EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/CHMP/583014/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MULTAQ

International non-proprietary name: dronedarone

Procedure No. EMEA/H/C/001043/II/0020

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, Sanofi submitted to the European Medicines Agency on 25 July 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
MULTAQ	dronedarone	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed an update of sections 4.3, 4.4 and 4.5 of the SmPC in order to contraindicate the concomitant use of dronedarone and dabigatran following the results of a phase 1 drug-drug interaction study. The Package Leaflet was proposed to be updated in accordance. In addition, Annex II (Conditions or restrictions with regard to the safe and effective use of the medicinal product) was proposed to be updated to reflect the change in the key messages of the Information Card.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	25 July 2012
Start of procedure:	21 August 2012
Rapporteur's preliminary assessment report circulated on:	12 September 2012
Rapporteur's updated assessment report circulated on:	17 September 2012
CHMP opinion:	20 September 2012

2. Scientific discussion

2.1. Introduction

Multaq (dronedarone) is indicated for the maintenance of sinus rhythm after successful cardioversion, in clinically stable adult patients with with paroxysmal or persistent atrial fibrillation (AF). It has the electrophysiological characteristics belonging to all four Vaughan-Williams classes of antiarrhythmic compound. Dronedarone is a multichannel blocker inhibiting the potassium currents (including IK (Ach), IKur, IKr, IKs) and thus prolonging cardiac action potential and refractory periods (Class III). It

also inhibits the sodium currents (Class Ib) and the calcium currents (Class IV). It non-competitively antagonises adrenergic activities (Class II).

In February 2011, the US product information (PI) of Multaq was updated to add the following information based on new information generated by a drug-drug interaction (DDI) study (INT11479):

"Exposure to dabigatran is higher when it is administered with dronedarone than when it is administered alone (1.7- to 2-fold)."

In April 2011 the CHMP, in line extension EMEA/H/C/829/X/0013 (CD: 01 August 2011), updated section 4.5 of the Pradaxa (dabigatran etexilate) SmPC with a non-recommendation of use for dabigatran and dronedarone. Similarly, in May 2011 the product information for Multaq was updated in variation EMEA/H/C/1043/II/004 (CD: 18 July 2011), based on study INT11479, with a non-recommendation for the combined use of dabigatran and dronedarone.

In February 2012 the MAH for Pradaxa (Boehringer Ingelheim International GmbH) submitted type II variation EMEA/H/C/829/II/0028 to amend SmPC sections 4.4, 4.5 and 5.2 based on new information obtained by the phase I study in male and female healthy volunteers to generate more comprehensive data on the effect of concomitant administration of dronedarone on the bioavailability of dabigatran etexilate. This clinical data was supplemented by post-marketing safety data.

The issue of the DDI between dabigatran and dronedarone was discussed at the May 2012 CHMP in the context of variation EMEA/H/C/000829/II/0028 for Pradaxa. The conclusion from this discussion was that in order for the CHMP to finalise its review, it was necessary to obtain data on this DDI from the MAH for Multaq. It was felt that such data would supplement the existing data provided by the MAH of Pradaxa, giving an overall picture of all available data on this DDI. Therefore on the 24th May 2012 the CHMP agreed to request the MAH for Multaq to provide their available data on this matter together with a variation in accordance with Article 16 of Regulation (EC) No 726/2004 or provide a justification for not doing so. At the same time a 2nd RSI was adopted for Pradaxa, requesting further argumentation/data in relation to the DDI to be put forward if applicable. The MAH for Pradaxa did not submit any further documentation to this respect.

As a result of this request the MAH for Multaq presented on the 18 June 2012 the available data on the DDI. Based on this data they also submitted a justification for supporting the maintenance of the current warning in the PI for Multaq. The data submitted consisted of a review of the pharmacokinetic interaction study INT11479 already assessed in variation EMEA/H/C/1043/II/004, post-marketing surveillance (PMS) data and an analysis of a US claim database.

The data submitted by the MAH for Multaq was assessed by both the Pradaxa and the Multaq Rapporteurs, and the assessment was shared with the MAH for Pradaxa. Similarly, the Pradaxa Rapporteur assessment report circulated on the 08 May 2012 was also shared with the MAH for Multaq. The decision to share these assessments was made on the basis of public interest according to Art. 4.2 and 4.3 of Regulation (EC) 1049/2001, which regulate public access to European Parliament, Council and Commission documents.

After having reviewed all the available data on this DDI, the CHMP agreed by majority, at its July 2012 plenary meeting, that a contraindication for the concomitant use of dabigatran with dronedarone should be implemented in both Pradaxa and Multaq product informations. As such, after variation II-28 was finalized for Pradaxa, the MAH for Multaq was requested to submit a type II variation in accordance with Article 16 of Regulation (EC) No 726/2004 to implement this contraindication.

2.2. Pharmacokinetic data

2.2.1. Methods – analysis of data submitted

Study INT11479 examined the effect of repeated administration of dronedarone 400 mg BID on the PK profile of dabigatran, both drugs being given concomitantly. This was a randomized, open-label, 2-treatment, 2-period, 2-sequence crossover study, conducted in 16 healthy male and female subjects. Subjects received repeated doses of dabigatran etexilate 150 mg OD for 4 days, and repeated 400 mg BID doses of dronedarone for 10 days. Both study drugs were given under fed conditions (standardized meals).

2.2.2. Results

The results of study INT11479 show that steady-state exposure to dabigatran was increased by 2.0 fold. Given that dabigatran etexilate, but not dabigatran, is a substrate of P-gp, the extent of increase of dabigatran exposure depends on the timing of P-gp inhibitor administration. A greatest increase is observed if the P-gp inhibitor is present in the gut when dabigatran etexilate is taken (table 1).

Table 1: Summary statistics of pharmacokinetic parameters of dabigatran following repeated oral administration of 150 mg dabigatran OD alone and in combination with dronedarone (Study INT11479)

Treatment	AUC_{0-24} ng*hr/ml	C_{max} ng/ml	t_{max} hr	Ae_{0-24} mg	fe_{0-24} %	CLR_{0-24} l/hr
dabigatran alone (N=14)	1020 ± 301	134 ± 40.8	3.00 (2.00 - 4.02)	3.21± 1.28	2.14 ± 0.857	3.15 ± 1.02
dabigatran+dronedarone (N=15)	2000 ± 507	229 ± 59.5	4.00 (3.00 - 5.00)	6.60 ± 1.56	4.40 ± 1.04	3.36 ± 0.634
*Ratio dabigatran+dronedarone / dabigatran alone (90% CI)	1.99 (1.79-2.21)	1.73 (1.54-1.93)	-	-	2.16 (1.81-2.58)	1.10 (0.92-1.30)

t_{max}: median and range
** Geometric mean estimates of treatment ratio*

2.2.3. Discussion

The conclusions of study INT11479 were that repeated oral doses of dronedarone at 400 mg BID increased the C_{max} and AUC_{0-24} of dabigatran after repeated oral doses of dabigatran at 150 mg OD by 1.73-fold (90% CI: 1.54 to 1.93-fold) and 1.99-fold (90% CI: 1.79 to 2.21-fold), respectively. The pharmacodynamic measurements confirmed this finding; a 1.5 fold increase of the ecarin clotting time (ECT) profile of dabigatran was observed when the drugs were co-administered, which is consistent with the observed PK interaction. The effect was less pronounced for the activated thromboplastin time (aPTT), only a 13% increase of the aPTT profile of dabigatran was observed. As the number of subjects is limited no definite conclusions can be drawn on the clinical relevance of these findings.

It can be concluded that the results of this study are in line with the data provided by the MAH of Pradaxa, showing a doubling in AUC of dabigatran that can be reduced when both drugs are not given concurrently.

2.3. Clinical Safety aspects

2.3.1. Review of post marketing surveillance (PMS) data

2.3.1.1. Methods – analysis of data submitted

Dronedarone has been marketed since July 2009 with an approximate cumulative exposure of 730,000 patients as of 31 March 2012.

Search in the global post marketing dronedarone database was performed to retrieve cases since launch of dronedarone in which dabigatran was reported as a co-suspect or a co-administered drug. This search with a cut-off date of 15 May 2012 retrieved 147 cases. Among these, 123 cases were reported in the USA.

Among the 147 cases, 40 cases were also identified using the standardized MedDRA query version 15.0 “Haemorrhage_broad+narrow”. Healthcare professional cases as well as consumer cases and both serious and non-serious case were considered by this query.

Among the latter, one case of bleeding had occurred before dabigatran initiation and was actually the cause of switch from warfarin to dabigatran.

Thirty nine out of the 40 cases retrieved by the above MedDRA query were analyzed as cases of potential interaction between dronedarone and dabigatran.

In 6 cases the reported reaction of interest was an isolated abnormal laboratory test finding, typically an increase of INR, without documented bleeding. One of these cases was associated with renal failure and 3 cases with liver failure. Information available was limited in 2 other cases. It is noteworthy to mention that INR is not an appropriate test for measuring the anticoagulant effect of dabigatran. Among the 33 remaining cases with concomitant use of dabigatran retrieved by the query, one case was associated with concomitant use of warfarin and 3 additional cases were associated with use of an antithrombotic agent (clopidogrel and ASA or ASA alone).

For the 33 cases with a bleeding event, the most frequently reported site of bleeding was gastrointestinal tract (18 cases). In only 4 cases overall more than 1 site of bleeding was reported.

In 14 out of the 39 cases, several possible alternative explanations/ contributive factors were documented. They were mainly concomitant use of at risk medication for bleeding, concomitant relevant disease or context (e.g. acute renal failure, acute liver disorder, thrombocytopenia, recent major surgery etc.). In the remaining cases, limited information did not allow a valid medical assessment.

Fatal outcome was reported in 1 case of gastrointestinal haemorrhage with limited information. The patient was hospitalized for an unknown reason leading to dronedarone withdrawal and gastrointestinal haemorrhage occurred thereafter. The reporter attributed fatal outcome to post-hemorrhagic cerebral ischaemia.

2.3.1.2. Discussion

Thirty nine cases of bleeding associated with the concomitant use of Pradaxa and Multaq are reported out of a database reporting the concomitant use in 147 patients. Most of the reports were identified in the USA. It should be clarified that in US, only the 150 mg Pradaxa is authorized, while in EU 2 doses are registered based on the bleeding risk: 150 and 110 mg. In only 4 cases, the administered dose is documented, in three of these it is 150 mg. In 33/39 cases, an event of bleeding was recorded; in the 6 remaining cases, only a laboratory value was increased. It can be agreed with the MAH, that in many

of the reported cases, other factors could have contributed to the event, though the association with dronedarone cannot be excluded.

2.3.2. Claim database analysis

2.3.2.1. Methods – analysis of data submitted

To evaluate the risk of major bleeding associated with the interaction between dronedarone and dabigatran in a real life setting, a retrospective cohort study was performed using the US Invision Datamart® (formerly LabRx®) claim database. The study population included patients aged 18 years and older with a diagnosis of atrial fibrillation or flutter (AF/AFL) who filled a prescription of dabigatran alone or dabigatran + dronedarone between 20 July 2009 and 30 September 2011 (the date of the latest data update received from the database vendor for the current analyses), identified in the US LabRx® database. Cohort entry date (baseline) was defined as the date of the first prescription of dabigatran or dabigatran + dronedarone dispensed after 20 July 2009.

The exposure duration for dabigatran alone episode began accumulating on the first day of dabigatran prescription and continued with the subsequent continuous dabigatran prescriptions until one of the following endpoints: 1) the end of dabigatran days supplied, 2) concomitant use of dronedarone and dabigatran, 3) the occurrence of the outcome event, 4) the end of the enrollment membership, or 5) the end of the observation period, whichever came first. Likewise, the treatment duration of the concomitant use of dronedarone and dabigatran began accumulating on the first day that patients received both dabigatran and dronedarone and continued with the subsequent continuous concomitant prescriptions of dabigatran and dronedarone until one of the following endpoints: 1) the end of the dronedarone days supplied, or 2) the end of dabigatran days supplied, 3) the occurrence of the outcome event, 4) the end of the enrollment membership, or 5) the end of the observation period, whichever came first. To account for potential non-adherence to drug therapies, an additional grace period of 30 days was added as exposure time in addition to days supplied of the prescribed drug.

The outcome of interest was major bleeding. Age and gender were included in the analysis as covariates. Drugs that might be associated with bleeding were also included as covariates, including: 1) anticoagulants and antiplatelet aggregation agents, 2) heparin and heparin derivatives (unfractionated heparin, low molecular weight heparins, heparin derivatives such as fondaparinux, desirudin), 3) anti thrombotic agents, and 4) vitamin K antagonists.

A total of 5,201 patients with AF/AFL who used dabigatran alone and 638 who used dabigatran in combination with dronedarone were included in the analysis. A total of 94 cases of major bleeding were identified within 2128.8 person-years period in the dabigatran only group resulting in incidence rate (IR) of 4.42 (95% CI 3.52 – 5.31) cases per 100 person years. For dabigatran + dronedarone group, there were 7 cases of major bleeding within 175.2 person-years follow-up, an IR of 3.99 (95% CI 1.61 – 8.23) cases per 100 person-years. The unadjusted Hazard ratio (RR) of major bleeding for dabigatran + dronedarone was 0.80 (95% CI 0.37 – 1.73) using dabigatran only as the reference. After adjusting for age, gender, and other covariates and using the same reference group, the HR of major bleeding for dabigatran + dronedarone was 0.82 (95% CI 0.32, 2.13).

2.3.2.2. Discussion

In conclusion, in this study among patients with AF/AFL in a US database, no increased risk of major bleeding associated with concomitant use of dabigatran and dronedarone relative to dabigatran alone, was found.

The above results are based on an adequately wide database, and do not indicate an increased incidence of major bleeding with co-administration of Pradaxa and dronedarone compared to dabigatran alone.

2.4. Risk management plan

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Changes to the SmPC

Section 4.3 – Contraindications

The following new contraindication was added:

"Co-administration with dabigatran"

Section 4.4 - Special warnings and precautions for use

The following warning was removed:
"~~Dabigatran~~

~~Dronedarone increases the exposure of dabigatran (see section 4.5). No clinical data are available regarding the co-administration of these drugs in AF patients. Their co-administration is not recommended.~~"

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The wording referring to dabigatran has been modified as follows:

"*Dabigatran (…). Their co-administration is ~~not recommended~~ contraindicated (see section 4.~~4~~3).*"

Changes to Annex II

Dabigatran was added to the list of drugs which are contraindicated with Multaq in the Multaq Information Card.

Changes to the Package Leaflet

The Package Leaflet was updated in accordance to the SmPC.

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

The submitted post-marketing data and the analysis of data from a retrospective cohort study using the claim database did not suggest a signal of an excess bleeding risk when co-administering dabigatran etexilate and dronedarone.

However, the results of the DDI study INT11479 showed that steady-state exposure to dabigatran was increased by 2.0 fold after repeated oral doses of dronedarone. These results were in line with those presented by the MAH of Pradaxa in the context of variation EMEA/H/C/000829/II/0028.

Following the assessment of all the data submitted by Sanofi and by the MAH for Pradaxa, the CHMP concluded that the phase I DDI studies indicated a significant interaction markedly increasing the exposure of dabigatran when co-administered with dronedarone. Therefore, the CHMP was of the opinion that both products should be contraindicated.

In this variation the MAH proposed to amend the wording in the Multaq product information to include this contraindication; the amendment was accepted by the CHMP.

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:

Variation accepted		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to contraindicate the concomitant use of dronedarone and dabigatran following the results of a phase 1 drug-drug interaction study. The Package Leaflet was updated in accordance. In addition, Annex II (Conditions or restrictions with regard to the safe and effective use of the medicinal product) was updated to reflect the change in the key messages of the Information Card.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.