INTEGRA
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To the attention of Quality Assurance Dpt or Regulatory Affairs Dpt or Management

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Saint Priest, March 21, 2014

Subject: **URGENT - FIELD SAFETY NOTICE**
Medical devices:
SynPlug® Cement Restrictor */ 804030, 804015, 804016, 804017, 804018, 804019, 804020, 804021, 804022, 804024, 804026*
OptiPlug® Cement Restrictor */ 804036, 804038, 804040, 804042, 804044, 804046*
Legal manufacturer: ISOTIS Orthobiologics, Inc. – 2 Goodyear – Suite A – Irvine – California – 92618 USA
Concerned batches: *All batches*

Dear Valued Customer,

This Field Safety Notice (FSN) is to notify healthcare professionals about reports in literature of patients experiencing osteolysis (bone loss) following the use of OptiPlug® Biodegradable Cement Restrictors in cemented total hip arthroplasty procedures. This unanticipated adverse event was reported in three medical publications, one of which reported a periprosthetic fracture associated with osteolysis.

OptiPlug® Biodegradable Cement Restrictors are intramedullary cement restrictors intended to be used to occlude the intramedullary canal prior to the cementation of hip or shoulder arthroplasty. SynPlug® Biodegradable Cement Restrictors are identical to OptiPlug® Biodegradable Cement Restrictors except with respect to their mass and the sizes of cement restrictors offered. Due to the similarity between the two products, the information in this letter applies to both OptiPlug® and SynPlug® Biodegradable Cement Restrictors.

IsoTis OrthoBiologics has become aware of recent publications in medical literature that report instances of osteolysis and associated periprosthetic fracture near the site of OptiPlug® Cement Restrictors after total hip arthroplasty procedures. These adverse events were observed between 1 and 5 years post-implantation in post-operative follow-up x-rays. A total of 132 patients were affected by osteolysis, including one patient with a periprosthetic fracture, in the three publications.

Through a literature review, one earlier publication was identified that provided information on SynPlug® Cement Restrictor use and long term follow-up. This 11-year study was not specifically designed to look at the outcome of SynPlug® Cement Restrictor use, but osteolysis was one of several parameters examined. The study authors did not find osteolysis or periprosthetic fractures in the vicinity of the SynPlug® Cement Restrictors.

In the last 24 months, IsoTis OrthoBiologics has received 14 complaints of osteolysis in patients who received OptiPlug® or SynPlug® Cement Restrictors, including 2 patients who experienced associated periprosthetic fractures. All but 1 osteolysis complaint were received by IsoTis OrthoBiologics 4 to 8 years following implantation. No complaints for osteolysis or associated periprosthetic fracture were received between early 2001 and November 2011. All of the patients cited in the publications and complaint reports received by IsoTis OrthoBiologics were asymptomatic, with osteolysis detected through x-rays performed as part of follow-up exams post-implantation. IsoTis Orthobiologics has not made a determination as to the root cause of these reported incidents.

Healthcare professionals should be aware of the reports in medical literature regarding the risk of osteolysis and periprosthetic fracture following the use of OptiPlug® and SynPlug® Cement Restrictors, in cemented hip arthroplasty procedures.

At this time, healthcare professionals should consider the information in these publications in the context of their normal practice protocols and post-operative follow-up treatment of any patients implanted with OptiPlug® and/or SynPlug® Biodegradable Cement Restrictors during hip arthroplasty.

IsoTis OrthoBiologics will continue to monitor adverse events and investigate reports in medical literature. We are committed to providing safe and effective products, and our ultimate goal is to assure that we provide important safety information to our customers.

Healthcare providers and OptiPlug® and SynPlug® patients are encouraged to report any adverse events in patients implanted with OptiPlug® and/or SynPlug® Biodegradable Cement Restrictors to IsoTis OrthoBiologics at emea-fsca-orthobio@integralife.com.

We are notifying you of the FSN as our records indicate that you have been supplied with SynPlug® or OptiPlug® Cement Restrictors.

Description of affected product	Reference	Affected Lot Number
SynPlug® Cement Restrictor	*804030* *804015* *804016* *804017* *804018* *804019* *804020* *804021* *804022* *804024* *804026*	All lot numbers
OptiPlug® Cement Restrictor	*804036* *804038* *804040* *804042* *804044* *804046*	All lot numbers

We kindly ask you to contact your final customers who may use the SynPlug® or OptiPlug® Cement Restrictors and provide them with this letter.

When your final customers will be informed, please sign and return the "Field Safety Notice acknowledgment and Return Form" enclosed, by which you confirm that you have received this FSN notification and you intend to fully comply with it.

With this form, you confirm that this notification has been forwarded to every concerned user / customer.

The receipt of this form ensures that Integra has achieved a level of effectiveness in communicating this information.

We also recommend that you keep a copy of this notification and a signed copy of the acknowledgement form for your records.

The European National Competent Authority of your country has been alerted of this Field Safety Corrective Action and they may perform audits of field actions of this nature to verify that our customers have been notified and understand the nature of the field action being taken.

Finally, if you distribute the SynPlug® or OptiPlug® Cement Restrictors outside Europe, please ensure this Field Safety Corrective Action is notified to your national competent authority if it is required by the national medical device regulation.

Please feel free to contact me for any additional questions. Your cooperation is appreciated, and we thank you for your continued collaboration.

Yours Sincerely,

Jérémie NADAM
Regulatory Affairs Manager
Europe, Middle East & Africa

Enclosed: List of the articles (Annex 1) and Field Safety Notice Acknowledgment and Return Form

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ANNEX 1

References of the articles

1. Boyer, P., Lazennec, J.-Y., Poupon, J., Rousseau, M.-A., Ravaud, P., & Catonné, Y. (2009). Clinical and biological assessment of cemented titanium femoral stems: an 11-year experience. International Orthopaedics, 33(5), 1209–15.

2. Dhawan, R. K., Mangham, D. C., & Graham, N. M. (2012). Periprosthetic femoral fracture due to biodegradable cement restrictor. The Journal of Arthroplasty, 27(8), 1581.e13–5.

3. Hanssen, N. M. A I., Schotanus, M. G. M., & Verburg, A D. (2013). Osteolysis in cemented total hip arthroplasty involving the OptiPlug cement restrictor: more than an incident? European Journal of Orthopaedic Surgery & Traumatology: [Epub ahead of print] doi:10.1007/s00590-013-1366-z

4. Ockendon, M., Oakley, J. E., & Graham, N. M. (2011). Osteolysis associated with OptiPlug Bioabsorbable Cement Restrictors. Journal of Bone & Joint Surgery, British Volume, 93-B(SUPP IV), 547.

FIELD SAFETY NOTICE ACKNOWLEDGMENT AND RETURN FORM

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Legal manufacturer: ISOTIS Orthobiologics, Inc. – 2 Goodyear – Suite A – Irvine – California – 92618 USA

Concerned batches: *All batches*

Please sent the form back to :

By fax/telecopy: +33 (0)4 37 47 59 30
Or by e-mail: emea-fsca-orthobio@integralife.com

With this form, I confirm that:

- I have received, read and understood the information provided in the Integra *Field Safety Notice* notification regarding *SynPlug® and OptiPlug® Cement Restrictor.*
- I am a distributor and I have transferred this form together with the explicative letter to the persons to whom I have sold and/or place on consignment the concerned products. I will ensure that the form is duly returned to me signed by these persons.

Distributor / Healthcare facility name

Contact Name

Street Address

City, Country, Postal Code

Telephone

Email

Signature