



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

6 Month 2019<sup>1</sup>  
EMA/PRAC/219990/2019  
Pharmacovigilance Risk Assessment Committee (PRAC)

## New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 8-11 April 2019 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found [here](#) (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

### **1. Direct-acting oral anticoagulants (DOACs): apixaban; dabigatran etexilate; edoxaban; rivaroxaban – Recurrent thrombosis in patients with antiphospholipid syndrome (EPITT no 19320)**

#### **Summary of product characteristics**

*Rivaroxaban/apixaban/edoxaban/dabigatran etexilate*

#### 4.4. Special warnings and precautions for use

##### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban/apixaban/edoxaban/dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

*Rivaroxaban*

#### 5.1. Pharmacodynamic properties

---

<sup>1</sup> Intended publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).



### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) <50 mL/min) and 61 to warfarin (INR 2.0- 3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomized to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

### **Package leaflet**

*Rivaroxaban/dabigatran etexilate*

#### 2. What you need to know before you take Xarelto/Pradaxa

Take special care with Xarelto/Pradaxa

- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

*Apixaban/edoxaban*

#### 2. What you need to know before you take Eliquis/Lixiana/Roteas

Warnings and precautions

Take special care with Eliquis/Lixiana/Roteas

If you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

## **2. Modafinil – Evaluation of data on foetal outcomes including congenital anomalies from a single observational study in the US (EPITT no 19367)**

### **Summary of product characteristics**

#### 4.6. Fertility, pregnancy and lactation

~~There is limited data on the use of modafinil in pregnant women.~~

Based on limited human experience from a pregnancy registry and spontaneous reporting modafinil is suspected to cause congenital malformations when administered during pregnancy.

Studies in animals have shown reproductive toxicity (see section 5.3).

~~Modafinil is not recommended for use during pregnancy or in women of childbearing potential unless they are using effective contraception.~~

[Product name] should not be used during pregnancy.

Women of childbearing potential have to use effective contraception. As modafinil may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see sections 4.4 and 4.5).

### Package leaflet

#### 2. What you need to know before you take [product name]

##### Pregnancy and breast-feeding

If you are pregnant (or think that you may be), are planning to become pregnant, or are breast feeding, you should not take [product name]. ~~It is not known if your medicine may harm your unborn baby.~~

Modafinil is suspected to cause birth defects if taken during pregnancy.

[...]

### 3. Selective serotonin reuptake inhibitors: citalopram; escitalopram – Drug interaction with fluconazole (EPITT no 19327)

#### Summary of product characteristics

##### 4.5 Interaction with other medicinal products and other forms of interaction

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of [active substance] may be necessary based on monitoring of side-effects during concomitant treatment (see section 4.4).

### Package leaflet

#### 2. What you need to know before you take [Product name]

##### Other medicines and [Product name]

Cimetidine, lansoprazole and omeprazole (used to treat stomach ulcers), fluconazole (used to treat fungal infections), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). These may cause increased blood levels of [active substance].