

Drug Safety Update



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**

Volume 6, Issue 8, March 2013

Contents

Drug safety advice	Dabigatran (Pradaxa): contraindicated in patients with prosthetic heart valve(s) requiring anti-coagulant treatment, because of the risk of thrombosis and haemorrhage	A1
	Aqueous cream: may cause skin irritation, particularly in children with eczema, possibly due to sodium lauryl sulfate content	A2
	Botulinum toxin type B (Neurobloc): serious known risks such as toxin spread reported mostly with off-label use	A3
Other information from the MHRA	Learning about reducing risks associated with medicines – Benzodiazepines	O1

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.



For full details on our accreditation visit **NHS Evidence**

<http://www.evidence.nhs.uk/Accreditation>

In this issue: **dabigatran** (Pradaxa) is now contraindicated in patients with prosthetic heart valves requiring anti-coagulant treatment related to their valve surgery, because of the risk of thromboembolic and bleeding events. The contraindication follows an assessment of data from a new clinical trial (RE-ALIGN) (see article A1).

Also this month: **aqueous cream** may be associated with skin reactions, particularly in children with atopic eczema. These reactions may be due to the presence of sodium lauryl sulfate (SLS) or other ingredients. Following a UK review, the aqueous cream labelling and information leaflet will be updated with a warning on the potential for local skin reactions, and SLS will be listed as an ingredient. See article A2 for more information.

Finally in this issue: cases of toxin spread reported with **botulinum toxin type B** (Neurobloc) have mostly been reported with off-label use. Toxin spread is a known rare but serious risk with all botulinum toxin products and can result in muscle weakness, or difficulties in breathing or swallowing which may be life-threatening. We recommend that prescribers adhere to the licensed indication (article A3).

Priya Venkatesan, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Dabigatran (Pradaxa): contraindicated in patients with prosthetic heart valve(s) requiring anti-coagulant treatment, because of the risk of thrombosis and haemorrhage

Dabigatran (Pradaxa) is now contraindicated in patients with prosthetic heart valves requiring anti-coagulant treatment related to their valve surgery, regardless of the length of time elapsed since valve replacement took place.

The contraindication is based on new clinical trial data in this population, which showed an increased frequency of thromboembolic and bleeding events in the group of patients treated with dabigatran, compared with warfarin.

Dabigatran (Pradaxa) is a reversible inhibitor of free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. It is licensed for primary prevention of venous thromboembolic events in adults who have had elective total hip or knee replacement surgery (at 220 mg/day), and for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors (at 300 mg/day).

Increased risk of thrombosis and bleeding events

Previously, the product information for dabigatran recommended not to use dabigatran in patients with prosthetic heart valves. This warning has now been upgraded to a contraindication as a result of new data from the RE-ALIGN trial.

RE-ALIGN was an investigational phase II trial involving 252 patients, which compared dabigatran with warfarin in patients with recent mechanical heart valve replacement (during the current hospital stay), and in patients who underwent heart valve replacement more than three months beforehand.

There was a higher frequency of either thromboembolic events or bleeding events in patients treated with dabigatran compared with warfarin, regardless of the length of time elapsed since valve implantation. In the early post-operative patients, major bleeding manifested mainly as haemorrhagic pericardial effusion (unpublished data).

The reasons for these anomalous findings are not yet known; possible explanations include the higher-than-approved doses that the majority of patients in the dabigatran-treated group received (up to 300 mg twice daily) which may have been associated with the bleeding events, and that the trough plasma concentrations of dabigatran were lower than expected which may have led to thrombotic events in some patients.

Updated advice on the timing of using dabigatran after cardiac surgery may be issued when this has been further assessed.

No change to licensed indications

The results of the RE-ALIGN trial do not impact on the positive balance of benefits and risks of dabigatran in its currently licensed indications for:

- primary prevention of venous thromboembolic events after elective total hip or knee replacement
- prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more cardiovascular risk factors.

A full list of contraindications and warnings, together with updated product information for dabigatran, can be found in the Summaries of Product Characteristics (link to eMC: <http://www.medicines.org.uk/EMC/default.aspx>)

Further information:

Letter sent to healthcare professionals in January 2013 <Link to <http://www.mhra.gov.uk/home/groups/comms-ic/documents/websitesresources/con228791.pdf> >

Information from European Medicines Agency on Pradaxa: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/smops/Positive/human_smop_000464.jsp&mid=WC0b01ac058001d127]

BNF section 2.8.2: Oral anticoagulants [link to: <http://www.medicinescomplete.com/mc/bnf/current/PHP1503-dabigatran-etexilate.htm>]

Advice for healthcare professionals:

- Dabigatran is contraindicated in patients with prosthetic heart valve(s) requiring anticoagulant treatment related to their valve surgery, regardless of the length of time that has elapsed since valve replacement took place.

Article citation: *Drug Safety Update* March 2013 vol 6, issue 8: A1.

A2 Aqueous cream: may cause skin irritation, particularly in children with eczema, possibly due to sodium lauryl sulfate content

Aqueous cream may cause local skin reactions, such as stinging, burning, itching, and redness, when it is used as a leave-on emollient, particularly in children with atopic eczema. The reactions, which are not generally serious, often occur within 20 minutes of application but can occur later. Reactions may be due to the presence of sodium lauryl sulfate or other ingredients.

If a patient reports or shows signs of skin irritation with the use of aqueous cream, treatment should be discontinued and an alternative emollient that does not contain sodium lauryl sulfate should be tried.

Aqueous cream is a widely used product topically applied as an emollient for the symptomatic relief of dry skin conditions such as atopic eczema, and as a soap-substitute for skin washing.

Although aqueous cream is useful as a leave-on emollient in a substantial proportion of patients with eczema, it is known that in some patients, especially in children, it can cause skin reactions, such as stinging, burning, itching and redness.

In light of new information from the published literature all data on the benefits and risks of aqueous cream, particularly when used in children with eczema, have been recently reviewed in the UK [link to: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/UKsafetyPublicAssessmentReports/CON251956>].

Review outcome

Paediatric clinical guidelines from NICE and the National Eczema Society have reported that aqueous cream may be associated with skin reactions, such as burning, stinging, itching and redness, when used as a leave-on emollient but not when used as a wash product. The difference in the irritation potential in some patients may be related to the contact time with the skin, as soap substitutes are largely removed in the washing process.

An audit of 100 children attending a paediatric dermatology clinic reported that aqueous cream emollient was associated with an immediate skin reaction (stinging, burning, itching, and redness) within 20 minutes in 56% of exposures, compared with 18% with other emollients used.¹ Furthermore, several studies reported alterations in skin physiology (thinning of the outermost layer of the skin and increased skin water loss) following application of aqueous cream as an emollient in adults, both with and without eczema.^{2,3} A summary of all the evidence reviewed is available in our public assessment report [link to:

<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/UKsafetyPublicAssessmentReports/CON251956>]

The causative agent may be sodium lauryl sulfate (SLS), contained in emulsifying wax

Paediatric clinical guidelines from NICE [link to: <http://www.nice.org.uk/>]

Guidelines from the National Eczema Society [<http://www.eczema.org/>]

References

1. Cork MJ et al (2003). An audit of adverse drug reactions to aqueous cream in children with atopic eczema. *Pharm J* 271(7277): 747 – 745

2. Tsang M and Guy RH (2010). Effect of aqueous cream BP on human stratum corneum in vivo. *Br J Dermatol* 163(5): 954 – 958

3. Danby SG et al (2011). The effect of aqueous cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *Br J Dermatol* 165 (2):329 –334.

which is one of the ingredients of aqueous cream. SLS functions as a stabiliser and cleansing agent, and is a known skin irritant. However, aqueous cream products often contain other ingredients such as chlorocrescol, cetostearyl alcohol and parabens, which may also cause or contribute to adverse skin reactions.

Despite the potential irritant effects reported in the literature, in clinical practice aqueous cream used both as an emollient and a wash-off soap substitute has been useful in a substantial proportion of patients with atopic eczema.

New information: on the basis of the review, aqueous cream labelling and information leaflet will be updated with a warning on the potential of local skin reactions, and SLS will be listed as an ingredient.

Further information:

MHRA Public Assessment Report [link to: <http://www.mhra.gov.uk/home/groups/s-par/documents/websiteresources/con251957.pdf>]

MHRA aqueous cream patient information article [link to: <http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con254828.pdf>]

NICE Guideline Clinical Guideline: Atopic eczema in children (CG57) [link to: <http://guidance.nice.org.uk/CG57>]

Advice for healthcare professionals:

- Some patients with eczematous conditions, particularly children, may develop adverse skin reactions if aqueous cream is used as a leave-on emollient, often within 20 minutes of application. These reactions are not generally serious. However, patients and their carers should be warned of this risk during an eczema treatment consultation.
- If a patient reports skin irritation (burning, stinging, itching or redness) after the use of aqueous cream, they should discontinue treatment, and an alternative emollient that does not contain sodium lauryl sulfate should be tried.
- A patient article on potential skin reactions with aqueous cream is available here to download and print [link to: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON254827>].

Article citation: Drug Safety Update March 2013 vol 6, issue 8: A2.

A3 Botulinum toxin type B (Neurobloc): serious known risks such as toxin spread reported mostly with off-label use

Botulinum toxin type B (Neurobloc) is indicated only for the treatment of cervical dystonia (torticollis) in adults. We recommend that prescribers adhere to the licensed indication as its safety outside these circumstances has not been established. Cases of the known rare risk of toxin spread have been reported with all botulinum toxin products. Importantly, the cases with botulinum toxin type B were mostly reported with its off-label use.

All patients receiving any product containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects may be life-threatening.

Botulinum toxin type B (Neurobloc) is indicated only for the treatment of cervical dystonia (torticollis) in adults. The safety of botulinum toxin type B has not been established outside this licensed indication. We recommend that prescribers adhere to the licensed indication.

Possible risks associated with off-label use

Drug Safety Update, October 2007
[link to:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON079276>
]

Rare cases of distant toxin spread from the site of injection have been reported with botulinum toxin type B (and botulinum toxins as a class) – see article in October 2007 Drug Safety Update.

Some of the cases with botulinum toxin type B occurred in patients with underlying neuromuscular deficits, in children, and other off-label use. Medically severe adverse reactions related to the spread of toxin, such as dysphagia and breathing difficulties have usually occurred in association with incorrect clinical use or off-label use, such as the use in children or patients with significant neuromuscular disease, or the use of higher than recommended doses.

Further information:

Updated product information for Neurobloc [link to:
<http://www.medicines.org.uk/EMC/searchresults.aspx?term=Neurobloc&searchtype=QuickSearch>]

Letter to healthcare professionals on Neurobloc sent in February 2013 (link to:
<http://www.mhra.gov.uk/home/groups/comms-ic/documents/websitesources/con241829.pdf>)

BNF section 4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders [link to:
<http://www.medicinescomplete.com/mc/bnf/current/PHP3174-botulinum-toxin-type-b.htm>]

Advice for healthcare professionals:

- Reported cases of toxin spread with botulinum toxin type B have mostly occurred with off-label use; we therefore recommend that prescribers adhere to the licensed indication
- Botulinum toxin type B should not be used in children, or in patients with known neuromuscular disease or neuromuscular junction disorders.
- The risk of toxin spread with botulinum toxins is rare but serious and has been reported with all products in this class. All patients receiving a medicine containing botulinum toxin should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties, and advised to seek medical attention immediately if they experience breathing difficulties, choking, or any new or worsening swallowing difficulties, as such side effects can be life-threatening.

Article citation: Drug Safety Update March 2013 vol 6, issue 8: A3.

Other information from the MHRA

O1 Learning about reducing risks associated with medicines – Benzodiazepines

Link to Benzodiazepine module:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/Benzodiazepineslearningmodule/index.htm>

We have developed a learning module on benzodiazepines for clinical practitioners.

The self-directed learning package, which is approved for continuing professional education (CPD), outlines the key risks of this widely prescribed class of medicines.

For the different adverse effects, the module outlines:

Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom [link to:
<http://www.fpm.org.uk/>]

SSRI learning module [link to:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/SSRIlearningmodule/index.htm>]

- The main features of the adverse effect
- Factors that increase the risk
- How the risk can be reduced
- Specific treatment for the adverse effect

Opioids learning module [link to:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/Opioidslearningmodule/index.htm>]

Antipsychotics learning module [link to:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/Antipsychoticslearningmodule/Antipsychotics%20learning%20module>]

Education page [link to:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/index.htm>]

Self-assessment questions, together with full feedback, complement the learning material. Surveys tell us that learners greatly value the questions and the accompanying detailed feedback.

Participants are invited to complete a short online evaluation form at the end of the module – the responses help us tailor the modules to users' needs.

The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom has approved the benzodiazepine learning module for up to 2.5 CPD credits.

The benzodiazepine learning module joins similar ones on selective serotonin reuptake inhibitors (SSRIs), [opioids](#), and [antipsychotics](#). The education page on our website lists other learning materials and gives information on obtaining CPD credits.

Article citation: Drug Safety Update March 2013 vol 6, issue 8: O1.

© Crown Copyright 2013