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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with atrial fibrillation

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia.

Current Note for Guidance on Antiarrhythmics (CPMP/EWP/237/95) and its addendum on atrial fibrillation and flutter (EMA/CHMP/EWP/213056/2010) do not cover stroke prevention. The aim of this concept paper is to provide a rationale for a further guidance to industry when performing trials to develop drugs in prevention of stroke and systemic embolic events (SEE) in patients with AF, and also to provide a clear basis for the CHMP when assessing data from studies for anticoagulant drugs in this indication.

2. Problem statement

AF is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages [Camm et al, 2010; Furie et al, 2011]. Ischaemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. Based on the presentation and duration of the arrhythmia, AF is classified as: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF [Camm et al. 2010].

Current recommendations for antithrombotic therapy are based on the presence (or absence) of risk factors for stroke and thromboembolism [Camm et al. 2010; Hughes & Lip, 2008; Stroke in AF working group, 2007]. The simplest risk assessment scheme is the $CHADS_2$ score [cardiac failure, hypertension, age, diabetes, prior stroke or TIA (transient ischaemic attack) (doubled)] [Gage et al, 2001]. The original validation of this scheme classified a $CHADS_2$ score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk. The CHA_2DS_2 -VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)] extends the $CHADS_2$ scheme by considering additional stroke risk factors that may influence a decision whether or not to start anticoagulation therapy [Lip et al, 2010]. Many recently performed clinical trials of stroke prevention in AF have included some of these additional risk factors as part of their inclusion criteria [Connolly et al, 2006; Connolly et al, 2009a,b]. In patients with a $CHADS_2$ score of ≥2, chronic anticoagulation therapy with a vitamin K antagonist (VKA) is currently recommended in a dose adjusted manner to achieve an International Normalised Ratio (INR) value in the range of 2.0–3.0. In these patients, antiplatelet therapy could be considered as alternative therapy only when VKA therapy is unsuitable. In patients with a $CHADS_2$ score of 0–1, or where a more detailed stroke risk assessment is indicated, it is recommended to use a more comprehensive risk factor-based approach (e.g. CHA_2DS_2-VASc score), incorporating other risk factors for thromboembolism. In patients with CHA_2DS_2-VASc score of 1, VKA is preferred over ASA, while in patients with CHA_2DS_2-VASc score of 0, no antithrombotic therapy is preferred over ASA [Camm et al, 2010].

Various bleeding risk scores have been validated in anticoagulated patients, but all have different modalities in evaluating bleeding risks and categorization into low-, moderate-, and high-risk strata. Recently, a bleeding risk score has been proposed and validated [Pisters et al, 2010; Lip et al, 2010].

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Approximately only 30-60% of eligible patients receive oral anticoagulation with VKA and its use in clinical practice is challenging for several reasons, including a narrow therapeutic window, variability in response, interactions and laboratory standardisation [Ansell et al, 2008]. On average, patients may stay within the therapeutic INR range of 2.0–3.0 for 60–65% of the time in controlled clinical trials, but many 'real-life' studies suggest that this figure may be <50%. Indeed, having patients below the therapeutic range for <60% of the time may completely offset the benefit of VKA [Camm et al, 2010].

Several emerging new oral anticoagulants are being developed to overcome these limitations and some of the clinical trials protocols for stroke prevention in AF with new oral anticoagulants have been published [Ezekowitz et al, 2009; Eikelboom et al, 2010; ROCKET AF Study Investigators, 2010; Ruff et al, 2010].

3. Discussion

The following critical aspects will need to be discussed and covered as appropriate by the proposed guideline:

1. Categorisation of patients with AF according to current clinical criteria [Camm et al, 2010].

2. Ensuring adequate representativeness of the population studied across the entire clinical development while keeping the necessary assay sensitivity of individual studies, including an appropriate description of the population included in clinical trials: Demographic characteristics; Cardiovascular risk factors and categorisation of risk factors for stroke; Bleeding risk factors; Valvular versus non-valvular AF; Presence of any contraindications to VKA or other applicable antithrombotic treatment (yes/no) and definition of these contraindications; Naïve versus experienced patients on VKA therapy or other applicable antithrombotic treatment; Concomitant antithrombotic medication (e.g. antiplatelet therapy)

3. Demonstration of dose-response relationship in dose-finding studies.

4. Key methodological issues in pivotal trials: Open label versus double-blind designs; Choice of control group; Definition of primary efficacy endpoint (i.e.: time to first stroke and/or systemic embolic event), primary safety endpoint (i.e.: major bleeding) and secondary endpoints; Primary analysis (non-inferiority or superiority and definitions for declaring non-inferiority or superiority); on-treatment only versus on-treatment and off-treatment endpoint events; Adjudication of events; Assessment of stroke severity; Investigation of possible heterogeneity between on- and off-treatment events and potential for rebound effect after treatment cessation; Control of optimal concomitant pharmacological and non-pharmacological measures used for treatment of common vascular risk factors for stroke; Documentation of concomitant medications and doses given; relevant procedures performed before and during the trial; Treatment compliance and quality of oral anticoagulation; Management of bleeding events; Additional investigations during pivotal trials aimed at providing more accurate assessment of thromboembolic and bleeding risks (quality of life measurements, PK/PD relationship, pharmacogenetics, biomarkers, electrocardiographic and/or echocardiographic sub-studies).

5. Assessment of efficacy and safety in special populations

6. Assessment of the need for specific tests to monitor anticoagulant effect.

7. Assessment of the need for development of a specific antidote.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

4. Recommendation

The Working Party recommends that prior to start drafting the guideline it seems prudent to initiate discussion with other Regulatory Authorities and experts from academia to exchange views on the key issues identified in the clinical investigation of medicinal products for prevention of stroke and SEE in AF.

5. Proposed timetable

It is anticipated that a draft document may be agreed by the CVWP in January 2011. The draft may be adopted by the CHMP for release for consultation in February 2011. The draft document will then be released for 3 months of external consultation and following the receipt of comments it will be finalised within approximately 3 months.

6. Resource requirements for preparation

It is not anticipated that expert consultation will require convening any specific formal meeting at the EMA premises for the Concept Paper. The preparation will involve the CVWP (Cardiovascular Working Party) drafting group. Three rapporteurs from the EWP-CV will be involved and the document is predicted to be discussed on one EWP-CV meeting.

7. Impact assessment (anticipated)

The document is intended to provide guidance to industry when performing trials to develop drugs in prevention of stroke and systemic embolism in patients with AF. It should also provide a clear basis for the CHMP when assessing data from studies for anticoagulant drugs in this indication and providing advice in this field.

8. Interested parties

The interested parties in the guideline include the industry (PhARMA, EFPIA, JPMA and others), Academia, European Society of Cardiology, clinical trialists in AF and other Regulatory Agencies.

9. References

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