5.3.11 Post-marketing Safety Surveillance

OP-1 Putty (OP-1 Implant + CMC) has been marketed under HDE #H020008 since April, 2004 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. FDA regulations mandate that an IRB oversee the use of HUDs to continually monitor patient safety. Additionally, all IRBs are informed of Serious Adverse Events in real time as they are reported to FDA. There have been no actions on the part of any OP-1 IRB to curtail product use based on safety concerns. Over 25,000 patients have been treated under the HDEs for both OP-1 Putty and OP-1 Implant. Since the launch of OP-1 Putty in 2004, there has been an average of 0.28 adverse events reported per 100 units of OP-1 Putty sold in the US. The associated post-marketing surveillance program demonstrates no emerging patterns of any serious adverse events associated with the approved use of OP-1 products. In addition, OP-1 Implant is legally marketed as a pharmaceutical product (Osigraft) in the EU and Australia. No regulatory actions have been taken for safety reasons in any country. Ongoing post-marketing surveillance of these markets further supports the safety of OP-1 products.

Table 43 represents OP-1 Putty Post-marketing adverse events reported since product launch.

5.3.11 Post-marketing Safety Surveillance

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

Table 43: OP-1 Putty Post-Marketing Adverse Events

System Organ Class	Preferred Term (number of reported events*)
Cardiac disorders	Myocardial infarction (2)
	Palpitations
Gastrointestinal disorders	Dyspepsia
	Dysphagia
	Gastrointestinal ulcer
	Lip swelling
General disorders and administration site conditions	Asthenia (3)
	Device ineffective
	Difficulty in walking
	Fat necrosis
	Fatigue
	Hyperhidrosis
	Impaired healing
	Implant site effusion (2)
	Implant site swelling
	Inflammation (8)
	Influenza like illness
	Local swelling (2)
	Oedema peripheral
	Pain
	Postoperative fever (3)
	Pyrexia
	Wound secretion (2)
Immune system disorders	Lupus-like syndrome
	Hypersensitivity
Infections and infestations	Enterococcal infection
	Staphylococcal sepsis
	Staphylococcal infection (3)
	Wound infection bacterial
	Wound infection staphylococcal
Injury, poisoning and procedural complications	Device migration (3)

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(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

System Organ Class	Preferred Term (number of reported events*)
	Failure of implant
	Fall
	Incision site complication (3)
	Medical device complication (3)
	Medical device pain
	Post procedural haematoma
	Seroma
	Wound complication
	Wound dehiscence (2)
Inner ear and VIII cranial nerve disorders	Inner ear disorder
Investigations	Bacterial culture positive
	Blood pressure increased
Musculoskeletal and connective tissue disorders	Back pain (9)
	Connective tissue disorder
	Limb discomfort
	Muscle spasms (3)
	Musculoskeletal discomfort
	Musculoskeletal pain
	Pain in extremity (2)
	Post procedural discomfort (3)
	Pseudarthrosis
Neoplasms benign, malignant and unspecified	Lung adenocarcinoma stage III
	Renal cell carcinoma stage unspecified
Nervous system disorders	Burning sensation (2)
	Dysaesthesia
	Dysstasia
	Hyperaesthesia (2)
	Hypoaesthesia (4)
	Paraesthesia
	Paraesthesia oral
	Radicular pain
	Sensory disturbance (2)

System Organ Class	Preferred Term (number of reported events*)
Psychiatric disorders	Confusional state
Respiratory, thoracic and mediastinal disorders	Pneumonia
	Sinus disorder
Skin and subcutaneous tissue disorders	Erythema (2)
	Lip blister
	Pruritis
	Skin maceration
	Swelling face
	Urticaria (2)
Surgical and medical procedures	Wound drainage (3)
Vascular disorders	Arterial haemorrhage
	Deep vein thrombosis
	Haematoma
	Lymphoedema

*If reported in > 1 patient

Since OP-1 Putty has been available for commercial use, there has been 1 report of renal cell carcinoma and 1 report of lung adenocarcinoma (as shown in Table 43) in 2 patients who received OP-1 Putty.

A 41-year-old woman who received 2 units of OP-1 Putty on 15 November 2004 for spinal fusion revision for scoliosis was diagnosed with renal cell carcinoma in March 2005 (~ 106 days post surgery). Treatment included a laparoscopic left nephrectomy on 11 April 2005, which revealed no evidence of invasion of the regional lymph nodes, adrenal gland, or renal vein. Approximately 2 months following the nephrectomy, the patient developed extensive metastasis and died. The causality of the event was assessed by the investigator as probably related to OP-1 Putty.

A 64- year-old man who received OP-1 Putty in conjunction with Calstrux on 09 November 2004 was hospitalized for treatment of a stage IIIA adenocarcinoma of the right lung on 14 February 2007 (827 days post surgery). The patient's medical history included a 25-pack-per-year smoking history. Unspecified testing in May 2005 first identified a pulmonary nodule which was found to be stable in July and November 2005, but enlarged at a later date (not specified). A bronchoscopy on November 22, 2006, was positive for poorly differentiated non-small cell lung cancer. The onset of symptoms were first documented on 18 May 2005 with the patient reporting weight loss, loss of anorexia, light-headedness, daytime drowsiness, chest pressure, abdominal pain and a dry cough. Treatment included preoperative chemotherapy (not specified), preoperative radiation therapy and a right lower lobectomy. The outcome of the event is unknown. The causality of the event was assessed by the investigator as not related to OP-1 Putty.

No reports of AEs due to heterotopic bone formation have been received in postmarketing experience of OP-1 Putty.

Safety of Other OP-1-Containing Products

OP-1 Implant is an osteoinductive and osteoconductive material which consists of recombinant human Osteogenic Protein (rhOP-1) and Type I Bovine Bone Collagen Matrix (collagen matrix). (OP-1 Putty is OP-1 Implant plus the putty additive, Carboxymethylcellulose.) OP-1 Implant was granted marketing authorization in the United States as a Humanitarian Use Device (HUD) on October 17, 2001 via Humanitarian Device Exemption (HDE) No. H010002 for use as an alternative to autograft in recalcitrant long-bone nonunions where use of autograft is unfeasible and other treatments have failed. OP-1 Implant has also been approved in Europe (as a pharmaceutical product Osigraft), Australia, and Canada. Adverse events reported for OP-1 Implant in post-marketing experience are displayed in Table 44.

5.3.11 Post-marketing Safety Surveillance

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

Table 44: OP-1 Implant Post-Marketing Adverse Events

System Organ Class	Preferred Term (number of reported events*)
Blood and lymphatic disorders	Neutropenia
	Lymphoedema
Cardiac disorders	Atrial fibrillation (2)
	Cardiac failure congestive
Gastrointestinal disorders	Ageusia
	Diarrhoea
	Dysphagia (2)
	Nausea (2)
	Vomiting
General disorders and administration site conditions	Difficulty in walking
	Fibrosis (2)
	Impaired healing (5)
	Implant site calcification
	Implant site pain
	Induration (2)
	Inflammation (6)
	Localised oedema
	Local swelling
	Necrosis
	Night sweats
	Oedema peripheral (5)
	Pain (6)
	Postoperative fever (5)
	Pyrexia
	Sensation of pressure
	Swelling (6)
	Wound necrosis (2)
	Wound secretion (7)
Hepatobiliary disorder	Alcoholic liver disease
Infections and infestations	Abscess
	Acarodermatitis

5.3.11 Post-marketing Safety Surveillance

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

System Organ Class	Preferred Term (number of reported events*)
	Bacterial infection (13)
	Cellulitis
	Graft infection
	Implant site infection
	Osteomyelitis
	Postoperative infection (2)
	Postoperative wound infection (4)
	Purulent discharge
	Wound infection
	Wound infection staphylococcal (6)
Immune system disorders	Hypersensitivity (2)
Injury, poisoning and procedural complication	Device breakage
	Device failure (3)
	Device migration (12)
	Drug ineffective
	Extradural haematoma
	Fall
	Femur fracture
	Incisional hernia
	Medical device complication
	Nerve injury
	Postoperative heterotopic calcification (3)
	Post procedural complication
	Post procedural haematoma (4)
	Procedural pain (2)
	Road traffic accident
	Seroma (4)
	Vascular graft occlusion (2)
	Wound complication (2)
	Wound dehiscence (6)
	Wound secretion (2)
Investigations	Laboratory test abnormal (2)

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(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

System Organ Class	Preferred Term (number of reported events*)
	Weight decreased
	White blood cell count increased
	White blood cell scan
Musculoskeletal and connective tissue disorders	Back pain (2)
	Bone disorder
	Compartment syndrome (2)
	Fracture delayed union (2)
	Fracture malunion (2)
	Fracture nonunion (6)
	Joint crepitation
	Joint range of motion decreased
	Joint sprain
	Joint stiffness
	Monarthritis
	Muscle atrophy
	Muscle spasms
	Neck pain
	Osteolysis (3)
	Pain in extremity (5)
	Pathological fracture
	Shoulder pain (2)
	Tendon disorder
	Trigger finger
	Wrist deformity
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	B-cell small lymphocytic lymphoma
	Glioblastoma
Nervous system disorders	Aphonia
	Cerebral Haemorrhage
	Dysstasia
	Headache
	Hemianopia homonymous
	Monoparesis

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(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 6.1-6.2, Pages 94-108)

System Organ Class	Preferred Term (number of reported events*)
	Neurological symptom
	Sciatica
	Tinel's sign
	Paraesthesia (3)
Psychiatric disorders	Confusional state
	Premenstrual syndrome
	Suicide attempt
Respiratory, thoracic and mediastinal disorders	Dysphonia
	Dyspnoea (2)
	Obstructive airways disorder
	Pulmonary embolism
Skin and subcutaneous tissue disorders	Alopecia (2)
	Blister
	Cellulitis (3)
	Erythema (4)
	Hypertrophic scar
	Nail growth abnormal
	Pruritis
	Rash (3)
Surgical and medical procedures	Arm amputation
	Tendon operation
	Wound drainage (2)
Vascular disorders	Haematoma
	Haematoma infection
	Haemorrhage
	Hypotension

*If reported in >1 patient

There have been 2 reports of malignancy (as shown in Table 42) in 2 patients in OP-1 Implant post-marketing surveillance.

A 69-year-old woman who received 2 units of Osigraft (OP-1 Implant) for an instrumented posterolateral fusion of the lumbar spine on 01 April 2005 (Study EU 101) was hospitalized on 5 March 2007 (703 days post surgery) with a primary brain tumor. The patient presented with a confused state with right homonymic lateral hemianopsia that arose over a short period of time. A cranial CAT scan revealed the presence of an expansive left occipital lesion, and a cranial nuclear magnetic resonance scan confirmed the presence of a large expansive lesion in the left occipital lobe, reaching to the lateral ventricle. On 16 March 2007 the patient underwent extirpation of the mass. Histological examination of the tissue revealed a grade IV glioblastoma. The patient was reported to be terminally ill and was receiving only palliative care. She was subsequently lost to follow-up with the event ongoing. The investigator assessed the causality of the event as not related to OP-1 Implant.

A 61-year-old man who received 2 units of Osigraft (OP-1 Implant) on 11 May 2005 for an instrumented posterolateral fusion of the lumbar spine (Study EU 101) was diagnosed with

mature B cell lymphoma, small cell on 22 July 2005 (82 days post surgery) when a CT scan revealed a tumor in the perirenal fat of the left kidney. A biopsy performed on 17 April 2006 confirmed the diagnosis. Treatment information was not provided. The event is ongoing. The investigator assessed the causality of the event as not related to OP-1 Implant.

There have been 3 reports of AEs due to heterotopic bone formation in post-marketing experience with OP-1 Implant. None of the events were assessed as serious.

A 53-year-old female who received OP-1 Implant on 08 April 2002 for a nonunion of the proximal left humerus experienced a thick scar on 08 May 2002, shoulder pain and shoulder clicking on 29 May 2002 and heterotopic ossification and OP-1 was not contained by the soft tissue around the bone on 15 August 2002. The event outcomes are unknown. The investigator assessed the causality of the event as related to OP-1 Implant.

A 55-year-old female with a non-union femur fracture who received OP-1 Implant in combination with an allograft developed a hematoma, which is suspected to have pushed the OP-1 Implant into the muscle where heterotopic bone developed. During a re-graft procedure of the same non-union using OP-1 Implant, this heterotopic bone was removed. Follow-up with the surgeon was not possible because the surgeon was no longer working at the clinical site.

A 30-year-old man received 1 unit of OP-1 Implant in conjunction with 2 iliac crest dowels for a distal humeral nonunion experienced heterotopic ossification, elbow stiffness and decreased range of motion. At 10 weeks post surgery, his elbow range of motion had decreased from 10 degrees to 120 degrees at 2 weeks to 45 degrees to 100 degrees at 5 and 10 weeks. Radiographs showed profound heterotopic ossification posteriorly within the triceps muscle. The patient refused further treatment. The event was ongoing with follow-up information requested from the site. The event was assessed by the investigator as related to OP-1 Implant.

OP-1 in Combination with Other Products

In July 2006, Stryker Biotech identified an increased trend in adverse events associated with the use of Calstrux™ (a 510-K approved resorbable bone void filler composed of porous tricalcium phosphate granules and a putty additive) in combination with other products, including OP-1 Putty and OP-1 Implant (Osigraft). The adverse events reported included localized induration, swelling, inflammation, wound drainage, infection, and device migration. A global Class II corrective action, which included the addition of a precaution statement to the Calstrux™ Package Insert and distribution of a “Dear Doctor” letter to current Calstrux™ users, was initiated.

Stryker Biotech believes that this corrective action has been effective in notifying surgeons of the potential risk of adverse events and product migration if Calstrux™ is not used according to the current Package Insert.

The following tables (Table 45 and 46) present postmarketing adverse event reports of OP-1 Putty and OP-1 Implant combined with other products:

Table 45: OP-1 Putty in Combination with other Products

System Organ Class	Preferred Term (number of reported events*)
Ear and labyrinth disorders	
	Vertigo positional
General disorders and administration site conditions	
	Device ineffective
	Implant site effusion (2)
	Implant site swelling
	Inflammation (4)
	Pyrexia
Infections and infestations	
	Abscess (2)
	Enterococcal infection
	Staphylococcal infection (3)
	Wound infection bacterial
	Wound infection staphylococcal
Injury, poisoning and procedural complications	
	Device migration (3)
	Wound dehiscence (2)
Musculoskeletal and connective tissue disorders	
	Pain in extremity
	Shoulder pain
Neoplasms benign, malignant and unspecified	
	Lung adenocarcinoma stage III
Skin and subcutaneous tissue disorders	
	Erythema
Surgical and medical procedures	
	Wound drainage (3)

Table 46: OP-1 Implant in Combination with Other Products

System Organ Class	Preferred Term (number of reported events*)
Gastrointestinal disorders	
	Dysphagia (2)
General disorders and administration site conditions	
	Drug ineffective
	Impaired healing (2)
	Implant site calcification
	Induration (4)
	Inflammation (3)
	Localized oedema
	Local swelling
	Oedema peripheral
	Pain (4)
	Pyrexia
	Sensation of pressure
	Swelling (7)
Infections and infestations	
	Wound infection (4)
Injury, poisoning and procedural complication	
	Device failure
	Device migration (19)
	Extradural haematoma
	Extrusion of device (2)
	Seroma (2)
	Wound complication
Musculoskeletal and connective tissue disorders	
	Back pain
	Neck pain
	Osteolysis (2)
Nervous system disorders	
	Aphonia
	Monoparesis
	Neurological symptom
	Sciatica
Respiratory, thoracic and mediastinal disorders	

System Organ Class	Preferred Term (number of reported events*)
	Dysphonia
	Dyspnoea
	Obstructive airways disorder
Skin and subcutaneous tissue disorders	
	Blister
	Skin disorder (3)
	Skin inflammation
Surgical and medical procedures	
	Wound drainage (4)
Vascular disorders	
	Haematoma
	Haemorrhage