

5.3.10.3 Heterotopic Ossification

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 5.5, Pages 88-89)

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Fifteen patients in pivotal study S01-01US who received OP-1 Putty had radiographic evidence of heterotopic ossification at any time point during the study. Three patients (1501, 4405, and 4702) who received OP-1 Putty experienced heterotopic bone formation that was recorded as an AE. Each of the patients who had heterotopic bone formation designated as an AE had radiographic evaluations indicating “exuberant bone growth” or “exuberant ossification” prior to reporting heterotopic bone formation as an AE. These three patients were eligible for participation in 06-UPLF-01 (because they were not retreatment failures), and additional information received about these patients during the extension study 06-UPLF-01 is summarized below:

- Patient 1501 received OP-1 Putty at level L3-4 on 21 March 2002. Patient reported excessive bone pain over the right posterior iliac region in September 2002. Heterotopic bone formation was reported as an AE on 11 December 2002, and again on 6 March 2004, and 24 March 2005. The patient was subsequently diagnosed with recurrent lumbar spinal stenosis at L4-5 which required hospitalization and a revision micro-decompression of L4-L5 on 01 Jan 2005 (1017 days post initial surgery). CT scans for this patient were reviewed by the independent reviewer for neurological success/failure assessments, who determined that the spinal stenosis at this level was unrelated to the heterotopic bone formation. The event was considered resolved on 23 June 2005. An additional event was reported as an SAE in extension study 06-UPLF-01: right total knee arthroplasty on October 30, 2006. No additional complaints or findings of L4-L5 lumbar spinal stenosis nor any reports of HTO at the iliac crest have been reported for this patient in 06-UPLF-01.
- Patient 4405 from the OP-1 Putty group had discogenic bridging documented which was reported as an intervertebral disc disorder and required treatment with physical therapy. This patient did not return to participate in 06-UPLF-01, so no further information is available.
- Patient 4702 received OP-1 Putty at level L4-L5 on 10 January 2003. On 28 October 2003, patient was found to have heterotopic ossification extending from the right side of the fusion mass and the interval between the iliacus and psoas, extending into the pelvis. No new SAEs have been reported for this patient in extension study 06-UPLF-01.

There were 3 patients who had evidence of heterotopic ossification (2 had radiographic evidence and 1 reported as an AE) that subsequently required reoperations during the course of study S01-01US. Two patients developed lumbar spinal stenosis (which was determined by the independent reviewer for neurological success/failure assessments to be unrelated to the HTO) and one patient had a pseudarthrosis.

- Patient 1501 received OP-1 Putty at level L3-4 on 21 March 2002 and reported excessive bone pain over the right posterior ileac region in September 2002. Heterotopic bone formation was reported as an AE on 11 December 2002, and again on 6 March 2004, and 24 March 2005. The patient was subsequently diagnosed with recurrent lumbar spinal stenosis at L4-5 which required hospitalization and a revision

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- micro-decompression of L4-L5 on 01 Jan 2005 (1017 days post initial surgery). The event was considered resolved on 23 June 2005 and was determined to be not related to the HTO.
- Patient 1123 received OP-1 Putty at level L4-L5 on 26 November 2002, and had evidence of heterotopic ossification on her 9-month CT scan. The patient developed lumbar spinal stenosis at L3-L5 which occurred in November 2004 (approximately 720 days post surgery), and which was determined to be not related to HTO. She had a L2-L5 decompressive lumbar laminectomy with supplemental fixation performed and the event resolved on 21 Jan 2005. This patient is a study failure due to retreatment.
 - Patient 1310 received OP-1 Putty at level L4-L5 on 04 November 2002. On 25 February 2004 (478 days post surgery) the patient developed pseudarthrosis which required hospitalization. The patient subsequently underwent a posterior lumbar interbody fusion on 28 Jan 2005 with BMP (not specified) and a supplemental fixation (not specified). The event was considered continuing at the end of study S01-01US. Because the patient was a failure due to retreatment in pivotal study S01-01US, the patient was not eligible to participate in 06-UPLF-01, and no further information at 36+ months is available for this patient.