European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. EMEA/CHMP/EWP/352438/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

NOTE FOR GUIDANCE ON ANTIARRHYTHMICS

ADDENDUM ON ATRIAL FIBRILLATION

DRAFT AGREED BY EFFICACY WORKING PARTY	July 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2009

This addendum replaces some chapters of the NfG on Antiarrhythmics (CPMP/EWP/237/95).

Comments should be provided using this template to EWPsecretariat@emea.europa.eu.

KEYWORDS	*Atrial fibrillation, rhythm control, rate control, cardioversion*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

After a number of trials with anti-arrhythmics had shown detrimental effects of some anti-arrhythmics in patient with structural heart diseases, the popularity of these agents have declined dramatically, in particular those drugs that have class I and class III anti-arrhythmic effects. At the same time regulatory requirements have increased as indicated in the *CHMP NfG on anti-arrhythmics (CPMP/EWP/237/95*) that came into operation in June 1996. Since then, only a very small number of new drugs intended for the treatment of ventricular arrhythmias have been going through the central procedure and the same applies for the number of scientific advices for this purpose. As pro-arrhythmic effects appear to be less dominant in supraventricular arrhythmias, attention has focused on the prophylaxis and treatment of supraventricular arrhythmias, in particular atrial fibrillation. The CHMP NfG on anti-arrhythmics (CPMP/EWP/237/95) provides only partial and incomplete regulatory guidance for development of medicinal products for the treatment of these arrhythmias. This document aims to cover these deficiencies and substitutes those chapters of the mentioned document related to these arrhythmias.

2. BACKGROUND

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia 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. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality and cost. AF is often associated with structural heart disease, although a proportion of patients with AF have no detectable heart disease. Various cardiovascular and non-cardiovascular conditions have been associated in the induction and maintenance of AF. AF may be related to 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 (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 AF, in which cardioversion has failed or has been foregone.

A clinical interrelationship between atrial fibrillation and atrial flutter (AFL) has long been appreciated. Patients who primarily manifest AF commonly also manifest AFL and *vice versa*; in almost all instances antecedent AF is necessary for the development of AFL. Attention should be paid to the possibility that in a clinical trial for AF, the number of patients that exhibit such interconversion (fibrillation to flutter) may be too small to draw conclusions. Any claims regarding atrial flutter will need separate documentation.

Management of patients with AF involves 3 objectives – rate control, rhythm control and prevention of thromboembolism. 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 shocks. AF is often a chronic, progressive arrhythmia and after restoration of sinus rhythm, recurrence rate is high, occurring most frequently in the first weeks after cardioversion. In case of restoration of sinus rhythm, prevention of recurrence becomes another objective. Patients with chronic atrial fibrillation/flutter are increasingly managed by slowing of the heart rate instead of restoring the sinus rhythm. It has been shown that with this approach the outcome in terms of morbidity and mortality is not significantly altered. More recently, non pharmacological approaches have been proposed for patients in whom AF could not be managed adequately pharmacologically, but these approaches 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. 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.

3. 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.

3.1 Antiarrhythmic effects

Antiarrhythmics intended for atrial fibrillation 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 the sinus rhythm** by pharmacological cardioversion, the primary endpoint will be termination of the AF ("successful conversion") as measured during continuous ECG monitoring. As there is no widely accepted definition for success rates, these should be defined in advance. Time to recurrence and recurrence rates should also be monitored in order to assess its clinical relevance. The time limit for the primary end point 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, either by continuous ECG monitoring (immediate to intermediate) or scheduled regular ECG recordings through scheduled 24h/month Holter ECG or transtelephonic ECG recordings (TTEM) or resting ECG when an (symptomatic) episode is perceived by the patient. Successful cardioversion is defined in some guidelines as restoration of sinus rhythm for at least 30 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.. 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, e.g. PK and PD characteristics of the experimental drug, type of patients enrolled, planned further interventions, and whether or not the acute therapy will be followed by maintenance therapy. A distinction should be made between acutely compromised patients needing fast re-conversion and patients with chronic atrial fibrillation where a more sustained effect is required. Measurements of recurrence, in particular late recurrence, should also take into account changes in background medication as these will influence the results.
- If the claimed indication is **(1) maintainance of the sinus rhythm after cardioversion in patients with persistent AF** OR **(2) prevention of recurrence of AF in patients with paroxysmal AF**, time to first documented recurrence of AF from cardioversion or baseline will be the primary endpoint. In case of recurrence the number of such episodes should be taken into account as secondary endpoint. Any arrhythmia that has the ECG characteristics of AF that lasts longer than 30s should be reported as recurrent AF. This should be documented by scheduled regular ECG recordings through scheduled 24h/month Holter ECG or transtelephonic ECG recordings (TTEM) or resting ECG when an (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 more than half of all AF episodes. 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. Factors that predispose to recurrent AF such as advanced age, HF, hypertension, LA enlargement, and LV dysfunction should also be recorded.

- If the claimed indication is **rate control in patients with chronic atrial fibrillation**, effects on mean resting heart rate as measured by 12 lead ECG on 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 change over 24 hours or at rest may be used, but there is no consensus what parameter is best and other 24-hour Holter parameters need to 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 is 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 but usually involve achieving ventricular rates between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise. There is no accepted link between a specific heart rate during AF and intensity of symptoms, morbidity or mortality. For this reason clinical benefit in terms of improvement in symptoms and AF-related quality of life, exercise testing, morbidity and mortality (see below) should be assessed independently of the slowing of the heart rate.

3.2 Symptoms and AF-related quality of life

AF is associated with poor quality of life and the presence of symptoms is the main indication for rate and rhythm control. However, the relation between symptoms and AF recurrences and slowing of the ventricular rate is elusive, which renders symptom-related QOL a potentially unreliable outcome parameter in AF trials. 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. Several instruments have been used to measure AF-related QOL, but only the atrial fibrillation symptoms scale (AFSS) has been validated.

3.3 Left ventricular function and exercise testing

AF may impair LV function. On the other hand, AF and its complications frequently occur in the presence of LV dysfunction. Rate- or rhythm-control strategies can improve LV function. LV function should be measured at baseline by echocardiography or another validated method and during follow-up. This can be supplemented by a standardized submaximal exercise test as a general measure of cardiac performance.

3.4 Morbidity and mortality

AF is associated with increased morbidity and mortality. All deaths need to be monitored in any trial on an “intention-to-treat” basis from the time of randomisation and should be classified. In the majority of trials, death is not a feasible primary outcome parameter, but may be part of a composite outcome parameter when mortality data are required. The latter is the case if the claimed indication is to maintain sinus rhythm after cardioversion in case of persistent AF or to prevent recurrence in case of paroxysmal AF. AF-related death, should not substitute “total” cardiovascular death as an outcome parameter, because AF-related death will be difficult to assess.

Morbidity may involve both the incidence of stroke and heart failure, as both can be affected by the treatment. All strokes (ischaemic and haemorrhagic) and systemic events should be recorded separately and should be verified by brain imaging. Worsening of the heart failure should be a secondary endpoint in any long term controlled trial and may be particularly important if the claimed indication is slowing the ventricular rate of the arrhythmia. Both heart failure and stroke can be included in the composite endpoint to measure long term outcome.

Cardiovascular hospitalisations can only be considered as a secondary outcome parameter as local treatment routines will influence whether a given medical condition is treated on an out-patient basis or in the hospital. Duration of the hospitalisation should also be taken into account. A distinction should be made between hospitalisations that are AF-related and those that are not. Elective rhythm control interventions leading to hospitalisation (e.g. cardioversion, surgical and ablation therapy, pacing) should be recorded separately.

4. SAFETY CRITERIA

4.1 Morbidity and mortality

Mortality data must always be reported whatever the clinical claim. When there is any suspicion of a detrimental effect, or when specifically claimed, controlled mortality or mortality/morbidity studies are required.

4.2 Cardiac events

Effects on cardiovascular function, in particular on automaticity, AV conduction and QT prolongation should be monitored. Occurrence of arrhythmias, in particular sick sinus syndrome, 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 should be recorded. 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.

4.3 Haemodynamic effects

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

4.4 Stroke

Both cardioversion and chronic atrial fibrillation may result in stroke or peripheral embolism. Its occurrence should be monitored as both may be affected by treatment and utmost care should be taken for adequate anticoagulation.

4.5 Other adverse experiences

Non-cardiovascular adverse experiences should specifically address renal, gastrointestinal, visual and anticholinergic effects.

4.6 Interactions

Special attention should be paid to pharmacodynamic interaction with other cardiovascular drugs affecting automaticity, AV conduction and QT prolongation and with drug affecting its metabolism and elimination, especially with regard to effective institution of oral anticoagulation which is the case in the majority of patients.

5. SELECTION OF PATIENTS

Patients should be selected according to the type of AF (first detected, paroxysmal, persistent, permanent). The inherent risk for recurrent AF and AF-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, prior antiarrhythmic drug treatment and treatment at enrolment, concomitant cardiac disease with and without LV-dysfunction and/or heart failure. In particular sufficient percentage of patients with impaired LVEF (<35%) should be included in clinical trials when these patients reflect the true target population. An adequate number of elderly patients should be included in the clinical trials and both genders should be represented adequately.

6. STUDY DESIGN

The design of studies in AF 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 AF OR prevention of recurrences in patients with paroxysmal AF**

Both placebo-controlled and actively controlled double-blind studies should be considered. The choice of the active comparator will depend on the specific disease state. 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 hemodynamic function, and prevent tachycardia-induced cardiomyopathy due to AF. This will necessarily limit the duration of placebo treatment but actively controlled studies may last longer, up to 3-6 months. As recurrence rates will depend on the presence or absence of structural heart disease and duration of AF before cardioversion, this should be specified in the protocol. In case of prevention of recurrence in patients with paroxysmal AF, the use of placebo can be justified in subjects who experience brief or minimally symptomatic recurrences or paroxysmal AF.

Non antiarrhythmic drugs have been recently proposed to prevent AF recurrences (N-3 PUFA, statins, ACE-I, ARBs) and some trials are ongoing in this sense. The study design, target population, efficacy and safety end points should be the same as suggested for antiarrhythmics. These can be more easily tested versus placebo but on top of all the other standard antiarrhythmic treatments.

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

Both placebo-controlled and actively controlled studies should be considered. Patients with chronic AF are increasingly managed by slowing of the heart rate instead of cardioversion, in particular as a second line strategy when one or more attempts to restore and maintain sinus rhythm have been made and failed. 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 may last longer, up to 3 months.

7. REFERENCES

- Outcome parameters for trials in atrial fibrillation: Executive summary. Recommendations from a consensus conference organized by AFNET and EHRA. Eur Heart J (2007). 28, 2803-2817.
- ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary. Eur Heart J (2006), 27, 1979-2030.
- DeNus *et al*: Rate vs Rhythm control in patients with atrial fibrillation. A meta-analysis. Arch Int Med (2005), 165: 258-262.