Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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In this issue: cases of atypical femoral fracture have been reported rarely in patients with postmenopausal osteoporosis receiving treatment with **denosumab 60 mg** (Prolia▼) after long-term treatment. Discontinuation of denosumab treatment should be considered if atypical femoral fracture is suspected, while the patient is evaluated (see article A1).

Also this month: completion of a European review of the risk of life-threatening and fatal air embolism with **sprayable fibrin sealants**. Such events appear related to incorrect use, in particular when the spray is applied at higher-than-recommended pressures, or the product is sprayed too close to the tissue surface. Updated advice on the correct use of the fibrin sealants **Evicel, Tisseel** and **Artiss** is provided in article A2.

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Drug safety advice

A1 Denosumab 60 mg (Prolia▼): rare cases of atypical femoral fracture with long-term use

Atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving long-term (≥2.5 years) treatment with denosumab 60 mg (Prolia▼) in a clinical trial.

During denosumab treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated.

Denosumab is a human monoclonal IgG2 antibody. Denosumab 60 mg solution for injection (Prolia▼) is given once every 6 months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Denosumab 120 mg solution for injection (Xgeva▼) is given once every 4 weeks for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Possible risk of atypical femoral fracture

Two cases of atypical femoral fracture have been confirmed in patients receiving denosumab 60 mg for 2.5 or more years participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events occurred rarely (in ≥ 1/10 000 to < 10/10 000 patients), based on 8 928 subjects being exposed to denosumab 60 mg in bone loss studies.

A risk of atypical femoral fractures for denosumab 120 mg (Xgeva▼) cannot be excluded.

See:
Drug Safety Update June 2011 [link to: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213]

The nature of the fractures seen with denosumab 60 mg is similar to the atypical femoral fractures seen with long-term bisphosphonate therapy. For further information on this, and a list of clinical and radiographic features of atypical femoral fractures, see Drug Safety Update June 2011.

A letter was sent to healthcare professionals in February 2013, regarding the updated product information for denosumab 60 mg (Prolia▼)

Advice for healthcare professionals:

- During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.
- Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur.
- The contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral (as noted from the bisphosphonates assessment).
- Discontinuation of denosumab treatment should be considered if an atypical femur fracture is suspected, while the patient is evaluated. An individual assessment of the benefits and risks should be performed.

Further information:

Bisphosphonates assessment: Drug Safety Update, June 2011 [link to: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213]

BNF section 6.6: Drugs affecting bone metabolism [LINK to: http://www.medicinescomplete.com/mc/bnf/current/PHP4691-denosumab.htm]

Article citation: Drug Safety Update February 2013 vol 6, issue 7: A1.

A2 **Sprayable fibrin sealants (Evicel, Tisseel and Artiss): updated guidance on minimising risk of life-threatening and fatal air embolism**

Life-threatening and fatal cases of air embolism have been reported with incorrect use of sprayable fibrin sealants administered using a pressure regulator device.

To avoid potentially fatal air embolism, do not exceed the maximum recommended pressure for the regulator device, and do not spray the product closer than the minimum recommended distance from the tissue surface. Ensure that fibrin sealants are only sprayed using the appropriate gas.

Fibrin sealants (also known as tissue adhesives or glues) are used in a wide range of surgical procedures to rapidly arrest bleeding and assist in subsequent wound healing. They can be applied by dripping the solution, or by spraying the solution using a pressure regulator, onto bleeding tissue where they form a fibrin clot.

Four sprayable fibrin sealants are authorised in the UK:

- Evicel
- Tisseel Lyo
- Tisseel Ready to use
- Artiss solution for sealant, deep frozen

A European review on the safety of these products was started in 2012, following reports of life-threatening and fatal cases of air embolism occurring in association with the use of spray devices that use a pressure regulator to administer fibrin sealants.

Worldwide, a total of six reports of life-threatening or fatal air embolism have been received with the sprayable fibrin sealants Evicel (5 reports) and Tisseel (1 report), and a further four reports in association with Quixil, a sprayable fibrin sealant which is no longer available in the UK. These events appear to be related to the use of the spray device at higher-than-recommended pressures, and/or in closer proximity than recommended to the tissue surface. We first informed you of this risk in October 2010 and provided updated advice for Evicel in December 2012.

The review considered all available information on this issue, including clinical study data, case reports of suspected adverse reactions and published scientific literature[1-4]. The review concluded that the benefits of fibrin sealants in surgery for improvement of haemostasis outweigh the risks, when the instructions for use are followed.

Air embolism has been reported very rarely, however a small risk cannot be excluded. Therefore, a number of recommendations have been made for Evicel, Tisseel and Artiss to minimise the risk of air embolism when these medicines are applied as a spray during surgery.

References

1. Chalmers et al. Randomised clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. *BJS* 2010; **97**:1784-1789

2. D'Andrilli et al. A prospective randomized study to assess the efficacy of a surgical sealant to treat air leaks in lung surgery. European journal of cardio-thoracic surgery: *Official journal of the European Association for Cardio-thoracic Surgery* (2009); **35** (5): 817-820; discussion 820-821.

3. Fischer et al. A randomized trial of aprotinin-free fibrin sealant versus absorbable haemostat. *Clin Appl Thromb Hemost* 2011 Nov-Dec; **17**(6):572-577. Epub 2011 Aug 25

4. Foster et al. Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. *Journal of burn care & research*: official publication of the American Burn Association (2008) **29** (2) p 293-303

Further information:

Advice from the European Medicines Agency to surgeons on safer use of fibrin sealants – Evicel and Quixil [link to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/11/human_pha_detail_000069.jsp&mid=WC0b01ac058001d126]

Revised Summary of Product Characteristics for Evicel [link to: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135085.pdf]

Information from The European Medicines Agency on fibrinogen-containing solutions for sealant authorised for administration by spray application [link to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Fibrinogen-containing_solutions_for_sealant_authorised_for_administration_by_spray_application/human_referral_000332.jsp&mid=WC0b01ac05805c516f]

Advice for healthcare professionals:

To prevent life-threatening air embolism during spray application of a fibrin sealant during surgery, it is important that the following advice on pressure and distance is followed:

Type of surgery	**Product**	**Maximum pressure (do not exceed)**	**Minimum distance from tissue (do not spray closer)**
Open-wound surgery	Evicel	1.7 bar (25 psi)	10 cm
	Tisseel Lyo/Ready for use	2.0 bar (28.5 psi)	
	Artiss, deep frozen	2.0 bar (28.5 psi)	
Laparoscopic procedures*	Evicel	1.4 bar (20 psi)	4 cm
	Tisseel Lyo/Ready for use	1.5 bar (22 psi)	2 cm

*Only use Evicel or Tisseel in laparoscopic procedures if the minimum spray distance can be accurately judged.

For all products

- Prior to applying fibrin sealants by spray application using a pressure regulator device, the surface area of the wound should be dried using standard techniques (eg, intermittent application of compresses, swabs, and use of suction devices)
- Closely monitor blood pressure, heart rate, oxygen saturation and end-tidal CO_2 when spraying fibrin sealants because of the possibility of air embolism

For Evicel only

- For any spray application using a pressure regulator device, use only CO_2 gas (not pressurised air)
- In laparoscopic procedures only use when the minimum spray distance of at least 4 cm can be accurately judged
- Do not use in other endoscopic procedures

For Tisseel only

- For spray application in laparoscopic or minimally invasive procedures, use only CO_2 gas (not pressurised air). The product should only be used when the minimum spray distance of at least 2 cm can be accurately judged

For Artiss only

- Artiss is recommended for use in open-wound surgery only

See:
Letters sent to healthcare professionals for Evicel [link to: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con218764.pdf]

and for Tisseel and Artiss [link to: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con228792.pdf]

- Artiss is not recommended for laparoscopic use (or any other endoscopic procedures)

Please report suspected adverse reactions with fibrin sealants to the Yellow Card Scheme at www.mhra.gov.uk/yellowcard

A letter containing the recommendations was sent to healthcare professionals, in December 2012 for Evicel, and January 2013 for Tisseel and Artiss.

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