EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

Workshop - the role of pharmacodynamic and pharmacokinetic measurements in the use of direct oral anticoagulants

Background document

The aim of this document is to provide relevant references to information published on the European Medicines Agency (EMA) website in relation to the direct oral anticoagulants.
The direct oral anticoagulants approved in the EU through the centralised procedure are Pradaxa, Xarelto, Eliquis and Lixiana.

1. Pradaxa (dabigatran etexilate mesylate)

Pradaxa is authorised in the EU since 18 March 2008. The Product information currently authorised in EU is provided below:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf

Pradaxa - Table of main assessment reports (AR) published on the European Medicines Agency website

Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
23 April 2008	**Initial authorisation 75 and 110 mg strength** Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery (pVTEp orthopaedic surgery).	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000829/WC500041062.pdf EMEA/H/C/829/0000
23 August 2011	**New indication (110mg and 150mg) and new strength (150 mg)** Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors (SPAF).	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500110875.pdf EMEA/H/C/829/X/13/G
04 September 2012	**Safety variation II/31** Update of sections 4.2, 4.3, 4.4, 4.5, 4.9 (all 3 strengths) and 5.1 (110 and 150 mg strengths) of the SmPC in order to minimise the risk related to bleeding	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500131783.pdf

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Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
	events in patients treated with Pradaxa following the AR for FUM 029.	EMEA/H/C/829/II/31
05 September 2013	**PSUR 034** Update to section 4.3 of the SmPC The contraindication in lesion or condition at significant risk for major bleeding which is now in place for Pradaxa does not allow for medical judgement, especially with regard to the prevention of VTE in surgery indications where, for example, an AV malformation or an aneurysm should not necessarily exclude a patient from receiving one of the new anticoagulants. This concern was viewed in perspective of safety profile of Pradaxa during PSUR period and was acknowledged by PRAC (a decreasing trend of cumulative reporting rates for serious bleedings). Therefore, the contraindication about lesions and conditions is revised slightly allowing the prescribing physician some more room for clinical judgment on when to consider the listed lesions and conditions as absolute contraindications.	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Conclusion/human/000829/WC500148637.pdf EMEA/H/C/829/PSU/034
19 March 2013	**Safety variation II/55** Update of section 4.3 of the SmPC (to change a contraindication for a concomitant use with tacrolimus to a non-recommendation) and section 4.5 of the SmPC (to change a non-recommendation for concomitant use with posaconazole to a cautionary statement) for both registered indications following the Assessment Reports for PSUR No 8.	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500163396.pdf EMEA/H/C/829/II/55
17 July 2014	**New indications (treatment of DVT and PE and prevention of related death [aVTEt] + prevention of recurrent DVT and PE and related death [sVTEp]** Update of section 4.1 of the SmPC for 110mg and 150mg strengths in order to add the following two new related indications: (1) treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death (aVTEt), (2) prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death (sVTEp). Several sections of the SmPC for 75, 110 and 150mg strengths were proposed to be modified to include the data relevant for two new	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500169948.pdf EMEA/H/C/829/II/48/G

Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
	indications.	

For further information the European Public Assessment report (EPAR) for Pradaxa on the EMA website can be consulted:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124

2. Xarelto (rivaroxaban)

Xarelto is authorised in the EU since 30 September 2008. The Product information currently authorised in EU is provided below :

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf

Xarelto - Table of main assessment reports (AR) published on the European Medicines Agency website

Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
09 November 2008	**Initial authorisation 10 mg strength** Indication in surgery	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000944/WC500057122.pdf Procedure EMEA/ H/C/944/000
20 January 2012	**New indication and new strength (15 and 20 mg)** Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500120736.pdf Procedure EMEA/ H/C/944/X10
20 January 2012	**New indication** For 15mg and 20mg film-coated tablets: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500120735.pdf Procedure EMEA/ H/C/944/II12
19 October 2012	1) **New indication** Prevention of recurrent DVT and PE in adults. 2) **New contraindications** (for 15 mg and 20 mg) as follows: Lesion or condition at significant risk of 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	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500138505.pdf Procedure EMEA/ H/C/944/II18

Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
	surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Concomitant treatment with any other of the AR anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, apixaban, dabigatran, etc.) except under the circumstances of switching therapy to or from rivaroxaban (see section 4.2) or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter.	
22 March 2013	**New indication and new strength 2.5mg** Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500144718.pdf Procedure EMEA/ H/C/944/X17
27 June 2013	**Update of sections 4.3, 4.4, 4.5 and 4.9 of the SmPC and Package leaflet** update the contraindication related to bleeding across indications, add a warning related to increased haemorrhagic risk of with age, update the drug interaction information and add information related to the management of overdose upon request from CHMP/PRAC.	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500151973.pdf Procedure EMEA/ H/C/944/II23

For further information the European Public Assessment report (EPAR) for Xarelto on the EMA website can be consulted:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&mid=WC0b01ac058001d124

3. Eliquis (apixaban)

Eliquis is authorised in the EU since 18 May 2011. The Product information currently authorised in EU is provided below:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf

Eliquis - Table of main assessment reports (AR) published on the European Medicines Agency website

Date of EMA Publication of the AR	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
20 May 2011	**Initial authorisation 2.5 mg strength** Indication in surgery	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002148/WC500107726.pdf Procedure EMEA/ H/C/2148/000
20 December 2012	**1) New indication and a new 5 mg strength** "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)." 2) **New contraindications as follows** "Lesion or condition at significant risk of 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. Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UHF), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under the circumstances of switching therapy to or from apixaban (see section 4.2) or when UHF is given at doses necessary to maintain a patent central venous or arterial catheter" for the existing 2.5 mg strength and a new 5 mg	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002148/WC500136575.pdf Procedure EMEA/ H/C/2148/X0004
	Update of sections 4.3 and 4.9-PSUR Contra indication in lesion or conditions (see above) amended The contraindication about lesions and conditions is revised slightly allowing the prescribing physician some more room for clinical judgment on when to consider the listed lesions and conditions as absolute contraindications. The potential consultation of a coagulation expert may be an obvious	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Conclusion/human/002148/WC500149988.pdf Procedure EMEA/ H/C/2148/PSUV/0012

Date of EMA Publication of the AR	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
	consideration for most emergency ward physicians treating a major bleeding complication to an overdose with an anticoagulant. Harmonisation of information between the authorised products	
29 September 2014	**New indication** Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients)."	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002148/WC500173870.pdf Procedure EMEA/ H/C/2148/II0014G
29 October 2015	**Update of sections 4.8- PSUR** Inclusion of pruritus in section 4.8 undesirable effects - frequency uncommon	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_conclusions_and_grounds_recommending_the_variation/human/002148/WC500196207.pdf Procedure EMEA/ H/C/PSUSA/00226/201505

For further information the link to the European Public Assessment report for Eliquis published on the EMA website can be consulted:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002148/human_med_001449.jsp&mid=WC0b01ac058001d124

4. Lixiana (endoxaban)

Lixiana is authorised in the EU since 19 June 2015. The Product information currently authorised in EU is provided below:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf

Lixiana - Table of main assessment reports published on the European medicines Agency website

Date of EMA Publication of the AR:	Summary of Authorisation	Link to the Assessment report / Regulatory procedure number
03 July 2015	*Initial authorisation 15mg, 30mg and 60mg strengths* (1) Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) - SPAF. (2) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).	http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002629/WC500189047.pdf Procedure EMEA/ H/C/2629/000

For further information the European Public Assessment report (EPAR) for Lixiana on the EMA website can be consulted:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002629/human_med_001874.jsp&mid=WC0b01ac058001d124