



Biotech

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 I 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 2 units. Each unit is comprised of:

- A 20 mL vial of OP-1 Implant containing one gram of a sterile dry powder consisting of bovine collagen and OP-1
- A 10 mL vial of Putty Additive containing 230 mg of sterile carboxymethylcellulose (CMC)

One vial of OP-1 Implant and one vial of Putty Additive must be combined with sterile saline to produce one unit of OP-1 Putty. One unit of OP-1 Putty will be used for each side of the spine.

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

REF 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 products containing OP-1 and its influence on fetal development have not been completely assessed.

In an experimental animal study, OP-1 (rhBMP-7) administered to female rabbits prior to mating and during gestation elicited antibodies that crossed the placenta, exposing fetuses to anti-BMP-7 antibodies during organogenesis. The incidence of skeletal variations and malformations increased in fetuses of rabbit dams immunized to rhBMP-7 in the absence of significant maternal toxicity. The amount of increase was not above levels observed in historical controls. There are no adequate or well-controlled studies in human pregnant women. Women of childbearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments.

In clinical trials, 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.

The effect of maternal antibodies to rhBMP-7, which persist for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-7 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-7 with possible adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-7 is critical to fetal development and that a lack of BMP-7 activity may cause neonatal death or birth defects. It is not known if anti-BMP-7 antibodies may affect fetal development or the extent to which these antibodies may reduce BMP-7 activity.

- Products containing OP-1 should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with products containing OP-1. Women of childbearing potential, who are treated with products containing OP-1, should have antibody testing pre-op (to develop baseline titer) and prior to attempting to become pregnant.

- The safety and effectiveness of the OP-1 Putty device in nursing mothers has not been established. It is not known if BMP-7 is excreted in human milk.

- Inappropriate use of the product such as preparing it differently than described or mixing it with materials such as graft bone or bone void fillers may produce unexpected and potentially serious adverse events that may require surgical intervention. Reported events have included altered handling characteristics, graft migration, delayed wound healing, non-union and osteolysis.

- The use of OP-1 Putty with a synthetic bone void filler may lead to a risk of increase in local inflammation, infection and occasional migration of the implanted materials and is therefore not recommended.

- The maximum human dose should not exceed 2 units.

- 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 (Table 1) 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.

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%)

From the worldwide experience with OP-1, seven patients reported the occurrence of cancer. Six of the seven 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 consistent with population data associated with 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).

PREPARATION FOR USE:

One unit of OP-1 Putty (1 vial OP-1 Implant / 1 vial Putty Additive) will be used on each side of the spine. The patient will receive a total of 6.6 mg of OP-1 per bilateral posterolateral revision fusion. The preparation of OP-1 Putty is as follows:

1. Using sterile technique, remove the vials from their packaging.
 2. Lift the plastic flip-top and remove the metal crimps from the OP-1 Implant vial and the smaller vial containing the Putty Additive.
- Warning:** Handle the crimp with care. The edges of the crimp are sharp and may cut or damage gloves.
3. Using your thumb, pry up the edge of the stopper. After the vacuum is broken, remove the stopper from each vial while holding the vial upright to prevent loss of product.
- Warning:** Do not insert a needle through the stopper. Puncture of the stopper with a needle may result in particles of stopper material contaminating the device.
4. Carefully transfer contents of the OP-1 Implant vial and Putty additive vial to a suitable container, such as a sterile bowl.
- Warning:** To avoid breakage, do not tap the bottom of the vial when transferring contents.
5. Utilizing a sterile syringe, add 2-3 cc of sterile saline (0.9%) solution to the sterile container slowly and carefully.
 6. Gently stir the contents of the container with a sterile spatula to aid mixing.
 7. Use OP-1 Putty promptly following reconstitution.

The same procedure should be used to prepare OP-1 Putty for the contralateral side of the spine.

RECOMMENDED TECHNIQUE:

1. Debride and decorticate bone so that the OP-1 Putty will directly contact viable tissue.
2. Provide adequate hemostasis to ensure that the material stays at the surgical site. Irrigate the surgical site as necessary prior to implant of the OP-1 Putty. Where practical, surgical manipulations to the site should be completed prior to device implantation.
3. Carefully apply the OP-1 Putty to the prepared site, packing the combination into the desired area to its maximum capacity.
4. Close the soft tissues around the defect containing the OP-1 Putty using suture material of choice. Closure is critical for containment and maintenance of the OP-1 Putty in the area of fusion.
5. Do not place the drain in the graft site. Place it subcutaneously if possible.
6. After closure of the soft tissue around the defect, irrigate field if necessary to remove any stray particles of the product.
7. Following the procedure, apply the self-adhesive labels indicating the lot number of each device to the patient's chart.

CLINICAL EXPERIENCE:

Clinical experience with OP-1 Putty is summarized below. In a multicenter pilot primary spinal fusion study, 36 patients with symptomatic single level degenerative lumbar spondylolisthesis and spinal stenosis were treated with either OP-1 Putty or autograft in a 2:1 ratio. Success rates for clinical and radiographic endpoints at 12 months are shown in Table 2 below; Clinical success reflected improvement in pain and function as assessed by at least 20% improvement over the baseline Oswestry score. Radiographic success was defined as lack of motion of flexion/extension radiographs (i.e. not more than 5° angulation or 2 mm translation) and evidence of bridging trabecular bone.

Table 2 – Pilot Primary Spine Fusion Study Results

	OP-1 Putty n=24	Autograft n=12
Clinical	20/24	8/12
Radiographic	15/24	6/12
Overall success	12/24	4/12

A multicenter pivotal primary spinal fusion study is currently underway. This trial is evaluating the use of the product in patients with symptomatic single level degenerative lumbar spondylolisthesis and spinal stenosis who are treated with either OP-1 Putty or autograft in a 2:1 ratio. An analysis of these data is not yet available.

OP-1 Putty or a component thereof is the subject of one or more of the following patents:

US Patent Nos. 4,975,526, 5,162,114, 5,171,574, 5,258,494, 5,266,683, 5,750,651, 5,863,758, 5,674,292, 6,013,856, 6,028,242, 6,261,835, 6,461,630, 6,504,079, 7,078,221; JP Patent Nos. 2,113,455, 2,522,568, 2,548,414, 2,845,346, 2,869,381, 2,933,867, 3,430,474, 3,483,870; AU Patent Nos. 618,357, 627,850, 628,050, 648,997, 714,963, 751,451; CA Patent Nos. 1,338,663, 2,027,259, 2,223,049; AT Patent Nos. 0448,704, 0968012; BE Patent Nos. 0448,704, 0968012; CH Patent Nos. 0448,704, 0968012; DE Patent Nos. P68925773.2 (0362367), P68927153.0 (0372031), P69020254.7 (0411105), P69626205.3 (0837701); DK Patent Nos. 0448,704, 0968012; ES Patent Nos. 0448704, 0968012 ; FI Patent No. 0968012; FR Patent Nos. 0362367, 0372031, 0411105, 0448704, 0837701, 0968012; GB Patent Nos. 0362367, 0372031, 0411105, 0448704, 0837701, 0968012; GR Patent Nos. 0448704, 0968012 ; IE Patent No. 0968012; IT Patent Nos. 0362367, 0372031, 0411105, 0448704, 0837701, 0968012; LU Patent Nos. 0448704, 0968012 ; MC Patent No. 0968012; NL Patent Nos. 0448,704, 0968012; SE Patent Nos. 0448,704, 0968012.

OP-1 Implant or a component thereof is the subject of one or more of the following patents:

US Patent Nos. 4,975,526, 5,162,114, 5,171,574, 5,258,494, 5,266,683, 5,750,651, 5,863,758, 5,674,292, 6,013,856, 6,028,242, 6,261,835, 6,461,630, 6,504,079, 7,041,641, 7,078,221, 7,176,284; JP Patent Nos. 2,113,455, 2,522,568, 2,548,414, 2,845,346, 2,869,381, 2,933,867, 3,430,474, 3,483,870; AU Patent Nos. 618,357, 627,850, 628,050, 648,997, 714,963; CA Patent Nos. 1,338,663, 2,027,259, 2,223,049; AT Patent No. 0448,704; BE Patent No. 0448,704; CH Patent No. 0448,704; DE Patent Nos. P68925773.2 (0362367), P68927153.0 (0372031), P69020254.7 (0411105), P69032424.3 (0448704), P69626205.3 (0837701); DK Patent No. 0448704; ES Patent No. 0448704; FR Patent Nos. 0362367, 0372031, 0411105, 0448704; GB Patent Nos. 0362367, 0372031, 0411105, 0448704, 0837701; LU Patent No. 0448704; MC Patent No. 0968012; NL Patent No. 0448704; SE Patent No. 0448704.

(issued/granted patents as of 03-31-08)

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