EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2013
EMA/784266/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pradaxa

International non-proprietary name: dabigatran etexilate

Procedure No. EMEA/H/C/000829/II/0055

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 6 November 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Pradaxa	dabigatran etexilate	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	II

The MAH proposed the 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 (012).

Section 2 in the Package Leaflet was proposed to be updated accordingly.

In addition, the MAH took the opportunity to make minor corrections to the Italian, Spanish and Icelandic translations of various sections of SmPC and Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Jens Heisterberg

1.2. Steps taken for the assessment

Submission date:	6 November 2013
Start of procedure:	19 November 2013
Rapporteur's preliminary assessment report circulated on:	25 November 2013
Rapporteur's updated assessment report circulated on:	17 December 2013
CHMP opinion:	18 December 2013

2. Scientific discussion

2.1. Introduction

Pradaxa® (dabigatran etexilate) was registered in the European Union (EU) in March 2008. The approved therapeutic indications are “Primary prevention of venous thromboembolic events (VTEs) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery” (pVTEp) and “Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors” (SPAF). Pradaxa® is marketed as capsules of 75 mg, 110 mg and 150 mg strengths.

In the frame of the Pradaxa PSUR 8 procedure the MAH was asked to provide supplementary information addressing requests for re-evaluation of SmPC wording on contraindications and drug-drug interactions. The final Assessment Report to the Pradaxa PSUR 8 contained a postauthorisation measure (LEG 12.1) that included among others a request to discuss whether a caution or non-recommendation for concomitant use of Pradaxa and tacrolimus is warranted or whether the current contraindication should be kept. Also the MAH was asked to provide a summary of available data on P-gp inhibitory potential of posaconazole and discuss its implications for Pradaxa.

In the Response Document submitted in May 2013 the MAH has proposed a cautionary statement for concomitant use of Pradaxa with tacrolimus and posaconasole.

In the final Assessment report to the follow-up measure LEG 12.1 the proposal of the MAH for a cautionary statement for tacrolimus was not endorsed, instead a non-recommendation regarding the concomitant use with Pradaxa was requested. The proposal of the MAH for a cautionary statement for posaconazole was endorsed.

The present variation application, C.I.3 is herewith submitted to implement the outcome of the LEG 012.1 assessment.

This variation affects sections 4.3 and 4.5 of the SmPC as well as section 2 of the Pacage Leaflet of both registered indications.

1) Tacrolimus is removed from the list of P-gp inhibitors contraindicated for the concomitant use in both sections 4.3 and 4.5
2) A non-recommendation for concomitant treatment of Pradaxa and posaconazole is removed from the section 4.5
3) A label proposal for a non-recommendation on concomitant use of Pradaxa and tacrolimus and caution on concomitant use of Pradaxa and posaconazole is included in the section 4.5
4) Tacrolimus is removed from the section 2 subsection "Do not take Pradaxa"
5) Posaconazole is included in the section 2 subsection "Other medicines and Pradaxa"

Furthermore, Corrigenda for Italian, Spanish and Icelandic translations of various sections are enclosed as attachments to the application form. The respective changes do not result from this variation, but the individual translations of the currently registered texts needed corrections.

2.2. Clinical Pharmacology aspects

Tacrolimus was listed as an *in vitro* P-gp inhibitor in the FDA`s 2006 draft guidance for industry "Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling"; but the current FDA 2012 draft guidance lists tacrolimus as CYP3A substrate.

The P-gp inhibitory potency of tacrolimus was deduced from MAH generated *in vitro* data as presented in Table 1 below and the effect on the efflux of dabigatran etexilate was similar to cyclosporine A or itraconazole.

Table 1 Comparison of effects of P-gp inhibitors on the in vitro basolateral apical transport of dabigatran etexilate through Caco-2 cell monolayers

Inhibitor (conc. range)	µmol dose/250 mL [I][2]	IC_{50} Basolateral to Apical	$[I]/IC_{50}$	% reduction of efflux ratio at various inhibitor concentrations		
		µM		1 µM[1]	3 µM[1]	max conc.[1]
Itraconazole (0.3 – 10 µM)	1134	0.47	2413	79.7	89.6	≥100
Cyclosporine A (0.1 – 12 µM)	4200	0.69	6087	99	≥100	≥100
Tacrolimus (0.1 – 6 µM)	**69.7**	**0.66**	**106**	**88.0**	**≥100**	**≥100**

[1] inhibitor conc. used in the experiment

[2] Estimated intestinal concentration (maximum single molar dose / 250 mL); MW of base

Source: U07-3554-02

According to our information there is no clinical drug-drug interaction evaluation available which assesses directly the P-gp inhibitory potency of tacrolimus with the probe drug digoxin (=P-gp substrate).

2.3. Clinical Safety aspects

From the post marketing experience the MAH received in total 10 case reports on concomitant administration of tacrolimus with Pradaxa®. Out of these, 4 cases with reported bleeding events were received. The percentage of bleeding events in cases involving concomitant medication with tacrolimus is comparable with the overall bleeding reporting.

2.4. Risk management plan

There was no updated RMP submitted within current variation. The pVTEp and SPAF Prescriber guides have been consequently revised, namely: tacrolimus is removed from the list of contraindicated P-gp inhibitors for the concomitant use with Pradaxa.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI):

PRESENT	PROPOSED
Annex I, section 4.3 (75 mg, 110 mg, 150 mg) Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone (see section 4.5)	Annex I, section 4.3 (75 mg, 110 mg, 150 mg) Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole~~, tacrolimus~~ and dronedarone (see section 4.5)
Annex I, section 4.5 (75 mg, 110 mg, 150 mg) The following strong P-gp inhibitors are contraindicated:systemic ketokonazole, cyclosporine, itraconazole, tacrolimus and dronedarone (see section 4.3). Caution should be exercised with mild to moderate P-gp inhibitors (e.g. amiodarone, quinidine, verapamil and tricagrelor (see sections 4.2 and 4.4)	Annex I, section 4.5 (75 mg, 110 mg, 150 mg) The following strong P-gp inhibitors are contraindicated:systemic ketokonazole, cyclosporine, itraconazole~~, tacrolimus~~ and dronedarone (see section 4.3). Caution should be exercised with mild to moderate P-gp inhibitors (e.g. amiodarone, quinidine, verapamil and tricagrelor (see sections 4.2 and 4.4)
Annex I, section 4.5 (75 mg, 110 mg, 150 mg) The following potent P-gp inhibitors have not been clinically studied but from *in vitro* results a similar effect as with ketoconazole may be expected: Itraconazole, tacrolimus and cyclosporine, which are contra-indicated (see section 4.3) Neither clinical nor in vitro tests results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa	Annex I, section 4.5(75 mg, 110 mg, 150 mg) The following potent P-gp inhibitors have not been clinically studied but from *in vitro* results a similar effect as with ketoconazole may be expected: Itraconazole~~, tacrolimus~~ and cyclosporine, which are contra-indicated (see section 4.3) **Posaconazole and tacrolimus affect P-gp, but have not been clinically studied. The concomitant use of Pradaxa and tacrolimus is not recommended, caution should be exercised when Pradaxa is co-administered with posaconazole.** ~~**Neither clinical nor in vitro tests results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa.**~~
Annex IIIB, section 4.8 (75 mg, 110 mg, 150 mg) Do not take Pradaxa -if you are taking cyclosporine or tacrolimus, medicines to prevent organ rejection after transplantation Other medicines and Pradaxa -Medicines to treat fungal infections (e.g. ketokonazole, itraconazole), unless they are only applied to the skin	Annex IIIB, section 2 (75 mg, 110 mg, 150 mg) Do not take Pradaxa -if you are taking cyclosporine ~~**or tacrolimus**~~**, a medicines** to prevent organ rejection after transplantation Other medicines and Pradaxa -Medicines to treat fungal infections (e.g. ketokonazole, itraconazole**, posaconazole**), unless they are only applied to the skin

During the procedure, the CHMP requested the following additional amendments to the Product Information:

The non-recommendation regarding tacrolimus and the cautionary statement regarding posaconazole are supported. However, more precise information about the rationale should be included in the SmPC.

The following wording of the SmPC was finally agreed by the CHMP (additions **in bold**, deletions ~~strikethrough~~):

4.3 Contraindications

"• Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, ~~tacrolimus~~ and dronedarone (see section 4.5)"

4.5 Interaction with other medicinal products and other forms of interaction

"P gp inhibitors

…

The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole, ~~tacrolimus~~ and dronedarone (see section 4.3). **Concomitant treatment with tacrolimus is not recommended.** Caution should be exercised with mild to moderate P gp inhibitors (e.g. amiodarone, **posaconazole,** quinidine, verapamil and ticagrelor) (see sections 4.2 and 4.4)."

…

"The following potent P gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected:

Itraconazole, ~~tacrolimus~~ and cyclosporine, which are contra indicated (see section 4.3).

Tacrolimus has been found in vitro to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors. Based on these data concomitant treatment with tacrolimus is not recommended.

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.

~~Neither clinical nor in vitro test results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa.~~"

In addition, the MAH took the opportunity to make minor corrections to the Italian, Spanish and Icelandic translations of the SmPC and the PL.

3. Overall conclusion and impact on the benefit/risk balance

The benefit-risk remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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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 (012).

Section 2 in the Package Leaflet was updated accordingly.

In addition, the MAH took the opportunity to make minor corrections to the Italian, Spanish and Icelandic translations of various sections of SmPC and Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.