prevent the product from being displaced.
- Inadequate vascularity in the surrounding tissues may diminish the probable benefit of OP-1 Putty. Make every effort to surround the product with viable tissue.
- For single use only. Do not re-use OP-1 Putty. Discard unused product and use a new device for subsequent applications
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, don't use the product. Retain the packaging and vial, and contact a Stryker Biotech representative.
- Do not use after the printed expiration date on the label.

ADVERSE EVENTS:

The following table was compiled from multi-center pilot and pivotal studies of OP-1 Putty in patients with degenerative spondylolisthesis requiring primary fusion of the affected spinal level. This table contains all of the reported events for the two groups that were reported to the studies as of October 17, 2003.

**Summary of Adverse Events for All Patients
in the Pilot and Pivotal Posterolateral Spinal Fusion Studies**

Body System	OP-1 (n=228)	Autograft (n=98)
Abnormal lab values	6 (3%)	8 (8%)
Blood and lymphatic system disorders	8 (4%)	14 (14%)
Cardiac disorders	9 (4%)	1 (1%)
Ear and labyrinth disorders	2 (1%)	1 (1%)
Eye disorders	2 (1%)	0 (0%)
Gastrointestinal disorders	30 (13%)	10 (10%)
General disorders and administration site condition	36 (16%)	18 (18%)
Immune system disorders	2 (1%)	2 (2%)
Infections and infestations	18 (8%)	8 (8%)
Injury, poisoning and procedural complications	44 (19%)	23 (24%)
Metabolism and nutrition disorders	6 (3%)	1 (1%)
Musculoskeletal and connective tissue disorders - other	50 (22%)	23 (24%)
Musculoskeletal and connective tissue disorders - joint inflammation	24 (11%)	6 (6%)
Musculoskeletal and connective tissue disorders - pseudarthrosis	12 (5%)	3 (3%)
Neoplasms benign, malignant and unspecified	2 (1%)	2 (2%)
Nervous system disorders - other	26 (11%)	10 (10%)
Nervous system disorders - TIA	4 (2%)	0 (0%)
Psychiatric system disorders	10 (4%)	3 (3%)
Renal and urinary disorders	13 (6%)	9 (9%)
Reproductive system and breast disorders	1 (0.4%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	15 (7%)	4 (4%)
Skin and subcutaneous tissue disorders - other	8 (4%)	1 (1%)
Skin and subcutaneous tissue disorders - wound infection	15 (7%)	2 (2%)
Social Circumstances	1 (0.4%)	0 (0%)
Surgical and Medical Procedures	2 (1%)	0 (0%)
Vascular Disorders	17 (8%)	10 (10%)

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stryker®
BIOTECH



OP-1™ Putty

Facts you should know about the use of OP-1 Putty as an alternative to autograft in compromised patients (examples include osteoporosis, smoking and diabetes) requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion.

HUMANITARIAN DEVICE OP-1 Putty is authorized by Federal law for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes. The effectiveness of OP-1 Putty for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

[Patient Information Booklet]

Read all of this booklet carefully before you are treated with OP-1 Putty.

- **Keep this booklet. You may need to read it again.**
- **If you have further questions or do not understand the information provided in this booklet, please ask your doctor before your surgery.**

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INTRODUCTION

This booklet contains information to help you decide whether or not to have revision surgery with OP-1 Putty to fuse your spine. A procedure that requires your surgeon to take bone from elsewhere in your body (often part of your hip) to use as a graft, called autograft, can also be used for revision spinal fusion. OP-1 Putty is a replacement for autograft, and does not require your surgeon to take bone from another part of your body.

Please read this booklet completely and discuss your questions with your doctor. Only your doctor can determine whether OP-1 Putty is appropriate for you.

How does the spine fuse?

The spinal fusion procedure makes use of a bone graft that initiates bone formation. This process is initiated when cells in your body are activated by specialized proteins. These activated cells, called osteoblasts, then organize and calcify to produce new bone. As the newly formed bone matures it strengthens and fuses to vertebrae in your spine to prevent motion and instability.

[Picture Phase I] – To fuse the spine, cells in the body are recruited and activated by specific proteins to become new bone.

[Picture Phase II] – In the early stages of fusion, new bone is formed between the spinal segments and strengthens over time.

[Picture Phase III] – The bone will eventually calcify and mature.

What is pseudarthrosis and revision fusion?

The first graft procedure usually fuses the spine. Unfortunately there are certain situations where a bone does not heal normally due to issues that affect the blood supply, such as the effects of smoking, poor bone quality from osteoporosis or diabetes, for example. A spinal graft that does not fuse is called a pseudarthrosis. If left untreated, serious complications and pain may occur. A pseudarthrosis is typically treated by a second graft procedure called a revision fusion. Some patients may not have sufficient bone or bone marrow to attempt the second procedure.

OP-1 Putty

Currently, the available options for revision spinal fusion procedures involve using autograft (your own bone), autologous bone marrow harvest or allograft (bone from a donor). The first two procedures require removing bone or bone marrow from your hip and placing it at the fusion site. In some patients, this procedure may not be possible or may not work for spinal fusion, because of factors that lessen the ability of your own tissue to be effective. Some of these factors include osteoporosis, diabetes or smoking. The allograft procedure is generally not as effective in forming bone as the first and adds the potential risk of disease transmission.

OP-1 Putty is a genetically engineered product that is an alternative to autograft, bone marrow harvest and allograft bone. It contains OP-1, bovine (cow) collagen and a thickener that makes it easier to handle the product during surgery.

How does OP-1 Putty work?

OP-1 is a genetically engineered bone morphogenetic protein (BMP, specifically BMP-7) that is similar to the form of BMP-7 found naturally in the human body. This unique protein has the ability to transform cells in the body to become new bone and potentially fuse the spine. When used for revision spinal fusion, OP-1 Putty, containing OP-1, can activate the bone formation process by providing a therapeutic amount of OP-1 to the fusion site. Specific cells from the surrounding tissue are recruited to the fusion site and signaled to form new bone. Once OP-1 Putty has initiated the bone formation process, it is resorbed by the body and natural bone formation takes place.

[Picture Phase I] – OP-1 Putty is placed between the spinal segments during surgery.

[Picture Phase II] – OP-1 Putty begins to recruit cells from the surrounding tissue and activates them to become new bone.

[Picture Phase III] – Normal bone begins to strengthen over time and fuse the spinal segments.

When Should OP-1 Putty Be Used?

OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral spinal fusion of the lower back, when using the patient's own bone or bone marrow is not feasible or is not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

When Should OP-1 Putty Not Be Used?

You should not use OP-1 Putty if:

- you are allergic to OP-1, bovine (cow) products or any of the components of OP-1 Putty
- there has been a tumor removed at or near the vicinity of the fusion site.
- you have had a previous history of cancer.
- you are <18 years of age or you are still growing.
- you are pregnant or wish to become pregnant within the year after your revision spinal fusion surgery.

Please consult your physician if you are unsure of any of the above contraindications.

What should I know about OP-1 Putty before deciding to use it?

There are certain things you should know before deciding to be treated with OP-1 Putty. Please read the following carefully. If you have any questions about the use of OP-1 Putty, please ask your doctor before surgery.

What are the Risks and Benefits of OP-1 Putty?

These are the risks associated with the use of OP-1 Putty.

- Failure to fuse your spine.
- Allergic reaction to the product or any of its parts.
- Bone growth in other areas outside the treatment site if the product is misplaced.
- Other unknown risks and discomforts which are individual to each patient. (See Warnings and Precautions)

The possible benefits associated with the use of OP-1 Putty include:

- Fusion of your spine.

Are there any WARNINGS/PRECAUTIONS I should know about the use of OP-1 Putty?

WARNINGS:

WARNING: If you are a woman who is able to have children, you should know that you may develop antibodies (an immune reaction) to OP-1. In a clinical study, antibodies were measured before treatment and at 6 weeks and 6 months after treatment. Antibodies were detected in 23/24 (96%) of patients treated with OP-1 and in none of the patients who were not treated with OP-1. Neutralizing antibodies were detected in 7/24 (29%) of patients treated with OP-1. For six out of the seven patients, neutralizing activity was detected at 6 weeks following surgery, but not at 6 months following surgery. For the seventh patient, neutralizing activity was detected only at 6 months following surgery. The effect of a mother's antibodies on the OP-1 made naturally by an unborn baby is not known, both when the antibodies are detected during the first year following treatment with OP-1 and later when the antibodies may not be detectable by laboratory tests. Studies in mice have shown that OP-1 is necessary for proper development of an unborn baby and that lack of OP-1 may cause life-threatening birth defects.

- If you are a woman who is able to have children, you need to take measures to prevent pregnancy for one year after treatment with OP-1 Putty.

- Bone may form in the muscle or other tissues near the fusion site.
- The maximum human dose should not exceed 2 vials.

PRECAUTIONS:

- The safety or probable benefit of OP-1 Putty in patients with autoimmune disease has not been demonstrated.
- The effect of radiation therapy, chemotherapy, immunosuppressive or steroid therapy on the probable benefit of OP-1 Putty is not known.

- There are no data on the excretion of OP-1 in the breast milk of female patients who are nursing.
- OP-1 is important in the development of the kidney. Studies have not been performed to examine the effect of neutralizing antibodies to OP-1 in patients with impaired renal function.
- Your body may generate an immune response, or antibodies, against OP-1 Putty. In a clinical study, antibodies to OP-1 were measured before surgery and 6 weeks and 6 months following surgery. Antibodies were detected in 23 out of 24 (96%) patients treated with OP-1 Putty. No antibodies were detected in patients treated with autograft. Neutralizing antibodies were detected in 7/24 (29%) patients treated with OP-1 Putty. For six out of the seven patients, neutralizing activity was detected at 6 weeks following surgery, but not at 6 months following surgery. For the seventh patient, neutralizing activity was detected only at 6 months following surgery. The ability of these antibodies to block (or neutralize) the effects of OP-1 made naturally by your body or by a developing fetus is not known.
- A two year rat bioassay, in which approximately 17.5-70 times the equivalent maximum human dose of 2 vials of OP-1 Implant, a component of OP-1 Putty, was placed under the skin, produced more cancer growths at the site of implantation of the OP-1 compared to rats that had no OP-1. It is believed that this may be due to the Oppenheimer Solid State Tumor Effect, the formation of tumors at the site of implantation of inert objects under the skin in rats. This effect has not been reported in humans. Additional studies are ongoing to examine the effect of OP-1 on the growth of pre-existing tumors.

From the worldwide experience with OP-1, 7 patients reported the occurrence of cancer. Six of the 7 events reported were non-osseous cancers occurring in elderly patients. A seventh event of recurring chondrosarcoma was reported in a patient with a history of chondrosarcoma. Recurrence and disease progression were considered normal for this type of cancer. The incidence of cancer in patients treated with OP-1 is less than 1% and is within the range of cancer occurrence in the general populations of the U.S. and Australia (the countries in which most patients were treated).

Has OP-1 Putty been studied in humans?

No patients have been treated with OP-1 Putty for revision spinal fusion surgery. Few compromised patients, for example, those who smoke or have osteoporosis or diabetes, have been treated with OP-1 for primary spinal fusion surgery. The product has only been studied in patients requiring a primary posterolateral spinal fusion. Although the outcomes of revision spinal fusion surgery are different those of primary spinal fusion surgery and are not predictive, the following was observed in the study of primary spinal fusion surgery patients treated with OP-1 Putty.

In an early, small (pilot) study, 36 patients requiring a primary spinal fusion to treat degenerative spondylolisthesis (slippage of one bone in the spine relative to another) were treated with OP-1 Putty or autograft. Success rates for clinical and radiographic endpoints at 12 months are shown in the table below:

Pilot Study Success Rates at 12 Months

	OP-1 Putty	Autograft
Clinical (Pain and Function)	20/24	8/12
X-ray	15/24	6/12
Overall	12/24	4/12

A larger (pivotal) study of patients with the same type of disease is ongoing in the United States. An analyses of these data is not yet available.

What are possible complications?

As with any surgery, spinal surgery is not without risk. A variety of complications can occur. Some might be common side effects for the surgery and others might be related to the use of OP-1 Putty. These may occur singly or in combination. Some of these may be severe, affecting your outcome. You may also need to have additional surgery to correct these complications. Some of the possible complications include:

- allergic reaction to the implant materials;
- bending, breakage, loosening, and/or migration of the implants;
- bleeding, which may require a blood transfusion;
- bone formation that is abnormal, excessive or in an unintended location;
- bowel, bladder or gastrointestinal problems;
- cardiac problems;
- damage to nearby tissues;
- death;
- deep vein thrombosis;
- failure to fuse;
- fetal development complications; pain or discomfort;
- paralysis, numbness, tingling or other neurological problems;
- postoperative changes in spinal curvature, loss of correction or disc height;
- respiratory (breathing) problems;
- scar formation or other problems with the surgical incision;
- side effects from anesthesia or the surgical approach;
- spinal cord or nerve damage;
- tears of the dura (a layer of tissue covering the spinal cord); or
- vascular problems other than bleeding.

You should tell your doctor immediately if you do not feel well after your surgery, particularly if you experience back pain, fever, nausea and vomiting, infection, inflammation, redness or rash, itching, tenderness or swelling of the skin or surgery site. Tell your doctor or nurse if you notice anything else that is making you feel unwell, even if it is not on this list.

Ask your doctor if you do not understand anything in this list. Do not be alarmed by this list of possible side effects. You may not experience any of them.

What are my other options for treatment?

Alternative treatments for revision spinal fusion surgery are listed below. Discuss each treatment with your doctor to determine the best option for you.

- Autograft bone or bone marrow – This is when bone or bone marrow is taken from one part of your body and placed at the part of the spine being fused. If your doctor has recommended OP-1 Putty, then you probably have already been treated with autograft or are not a candidate for autograft or bone marrow. For those patients who have already been treated with autograft or bone marrow, obtaining bone or marrow from the same donor site or a new donor site may lead to increased risks, including but not limited to new or increased pain, fracture of the donor site bone because of larger bone loss, injury to the nerves or blood vessels in the donor site area because of scar tissue from the previous surgery, and complications from previous infection. Discuss this option with your doctor before being treated with OP-1 Putty.
- Allograft bone – Instead of using your own bone, a revision spinal fusion could be performed using bone from a human donor. While not as good at forming a spinal fusion as your own bone, the use of allograft does not have the risks described above associated with autograft. Because allograft bone is from a donor, there is the risk of disease transmission.
- Bone graft substitutes – These are man-made materials that provide a guide for the formation of your own new bone. While they are not as good at forming a spinal fusion as your own bone, bone graft substitutes do not have the risks described above associated with autograft or allograft.
- No surgical treatment – Some patients may choose to forego a second attempt at spinal fusion, in favor of pain management and non-surgical treatments.
- Bone Growth Stimulators - These are devices that apply electrical energy to the fusion site to promote healing.

Will my insurance pay for OP-1 Putty?

Most insurance plans will cover the cost of OP-1 Putty. Check with you plan administrator or contact a Stryker reimbursement specialist who will work with you to gain approval by the insurance company for your surgery. Call (866) GRO-BONE.

How much OP-1 Putty is Used?

Usually two units are required.

How is the surgery performed?

1. You will be under anesthesia during this procedure.

2. Your doctor will prepare the surgical site for the application of OP-1 Putty. This will include exposing the spine and cleaning away any unhealthy tissue from the previous failed fusion in the area of the surgery to ensure that only healthy tissue is in contact with OP-1 Putty.
3. OP-1 Putty is then mixed with sterile saline (salt water) to make a putty.
4. Your doctor will apply OP-1 Putty to both sides of the spine.
5. Your doctor will close the muscle and skin surrounding the surgery site (with stitches or staples) to contain the OP-1 Putty.

What should I expect before and after surgery?

Before your surgery

There are no specific instructions to follow before your treatment with OP-1 Putty. However, your doctor may advise you to stop smoking, or to stop taking certain drugs (e.g., blood thinners) before your surgery. Your doctor may also prescribe certain drugs (e.g., antibiotics) for you to take before your surgery. Please consult your doctor for specific instructions involving your surgery.

After your surgery

Your doctor will speak to you about the proper care and rehabilitation required after your surgery. This may include use of a back brace, physical therapy, or the use of antibiotics (drugs to help fight infection), or drugs to help reduce pain. Always follow the instructions of your doctor to ensure the best recovery after any surgery.

In most cases, immediately after surgery, your heart and lung function will continue to be monitored, a drainage tube will have been left in your wound and your doctor will prescribe medicines to control pain and nausea while you are in the hospital. A nurse will show you how to care for your wound before you are sent home and your doctor will discuss a program to gradually increase your activity.

Contact your doctor immediately if you get a fever, if the wound starts leaking fluids, if you have trouble swallowing or breathing, if you have trouble urinating, or if you have new or increased pain or numbness in your back or legs.

Your doctor will continue to monitor your progress after surgery

Consult your doctor if you have any questions or do not understand the information provided in this booklet.