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Addendum to the Guideline on antiarrhythmics on atrial fibrillation and atrial flutter

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Executive summary

This is an addendum to the Note for Guidance on Antiarrhythmics (CPMP/EWP/237/95). This addendum replaces some chapters of the above mentioned document.

1. Introduction

After a number of trials with some anti-arrhythmics had shown detrimental effects in patients with structural heart disease and ventricular arrhythmias, the popularity of these agents declined dramatically, in particular of those drugs that have class I and class III anti-arrhythmic effects. At the same time regulatory requirements have increased as indicated in the Note for Guidance on Antiarrhythmics (CPMP/EWP/237/95) that came into operation in June 1996. Since then, only a very small number of new antiarrhythmic drugs has been tested for the treatment of ventricular arrhythmias and attention has shifted to the prophylaxis and treatment of supraventricular arrhythmias, in particular atrial fibrillation (AF) and atrial flutter (AFL). The Note for Guidance on Antiarrhythmics (CPMP/EWP/237/95) provides only partial regulatory guidance for development of medicinal products for the treatment of these arrhythmias. This document aims to cover the remaining deficiencies and substitutes those chapters of the mentioned document related to these arrhythmias.

2. Scope

This guideline is intended to provide guidance for the evaluation of new medicinal products or drugs used in the antiarrhythmic treatment of atrial fibrillation.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83 as amended.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account, especially those on:

- Note for Guidance on General Consideration in Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice for Control Group for Clinical Trials (CPMP/ICH/364/96)
- Note for Guidance on the Investigation of Drug Interaction (CPMP/EWP/560/95)
- Note for Guidance on Population Exposure: The extent of population exposure to assess clinical safety (CPMP/ICH/375/95 adopted November 1994)

4. Background

Atrial Fibrillation is a supraventricular arrhythmia characterized by uncoordinated atrial activity with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. Haemodynamic impairment and thromboembolic events related to AF result in significant morbidity and mortality. AF is often associated with structural heart disease (e.g. hypertension with LVH, coronary artery disease, heart failure), and occurs much less frequent in patients without structural heart disease, accounting for only a minority of all cases of AF. AF may also be related to an acute temporary cause e.g. alcohol intake, pericarditis, acute coronary syndrome, and hyperthyroidism. In these settings, AF is not the primary problem, and treatment of the underlying disorder concurrently with management of the episode of AF usually results in termination of the arrhythmia without recurrence.

AF may follow various patterns. Distinction should be made into newly discovered AF (first detected episode), whether or not symptomatic or self-terminating, and recurrent AF (2 or more episodes).

If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 days, it is termed persistent. Termination with pharmacological therapy or direct-current cardioversion does not alter the designation.

First-detected AF may be either paroxysmal or persistent. The category of persistent AF also includes cases of long-standing AF (e.g. longer than 1 year), usually leading to permanent, accepted AF, when the therapeutic goal of sinus rhythm maintenance is no longer pursued.

A clinical interrelationship between AF and AFL has long been appreciated. Patients who primarily manifest AF commonly also manifest AFL and *vice versa*. Any claims regarding AFL will need separate, consistent documentation as sole AFL only represents a small proportion of the population with AF or AFL. Patients with sole AFL are usually amenable, often curable by catheter ablation without the need for antiarrhythmic drug therapy.

Management of patients with AF involves 3 primary objectives – rate control, rhythm control and prevention of thromboembolism. Relief of symptoms and improvement in quality of life are also important objectives. Ultimately, the main objective could be to reduce the risk of morbidity and mortality linked to AF/AFL. Prevention of thromboembolism is outside the scope of this guideline. The initial management decision involves primarily a rate or rhythm control strategy. Cardioversion may be achieved by means of drugs or electrical shock(s). AF is often a chronic, progressive arrhythmia and after restoration of sinus rhythm, recurrence rate is high, occurring most frequently in the first four weeks after cardioversion. In case of restoration of sinus rhythm, prevention of recurrence becomes another objective. Patients with non transitory AF/AFL are increasingly managed by slowing of the heart rate instead of restoring the sinus rhythm. More recently, non pharmacological approaches have been proposed for patients in whom AF/AFL could not be managed adequately pharmacologically which are outside the scope of this guideline.

The limited effectiveness and at times unfavourable side effect profile of available therapeutic options have resulted in a massive surge of randomised trials in AF/AFL. Due to the diverse therapeutic options and desired outcomes, trials that assess new medicinal products for AF often use completely different outcome parameters, depending on the aim of the treatment and the type of underlying disease. These outcome parameters therefore need to be defined better within the context of the selected patients and the design of these trials.

5. Efficacy criteria

Different AF trials will require different primary outcome parameters, but the complex consequences of AF will require assessment of a variety of outcome domains in every trial. The primary efficacy endpoint in most trials will focus on the arrhythmia *per se*, be it rhythm or rate control, but clinical benefit in terms of symptomatic improvement and/or morbidity and mortality needs to be assessed before a marketing authorisation can be obtained. This will be discussed further when the various specific parameters are discussed below.

5.1 Antiarrhythmic effects

The ECG is the only means to demonstrate that a drug has a direct effect on an arrhythmia. Therefore, antiarrhythmics intended for AF by definition need to demonstrate an effect either on the rhythm or rate, depending on the claimed indication:

- If the claimed indication is **restoration of sinus rhythm** by pharmacological cardioversion, the primary endpoint will be termination of the AF/AFL (“successful conversion”) as measured during continuous ECG monitoring. Successful conversion is defined in some guidelines as restoration of sinus rhythm for a few seconds. This definition, though valid from an electrophysiological point of view, is of questionable value to be used as definition of success in clinical studies aimed to assess the effect of a pharmacological intervention in the restoration of sinus rhythm. As there is no widely accepted definition for success rates, these should be defined in the protocol. From a clinical perspective, it is necessary to ensure that patients remain in sinus rhythm for a period of time that is deemed relevant in the clinical context where the study is conducted. This will depend on PK and PD characteristics of the experimental drug, type of patients enrolled, planned need for urgent cardioversion, and whether or not acute therapy will be followed by maintenance therapy. No clear recommendations can be given, but the issue should be discussed in the protocol. Usually, cardioversion studies are targeted at patients with recent-onset AF as patients with longer-lasting AF episodes (> 7 days) are more difficult to cardiovert with drugs alone.

Time to recurrence and recurrence rates should also be monitored in order to assess its clinical relevance. The time limit for assessment of the primary endpoint should be defined, as a too short time window may limit the possibility to observe the spontaneous cardioversion rate. Although there are no clear definitions for recurrence, a distinction between immediate (within 5 min), intermediate (between 6 min and 28 days) and late (more than 28 days) recurrence can be made. Methods for documentation of recurrence are discussed below. Measurements of recurrence, in particular late recurrence, should take into account changes in background medication as these will influence the results

- If the claimed indication is **(1) maintenance of sinus rhythm after cardioversion in patients with persistent or permanent AF/AFL**, time to first documented recurrence of the AF from cardioversion or baseline is a clinically meaningful primary endpoint. The number and duration of recurrent episodes of paroxysmal AF may be suitable secondary outcomes. If **(2) prevention of recurrence of paroxysmal AF** is the primary target, the primary outcome is more difficult to define. Suitable primary outcomes may consist of time to recurrence of AF or time in AF. In case of recurrence the number of such episodes should be taken into account as secondary endpoint. Any arrhythmia that has ECG characteristics of AF/AFL lasting longer than 30s should be reported as recurrent AF/AFL.

Recurrence should be documented by scheduled regular ECG recordings through scheduled 24h/month Holter ECG or transtelephonic ECG recordings (transtelephonic monitoring, TTM) or resting ECG when a (symptomatic) episode is perceived by the patient. Systematic ECG recordings are always required, and should be scheduled regularly, in particular during the first week after cardioversion, as ECG recordings by symptoms will miss about half of all AF/AFL episodes. In the early stages of a drug development, more intensified ECG monitoring may be desirable to detect antiarrhythmic effects. These can be achieved by performing studies in pacemaker patients, by implanting loop recorder devices, and/or by long-term ECG monitoring devices or event recorders that do not require implantation. Arrhythmia free-survival rate should be measured as a secondary endpoint. When started before cardioversion, pharmacological treatment may affect cardioversion rate and this should be recorded, taking into account the aforementioned comments.

Study design should take into consideration that early recurrences of AF are common after cardioversion. Often, initiation of drug therapy to achieve therapeutic drug levels at the time of cardioversion is more suitable than a "blinking period" immediately after cardioversion.

Factors that predispose to recurrent AF/AFL such as advanced age, heart failure, hypertension, LA enlargement, and LV dysfunction should also be recorded.

- If the claimed indication is **rate control in patients with chronic AF/AFL**, effects on mean resting heart rate as measured by 12 lead ECG and heart rate during moderate exercise testing are relevant measures of efficacy. They may give complementary information as the pharmacological effect may vary between rest and exercise. Alternatively, 24-hour Holter monitoring can be used. As primary endpoint the mean rates over 24 hours or at rest may be compared with the mean rates at baseline, but there is no consensus what parameter is best and changes in other 24-hour Holter parameters need to be included as secondary endpoints. 24-hour Holter monitoring is also useful to check for excessive bradycardias. Measurements should be performed at baseline, and when steady state concentrations have been achieved. Long term efficacy needs to be confirmed, depending on the duration of the study.

There is no widely accepted definition of a good rate control. Criteria for rate control vary with patient age and there is no accepted link between a specific heart rate during AF/AFL and intensity of symptoms, morbidity or mortality because this is patient dependent. Criteria used to define adequate control should be mentioned in the protocol, considering the rate at rest and/or during a level of activity that can typically be achieved by the individual patient. For this reason clinical benefit in terms of improvement in symptoms and AF/AFL-related quality of life, exercise testing, morbidity and mortality (see below) should be assessed in conjunction with the rate control intervention.

5.2 Mortality and morbidity

It should be recognised that incorrect anticoagulation increases morbidity and mortality and utmost care should be taken to optimise anticoagulation treatment before patients are included in the study. This should be defined in the protocol and should follow the present recommendations in the clinical practice guidelines.

AF/AFL is associated with increased rates of (cardiovascular) death, stroke and myocardial infarction, heart failure and hospitalisations.

- If the claimed indication is **reduction of cardiovascular events including mortality** the most favoured approach would be to choose one primary composite endpoint comprising of cardiovascular death and disease-related morbidity, such as new onset or worsening heart failure, stroke, and/or myocardial infarction.
All deaths need to be monitored in any trial on an "intention-to-treat" basis from the time of randomisation and should be classified. AF/AFL-related death should not substitute "total" cardiovascular death as an outcome parameter, because AF/AFL-related death will be difficult to assess.
Morbidity may involve both the incidence of non-fatal stroke and myocardial infarction and the occurrence of heart failure, as both can be affected by the treatment depending on the underlying mechanism. All strokes (ischaemic and haemorrhagic) and systemic events should be recorded separately and be evaluated using the best possible methods (including MRI/CT brain imaging, assessing intensity of anticoagulation, severity of stroke, and neurological end results). Worsening of the heart failure should be a separate secondary endpoint in any long term controlled trial and may be particularly important if the claimed indication is slowing of the ventricular rate of the arrhythmia. All events should be adjudicated by an independent committee.
- Time to first (cardiovascular) hospitalisation may be a reflection of the burden of AF/AFL and could be studied as a useful secondary endpoint to assess the clinical implications of the antiarrhythmic efficacy. Duration of the hospitalisation and number of in-hospital days should also be taken into account. As local treatment routines will influence whether a given medical condition is treated on an out-patient basis or in the hospital, the reasons for cardiovascular hospitalisations should be documented closely and major differences between the various centres should be ruled out. Elective rhythm control interventions leading to hospitalisation (e.g. cardioversion, surgical and ablation therapy, pacing) should be recorded separately. It may be difficult to differentiate between hospital admissions for treatment of AF (e.g. cardioversion) and for CV morbidity in general.

5.3 Symptoms and AF-related quality of life

AF/AFL is associated with poor quality of life (QOL) and the presence of symptoms is the main indication for rate and rhythm control. However, the relation between symptoms and AF/AFL recurrences or slowing of the ventricular rate is elusive and symptoms and QOL are therefore considered as secondary outcome parameters, but may be particularly important if the claimed indication is slowing the ventricular rate of the arrhythmia or prevention of symptomatic AF. Relating symptom assessment to rhythm may be useful for the interpretation of results. Any symptoms scale used needs to be validated.

5.4 Left ventricular function and exercise testing

AF/AFL may impair LV function. On the other hand, AF/AFL and its complications frequently occur in the presence of LV dysfunction. Rate- or rhythm-control strategies can improve LV function. Global LV function should be measured at baseline by echocardiography or another validated method and during follow-up by measuring LV volumes as well as ejection fraction. This can be supplemented by a standardized submaximal exercise test as a general measure of cardiac performance. Serial echocardiography can also be used to measure atrial diameters that may be reduced after restoration and maintenance of sinus rhythm.

6. Safety Criteria

6.1 Morbidity and mortality

Mortality and morbidity data must always be reported whatever the clinical claim. Hospitalisations both for cardiovascular adverse events and for non-cardiac causes should be monitored closely. When there is any suspicion of a detrimental effect, controlled total and cardiovascular studies are required.

This is especially the case when drugs are targeting cardiac ion channels and when patients with grade II – IV heart failure are the target population in the trial. Information by means of clinical studies on the use in patients with more severe forms of heart failure should be actively pursued as AF/AFL occurs frequently in these patients. If such studies are not completed by the time of authorisation, a clear contraindication of use of the drug in patients with heart failure will ensue.

6.2 Cardiac events

Effects on cardiovascular function, in particular on automaticity, AV conduction and QT shortening and prolongation should be monitored. Occurrence of arrhythmias, in particular sick sinus syndrome or another cause of bradycardia, atrioventricular block and *torsade de pointes* and other (new) ventricular arrhythmias, should be carefully documented. Factors predisposing to drug-induced ventricular pro-arrhythmia such as long-QT interval, electrolytes disturbances, and rapid dose increase should be avoided. Numbers of implanted pacemakers and ICDs should be recorded. The scheduled ECG recordings that are performed to assess rhythm-based outcomes should be analyzed for pro-arrhythmic effects as well. Safety issues may require additional ECG recordings to detect tachycardia and bradycardia signals. Any arrhythmia that might constitute a pro-arrhythmic event must be reported as an adverse event. Patients at risk, in particular patients with structural heart disease and/or heart failure should be observed for any exaggerated pharmacological response. Continuous ECG monitoring is feasible by implantable devices and may be considered for assessing ECG related safety and efficacy, depending on the study purpose.

6.3 Haemodynamic effects

Effects on cardiac function and related symptoms and the occurrence of arrhythmia should carefully be documented.

6.4 Stroke

Both cardioversion and chronic AF may result in stroke or peripheral embolism. Its occurrence should be monitored as both may be affected by treatment. As stated earlier, utmost care should be taken for adequate anticoagulation according to current guidelines.

6.5 Other adverse experiences

Non-cardiovascular adverse experiences will depend on the pharmacological profile of the drugs and the organs that may be affected and specific monitoring is encouraged.

6.6 Interactions

Special attention should be paid to pharmacokinetic and/or pharmacodynamic interactions with other cardiovascular drugs affecting heart rate, automaticity, AV conduction, QT prolongation, and with antithrombotics, in particular anticoagulants.

7. Selection of patients

Patients should be selected according to the arrhythmia pattern of AF or AFL (first detected, paroxysmal, persistent, permanent). When selecting a particular patient population, it may be meaningful to choose patients who are likely to respond in the same way as overlap may occur (e.g. paroxysmal and persistent AF/AFL). The inherent risk for recurrent AF/AFL and AF/AFL-related complications is heavily influenced by patient characteristics. These characteristics should be carefully documented and care should be taken for an equal distribution as much as possible, in particular the duration of AF/AFL, prior antiarrhythmic drug treatment and treatment at enrolment, and specific cardiovascular conditions associated with AF/AFL. These include valvular heart disease, heart failure, coronary artery disease and hypertension, in particular when LV hypertrophy is present. A sufficient percentage of patients with impaired LVEF (<35%) should be included in clinical trials when these patients reflect the true target population. Mortality studies may be needed if the drug is specifically intended to be given to patients suffering from heart failure.

An adequate number of elderly patients should be included in the clinical trials and both genders should be represented adequately. It is important to separate AF from AFL as much as possible.

8. Study design

The design of studies in AF/AFL should follow the pattern of a potential antiarrhythmic agent as indicated in the *CHMP NfG on anti-arrhythmics (CPMP/EWP/237/95)*. Requirements may vary, however, depending on the claimed indication:

- **Restoration of the sinus rhythm**

Both placebo-controlled and actively-controlled studies should be considered, depending on the characteristics of the target population and the presence of alternative therapy. Sample size should be adequate, inclusion criteria standardised, and intervals from dose administration to assessment of outcome clearly defined, allowing conclusions about rapid, intermediate and late outcome. Duration of the studies may therefore vary from 48 hours to > 4 weeks, depending on the expected duration of the effect (see also **3.1 restoration of sinus rhythm**).

- **Maintenance of the sinus rhythm after cardioversion in patients with persistent/permanent AF/AFL and/or prevention of recurrences in patients with paroxysmal AF/AFL**

Both placebo-controlled and actively controlled double-blind studies should be considered. Active controlled studies are feasible and, in general, necessary from a regulatory perspective in particular when the balance between benefit and risk appears to be altered compared to the comparator. The choice of the active comparator will depend on the specific disease state and should take into account regulatory conditions of the marketing authorisation. In case of maintenance of sinus rhythm after cardioversion many patients eventually will need prophylactic antiarrhythmic drug therapy to maintain sinus rhythm, suppress symptoms, improve exercise capacity and haemodynamic function, and prevent tachycardia-induced cardiomyopathy due to AF/AFL. This will necessarily limit the duration of placebo treatment but actively controlled studies may last longer, up to 6 months or more, provided that these patients are monitored closely for patients with relapses of AF/AFL. As recurrence rates will depend on the presence or absence of structural heart disease and duration of AF/AFL before cardioversion, this should be specified in the protocol. In case of prevention of recurrence in patients with paroxysmal AF/AFL, the use of placebo can be justified in subjects who experience brief or minimally symptomatic recurrences or paroxysmal AF/AFL.

Non antiarrhythmic drugs have been recently proposed to prevent AF/AFL recurrences (N-3 PUFA, statins, ACE-I, ARBs) and some trials are ongoing to assess this further. The study design, target population, efficacy and safety end points should be the same as suggested for antiarrhythmics. Comparison can be made versus placebo, usually on top of other standard antiarrhythmic treatments.

- **Rate control in patients with chronic AF/AFL**

Both placebo-controlled and actively controlled studies should be considered. Patients with chronic AF/AFL are increasingly managed by slowing of the heart rate instead of cardioversion, not only as a second line strategy when one or more attempts to restore and maintain sinus rhythm have been made and failed but also as first line strategy. As it has been shown that with this approach the outcome in terms of morbidity and mortality is not significantly altered, the duration of placebo-controlled trials will be limited but actively controlled studies should last longer. Requirements in terms of duration, number and size of the trials will also depend on whether other antiarrhythmic indications are claimed as well.

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