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HPRA DRUG SAFETY
NEWSLETTER

64TH EDITION

In this Edition

Reminder regarding arrangements for **Drug Safety Newsletter (DSN) Distribution**

The DSN has been a fully electronic publication since January 2014. Changes to the arrangements for publication and distribution were highlighted in several editions of the DSN during 2013, inviting readers to register with the HPRA to receive alerts when new editions of the DSN are published on the HPRA website. The electronic version of the DSN is in PDF format, allowing readers to save the newsletter and/or print specific pages. The electronic version also contains hyperlinks to product information and other documents on the HPRA and European Medicines Agency (EMA) websites.

As previously highlighted, to ensure you can continue to receive all issues of the DSN, please register on the HPRA website (**www.hpra.ie**) to receive an alert when a new issue is published, or alternatively, submit your email address (or email addresses), details of your profession (i.e. doctor (G.P./hospital doctor), pharmacist (community/hospital), nurse, dentist etc.) to **medsafety@hpra.ie**, to allow an electronic version to be emailed directly to you.

It is also requested that you share the content of each DSN with relevant colleagues, staff members, Drug and Therapeutic committees etc, to aid comprehensive dissemination of this important safety information and consideration of recommendations to support safe and appropriate use of medicines.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Oral Anticoagulants - Update on National Monitoring Experience

Oral anticoagulants are used for managing thromboembolic complications in conditions such as primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery, prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, treatment of and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults and prevention of atherothrombotic events in adult patients after acute coronary syndrome (ACS). While there are some common indications and contraindications for use of these medicines, there are also a number of differences. As such, it is important to regularly check the full details of the licensed indications, contraindications, precautions and warnings for the individual oral anticoagulants, which are described in detail in the product information (Summary of Product Characteristics (SmPC) and Package leaflet (PL)) for each of these medicines. These documents are accessible from **www.hpra.ie**.

The older oral anticoagulants, such as warfarin, are vitamin K antagonists. The newer oral anticoagulants, apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto) collectively known as 'NOACs' exert their effects through inhibition of factor Xa or of thrombin. Apixiban and rivaroxaban inhibit factor Xa (activated factor X). Factor Xa is involved in the conversion of prothrombin to thrombin. Thrombin is involved in the conversion of fibrinogen to fibrin which then leads to formation of a fibrin clot. Dabigatran inhibits thrombin. It is given as the prodrug dabigatran etexilate, which is converted to dabigatran in the body.

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Haemorrhage is the most important hazard of all oral anticoagulants including vitamin K antagonists. This risk is increased in patients:

- with significant risk factors* for major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities, hepatic disease and associated coagulopathy, congential or acquired bleeding disorders, severe uncontrolled arterial hypertension.
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins, heparin derivatives, oral anticoagulants (warfarin etc.) except under the circumstances of switching to or from the medicine, or when unfractionated heparin is given at doses to maintain an open central venous or arterial catheter.
- receiving concomitant treatment with other medication associated with a risk of haemorrhage, e.g. antiplatelets or Non Steroidal Anti Inflammatory Drugs (NSAIDs).

In light of the risk of haemorrhage for all anticoagulants, prescribers should consider each individual patient's risk of haemorrhage and closely observe posology recommendations, contraindications, warnings and precautions for use to minimise this risk. This includes a careful benefit-risk assessment in patients with conditions, or undergoing procedures, such as those outlined above, all of which increase the risk of major haemorrhage. In addition, clinical surveillance for signs and symptoms of haemorrhage is recommended throughout the treatment period especially in patients at increased risk.

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Renal impairment may constitute a contraindication, or a reason to consider not using these medicines, or reducing the dose. Decreased renal function, age ≥ 75 years, low body weight and certain concomitant medications are associated with increased plasma levels of the NOACs. Therefore renal function should be assessed and monitored as appropriate, in accordance with the recommendations described in the product information for each of the medicines concerned.

Attention should also be paid to hepatic function. Hepatic impairment may constitute a contraindication or a reason to consider not using the medicines or reducing the dose. Please refer to the product information since recommendations differ between the medicines.

National Monitoring Experience

The HPRA continues to receive reports of suspected adverse reactions associated with the use of NOACs. The majority of the suspected reactions reported have been consistent with the known potential risks of anticoagulants medicines and the characteristics of the patients treated. Adverse reactions reported included nausea, vomiting, abdominal pain, dizziness and haemorrhagic events that range from bruising, contusions and oozing at wound sites post surgery to gastrointestinal haemorrhage. In many of the more serious cases the patients concerned had significant underlying illness (renal impairment, malignancy, heart failure) or were treated with multiple medicines and/or surgery, which may have contributed to the outcome.

In addition many of the cases were influenced by underlying disease or other complications unrelated to the medicine. There have also been some reports of DVT, pulmonary embolism and cardiac effects (e.g. angina, tachycardia etc.), which would not be unexpected in the patient population concerned.

These medicines are subject to additional monitoring and the HPRA, together with EMA, will continue to closely monitor experience with use of NOACs and will highlight any relevant, new information should it become available. Healthcare professionals should report any adverse reactions suspected to be associated with the use of NOACs to the HPRA electronically via the website (**www.hpra.ie**), using the online or downloadable versions of the Adverse Reaction Report Form. Alternatively reports may be submitted using the post-paid 'Yellow Card' available from the HPRA by telephone (01 676 4971) or fax (01 6762517).

Previous updates highlighting relevant information and recommendations regarding the use of these medicines included as follows:

Drug Safety Newsletter (DSN) Edition 49 August 2012, Edition 56 October 2013 available at ***www.hpra.ie****.*

DHPC from Marketing Authorisation Holders for NOACs- September 2013 available at ***www.hpra.ie****.*

Full details of all risk factors are included in the product information for each medicine available at* ***www.hpra.ie* *and* ***www.ema.europa.eu/ema***

Key Message

- Close clinical surveillance, including monitoring for signs of haemorrhage, to facilitate early intervention and management is recommended for all patients treated with oral anticoagulants.
- Renal and hepatic function should be assessed and monitored during treatment with the NOACs in line with the recommendations in the product information.
- Factors including decreased renal function, age ≥ 75 years, low body weight and certain concomitant medications are associated with increasing the plasma levels of NOACs. Please refer to the individual product information (SmPC) for further information.
- Patients and caregivers should be advised about the risk of bleeding complications associated with NOACs and of the importance of carrying their patient alert cards at all times.
- Detailed, product specific information and advice to support safe and appropriate use of NOACs is provided in the individual SmPCs and educational materials for each of the products.

Chlorhexidine cutaneous solutions - Chemical injury including burns when used in skin disinfection in premature infants

Bloodstream infections are an important cause of morbidity and mortality in neonatal intensive care units (NICUs). Before and during neonatal catheterisation, skin disinfection and aseptic technique are crucial for preventing catheter-related bloodstream infections. Chlorhexidine is an antiseptic frequently used for skin disinfection before catheterisation of premature infants.

Following identification of a signal of erythema and chemical burns in preterm infants who were treated with chlorhexidine solution prior to central venous catheterisation, this issue was reviewed at EU level, taking account of the available data, including information from spontaneous reports, clinical trials and the published literature. A number of literature studies reported low blood concentrations of chlorhexidine in preterm neonates following cutaneous exposure[1,2]. The clinical significance of this absorption in preterm infants is currently unknown. Other literature articles report on older children who sustained severe skin reactions with the use of chlorhexidine solutions or impregnated dressings also[3]. Based on the available evidence from spontaneous reports and the published medical literature, infants born at less than 32 weeks of gestational age and when chlorhexidine is applied within the first two weeks of life for skin disinfection prior to invasive procedures appear to be at the greatest risk of skin toxicity.

Pooling around the umbilicus or under the infant has been identified by clinicians as a significant risk factor for the occurrence of severe burns and deaths.

The outcome of the EU review highlighted the importance of communication of this important safety concern to healthcare professionals and relevant professional bodies, informing them of the risks, together with information to support safe use of chlorhexidine containing cutaneous solutions. The product information for chlorhexidine containing solutions that are classified as medicines will also be updated to highlight the recommendations to reduce the risk of chemical burns.

The proposed changes to product information will particularly highlight the need to change all wet or soaked materials, drapes and gowns before proceeding with catheter insertion and to avoid any prolonged contact exposure of the skin to chlorhexidine. Dripping or pooling of the antiseptic on materials in contact with the patient (sheets, padding etc.) or under the patient should also be avoided.

REFERENCES

1 Aggett PJ, Cooper LV, Ellis SH, McAinsh J. Percutaneous absorption of chlorhexidine in neonatal cord care. Arch Dis childhood. 1981;56(11):878-80.

2 Lee A, Harlan R, Breaud AR, Speck K, Perl TM, Clarke W, et al. Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infec Control Hosp Epidemiol. 2011;32(4):395-7.

3 Levy I, Katz J, Solter E, Samra Z, Vidne B, Birk E, et al. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children: a randomized controlled study. The Pediatric Infect Dis J. 2005;24(8):676-9.

Key Message

- There is a risk of severe chemical injuries when chlorhexidine-containing solutions are used in preterm infants for disinfection of the skin prior to invasive medical procedures.
- The risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation and within the first two weeks of life.
- The minimum amount of chlorhexidine solution required should be used and the solution should not be allowed to pool in skin folds or under patients. Any excess solution and any soaked materials, drapes or gowns from the skin should be removed.
- Patients should be observed closely to detect and manage cutaneous side effects at an early stage.

Further details on chlorhexidine-containing solutions are available at* ***www.hpra.ie* *and* ***www.ema.europa.eu/ema***

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
SonoVue (sulphur hexafluoride)	Revised contraindications and warnings and precautions for the use of SonoVue.
Xgeva (denosumab)	Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia.
Prolia (denosumab)	Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia.

Adverse Reaction Reporting - Reminder

Figure 1.
The HPRA website, www.hpra.ie

The HPRA greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions, facilitating the continued surveillance of the safety of medicines. While the time-consuming nature of form-filling and the provision of follow-up information to the HPRA is recognised and acknowledged; the collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines. Such reports are essential for the HPRA to ensure that regulatory action/proposals take account of all available data.

There are several options in place for reporting suspected adverse reactions to the HPRA. These are as follows:

- By following the links to the online reporting options accessible for the HPRA homepage (**www.hpra.ie**);
- Using the downloadable report form also accessible from the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost';
- Using the traditional 'yellow card' report, which also utilises a freepost system;
- By telephone to the HPRA Pharmacovigilance section (01-6764971).

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.
Tel: 01-6764971 Fax: 01-6762517

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