



**CPMP/EWP/237/95 final**

**CPMP**

**NOTE FOR GUIDANCE ON ANTIARRHYTHMICS**

<b>DISCUSSION IN THE WORKING PARTY</b>	JUNE - OCTOBER 1994
<b>TRANSMISSION TO THE CPMP</b>	OCTOBER 1994
<b>TRANSMISSION TO INTERESTED PARTIES</b>	OCTOBER 1994
<b>DEADLINE FOR COMMENTS</b>	15 APRIL 1995
<b>RE-SUBMISSION TO THE WORKING PARTY</b>	OCTOBER 1995
<b>RE-SUBMISSION TO THE CPMP</b>	NOVEMBER 1995
<b>FINAL APPROVAL BY THE CPMP</b>	NOVEMBER 1995
<b>PROPOSED DATE FOR COMING INTO OPERATION</b>	JUNE 1996

# GUIDELINES ON ANTIARRHYTHMICS

## Note for Guidance [EMA status as of November 1995]

These notes are intended to provide guidance for the evaluation of drugs in the treatment of cardiac arrhythmias. They should be read in conjunction with the norms and protocols (75-318/EEC ; 83-570/EEC) and are intended to assist in their interpretation.

### 1. INTRODUCTION

Critical evaluation of efficacy and safety of antiarrhythmic medicinal products is hampered by many difficulties. These difficulties are related to :

#### 1.1 The drugs, which may differ in their :

- mechanism of action
- activity, (e.g. when isomeric forms or active metabolites exist)
- other cardiac and extra-cardiac pharmacological effects
- kinetics
- drug interactions
- interaction with devices (pacemakers and implantable defibrillators)
- side effects/adverse pharmacological effects, especially proarrhythmic effects.

#### 1.2 The rhythm disorders, which are highly heterogeneous and may differ in :

- basic pathogenesis (re-entrant, triggered, increased automaticity)
- origin (supraventricular, ventricular)
- manifestations (asymptomatic, symptomatic)
- duration (acute, chronic, paroxysmal) and type (non sustained, sustained, incessant)
- prognostic significance (benign, potentially life threatening, life threatening)
- stability of pathogenetic mechanisms and reproducibility (good, poor)
- instability in clinical expression ; duration or worsening of arrhythmia pose major difficulties for patient selection and evaluation of activity.
- underlying and/or concomitant diseases (e.g. ischaemic heart disease, cardiomyopathy, compromised myocardial function, electrolyte disturbances).

Formulation of a study plan for any antiarrhythmic drug (A.A.) is complex and will necessarily be determined in some measure by specific findings in animal studies. Furthermore guidelines for the whole group cannot cover all problems that may arise

from different agents with varying mechanisms of action, especially when a new agent differs markedly from those already known.

Use of A.A. may be limited by :

- adverse mortality risk. In studies using class I (CAST) and III (SWORD) antiarrhythmics an increase mortality in "low risk" patients has been observed
- electrophysiological side effects limiting use
- major and minor drug related side effects impacting on drug tolerance or quality of life.

### 1.3 Aims of the treatment

Antiarrhythmic medicinal products may improve the patient's condition by :

- diminishing disabling symptoms and / or sequelae related to rhythm disturbances
- and/or increasing life expectancy

This treatment may be

- curative, e.g. termination of atrial fibrillation or ventricular tachycardia (VT)
- prophylactic, e.g., prevention of recurrence or deterioration of rhythm disturbances
- palliative, e.g. slowing ventricular rate in atrial fibrillation.

## 2. PRECLINICAL STUDIES

A.A. medicinal products require a detailed and sophisticated preclinical assessment, both in vitro in multicellular tissues and / or single myocytes and in vivo in appropriate animal models in order to determine their mechanism of action. The studies should allow a precise evaluation of the electrophysiological properties of the compound with regard to automaticity, conduction action potential duration, refractory period of the action potential, receptors and pumps and its effects on the autonomic nervous system. Comparison with reference *medicinal products* will have to be made. These studies should make it possible to consider the *medicinal products* in light of internationally recognised system (e.g. Vaughan-Williams classification, Sicilian-Gambit, ...) and / or to recognise unique properties of a drug. The possibilities of adverse haemodynamic effects, should be considered. A proarrhythmic effect should be investigated carefully in vitro and in vivo.

## 3. CLINICAL TRIALS

Any parameter used to assess efficacy in clinical trials should be clearly defined in the protocol. Major efficacy endpoints are not necessarily linked and cannot reliably serve as surrogates for others. As the therapeutic goals, i.e. improvement in symptoms, and/or reduction in mortality/morbidity, may be multifold, attention should be paid to each of these aspects, even when some specific indications are not claimed. Both benefits and risks should be clearly defined during the course of the development of a drug.

Sample size calculations should be performed with respect to the efficacy criterion but should consider safety aspects as well. The statistical considerations should include a realistic estimate of the risk in the targeted population, and arguments for acceptability of an increased risk/benefit ratio should be presented.

#### **4. METHODS TO ASSESS EFFICACY**

##### **4.1 Clinical status**

Symptomatology and physical findings should always be recorded. Special attention should be paid to symptomatology related to rhythm disturbances (e.g. decrease in physical performance, activities of daily living, dizziness, syncope).

##### **4.2 E.C.G.**

Multiple lead electrocardiograms (at least the standard 12 lead ECG) should be recorded, with full analysis of effects on automaticity, conduction (PR and QRS intervals), ventricular recovery period (QT, JT intervals), the ST segment and T waves, both at rest and during exercise.

##### **4.3 Holter monitoring (HM)**

Continuous long term ECG recording e.g. Holter monitoring should be considered for a minimum of 24 hours before as well as during antiarrhythmic therapy.

##### **4.4 Exercise testing**

Exercise testing is important when there is a suggestion that the action of the antiarrhythmic medicinal product is abolished or intensified by exercise, high heart rate or catecholamines.

Exercise testing should be performed if the arrhythmia is reproducible consistently on exercise.

##### **4.5 Transtelephonic monitoring**

Events monitoring by transtelephonic monitoring and telemetric monitoring of rhythm should also be considered particularly when the telemetered traces are recorded. This is of particular value in patients fitted with implantable cardioverter defibrillators (ICD), in patients with paroxysmal sustained VT or atrial fibrillation, and for monitoring asymptomatic arrhythmias.

##### **4.6 Electrophysiological studies (EPS)**

Invasive electrophysiological studies should evaluate the effects of the antiarrhythmic on automaticity, conduction refractoriness and arrhythmia induction. Depending on the indication(s) claimed, these studies may have to include the effect of the medicinal products on abnormal pathways and effect on tachycardia mechanism.

The largest cohort of patients evaluable by electrophysiological study (EPS) consists of patients with sustained ventricular tachycardia after healed myocardial infarction and

some patients with supraventricular tachycardias. EPS may fail to induce reproducible arrhythmias, especially in certain aetiologies and results of EPS must be discussed in this respect. Medicinal products acting primarily through modulation of b-receptors tend to give unreliable results when evaluated by EPS. Medicinal products that can be evaluated by EPS include but are not limited to Na and / or K channel blocking antiarrhythmics and / or other agents that alter conduction, repolarisation and / or impulse initiation.

When the drug is to be given to patients with life-threatening ventricular arrhythmias<sup>1</sup> or when the arrhythmias occur unpredictably or infrequently, programmed electrical stimulation may be necessary in certain high risk patients<sup>2</sup>. However, electrophysiological studies of this type should be limited to selected centres.

#### 4.7 Patients equipped with ICDs

In the case of treatment of life-threatening ventricular arrhythmias, studies in patients with automatic implantable cardioverter defibrillators (ICDs) are of particular interest. Even though the efficacy of ICDs has not been evaluated in placebo-controlled trials, patients equipped with ICDs may be included in placebo-controlled trials if the defibrillation threshold (DFT) is not increased by the medicinal product. Reduction in the number of sustained ventricular tachycardia and fibrillation episodes could be evaluated.

#### 4.8 Survival studies

As surrogate endpoints for survival are not available, the effect of any therapeutic intervention on mortality can be assessed in randomised placebo controlled trials including a large number of patients. The use of an active comparator would have to be justified.

Survival studies will be either mandatory or desirable depending on the indication claimed for the drug. If increased survival is claimed as a result of treatment, survival studies are mandatory. If increased survival is not claimed, mortality data must be reported whatever the clinical claim and the patients characteristics regarding the mortality data must be specified:

- In the treatment of life-threatening ventricular arrhythmias, the main efficacy criterion is immediate prolongation of life.
- In the treatment of major symptomatic ventricular arrhythmias and in the prevention of potentially life-threatening ventricular arrhythmias, it may be sufficient to demonstrate a significant reduction of morbidity and symptoms as long as the provided data do not support a reasoned suspicion of a negative effect on life

---

<sup>1</sup> patients with life-threatening ventricular arrhythmias: patients with sustained ventricular tachycardias or non sustained ventricular tachycardias on altered myocardium.

<sup>2</sup> high risk patients: patients with coronary heart disease and / or congestive heart failure plus non sustained or sustained ventricular tachycardias with impaired left ventricular function.

expectancy. To investigate this potentially negative effect, clinical trials should be carried out in relevant patient categories (e.g. : high risk patients).

- In the treatment of supraventricular arrhythmias, and in particular atrial fibrillation, several situations have to be considered :
  - if the claimed indication is slowing the ventricular rate of the arrhythmia, it may be sufficient to demonstrate a significant reduction of morbidity and symptoms provided that respective data do not support a reasoned suspicion of a negative trend on life expectancy demonstrated in high risk patients with decreased left ventricular function and/or ventricular arrhythmias and / or myocardial ischaemia.
  - if the claimed indication is to maintain sinus rhythm in patients with supraventricular arrhythmias, mortality data are required as an endpoint if the targeted population is not symptomatic. A reduction in clinically relevant morbidity endpoints (e.g. cerebrovascular accident) could be also of interest provided that there is no over mortality induced by the tested drug. In any case, safety data in patients with and without decreased left ventricular function and/or associated ventricular arrhythmias will be requested in order to eliminate a significant proarrhythmic effect.

## **5. SAFETY ASPECTS**

For life-threatening arrhythmias the primary concern is for efficacy. Inconvenience and even significant safety risks may be acceptable in order to control the rhythm disorder. Gender - related and age - related variations in drug effect / toxicity are important modifiers to consider.

For arrhythmias which are not life-threatening, safety is the paramount consideration.

In general the safety aspects of the studies should address the following :

- Arrhythmogenic action. A.A. medicinal products are known to cause worsening of pre-existing arrhythmia(s) and/or to provoke new form(s) of arrhythmia(s). This occurs most often in patients with a history of life-threatening arrhythmias, severe left ventricular dysfunction, electrolyte imbalance and conduction defects. It can be detected by symptoms, by using frequent continuous ambulatory monitoring techniques, exercise and to a lesser extent by electrophysiological testing.

Prolonged and extensive experience is necessary to assess this specific side effect. The way by which the activity of the drug can be most suitably monitored must be indicated (e.g. plasma level, QRS and/or QT prolongation).

- Effects on cardiovascular function (automaticity, conduction, contractility, vascular effects). This should be accurately explored, by appropriate methods both in the acute phase and the chronic phase. This is particularly important in patients who belong to high risk groups (see above). Special attention should be paid to patients with sinus node dysfunction, to patients with a pacemaker (pacing threshold) and patients with conduction defects.
- Adverse experience (e.g. visual effects, anticholinergic effects, gastrointestinal symptoms).

- Interactions: special attention to pharmacokinetic and pharmacodynamic interactions with other drugs. Clinically significant interactions at the absorption and excretion level have been reported with antiarrhythmic medicinal products and should therefore be investigated.

## **6. STRATEGY/SELECTION OF PATIENTS**

### 6.1 Initial studies

Initial studies of a potential A.A. agent will follow the normal pattern (pharmacodynamics, pharmacokinetics, single and repeated dose tolerance). It should be realised that A.A. agents usually have a small therapeutic index. Therefore these studies should be performed under the close supervision of investigators experienced in this field.

#### 6.1.1 Pharmacokinetic studies

Special attention should be paid to

- identification of isoenzymes involved in drug metabolism and of active metabolites
- any evidence of genetic influence on metabolism
- relationship between dose and plasma levels of the parent drug and active metabolites
- pharmacokinetics in risk groups (elderly, cardiac failure, hepatic/renal insufficiency patients)
- pharmacokinetic interactions
- dosage form ; preferably both the oral and parenteral forms should be studied.

#### 6.1.2 Pharmacodynamic studies

Pharmacodynamics of the parent drug and its active metabolites should be fully defined. These studies should include :

- effects on the cardiovascular system (blood pressure, heart rate, signs and symptoms) and ECG, both in human volunteers and patients.
- invasive electrophysiological studies on automaticity, conduction repolarisation, refractoriness and cardiac function and non invasive EPS in patients with ICD.
- invasive haemodynamic testing, including studies on cardiac output, indices of left ventricular function filling pressure and peripheral resistance
- concentration dose-response studies, with regard to a drug's haemodynamic and electrophysiological properties, in patients with non life-threatening arrhythmias and with no risk factors.

With regard to the evaluation of the drug's haemodynamic and electrophysiological properties patients with risk factors such as severe congestive heart failure altered

automaticity A-V conduction and bundle branch blocks should be enrolled, unless considered contraindicated.

## 6.2 Therapeutic studies

The therapeutic studies must enrol patients who may expect a potential benefit from the anti arrhythmic therapy. Every precaution must be taken to minimise risks with the initiation of treatment in specialised hospital units under close surveillance by investigators experienced in cardiology and with broad experience in A.A. medicinal products.

### 6.2.1 Initial studies

- The objective in this phase will be to obtain information on the type(s) of arrhythmias which react to the drug and to study the effective dosage, the duration of effect, and the frequency and severity of side effects.
- The frequency and the stability of the arrhythmia should be such that the therapeutic effects of the drug can be studied.
- Single and short term repeated administration should be evaluated. Initially the design of the study will be non controlled or single blind.

As mentioned above, drug testing should include non life-threatening arrhythmias in patients with no major identified risk factor. However, at the end of this phase, double-blind comparison with placebo, and/or reference drug and/or ICD is highly desirable. Most arrhythmias are unstable and the use of a cross-over design is not appropriate. In patients equipped with an ICD, a double-blind placebo controlled trial could be adequate if the defibrillation threshold is stable.

Special attention should be paid to patients with arrhythmias suffering from metabolic or electrolyte disorders, cardiac failure, liver or renal insufficiency. These patients are often excluded from pilot studies but these risk factors are known to influence dose-response. Since patients with risk factors are highly representative for the ultimate target population, these patients should be enrolled in an a priori stratified manner.

The relationship between dose/plasma level and A.A. activity should be carefully analysed.

### 6.2.2 Main therapeutic studies

The objective of the main therapeutic studies should be the demonstration of efficacy, in terms of a simultaneous reduction of arrhythmias and (major) symptoms and/or mortality, and the demonstration of safety. This should be done for various types of symptomatic and/or life-threatening arrhythmias included in the claimed indication.

- The objective of this phase is to establish antiarrhythmic efficacy and safety in various types of arrhythmias and different degrees of severity.
- Special attention should be paid to certain high risk groups, particularly patients with complications and concomitant cardiac disorders, such as



congestive heart failure, impaired left ventricular function and ischemic heart disease, elderly patients, patients requiring more than one A.A. agent or being treated with cardiac glycosides. Each group should be analysed separately, taking into account the possible differences in pharmacokinetics (drug distribution, metabolism and elimination as in patients with hepatic and renal dysfunctions), differences in pharmacodynamic responses (patients with ischaemic heart disease, cardiomyopathy, sick sinus syndrome, conduction defects, LV dysfunction) and concurrent medication.

- Randomised double-blind comparison with placebo is needed, unless considered unethical.
- In this phase it should be necessary to compare the investigational compound under randomised, double-blind conditions with one or more established drugs of various types in order to define its place in therapy.
- A medicinal product under investigation is not uncommonly incorporated into a so-called "emergency protocol" but such use rarely provides reliable information.
- If it is claimed that the medicinal product under study can prevent recurrence of arrhythmias, the trial should be design to test this specifically.
- Duration of the studies should be appropriate to the indication(s) claimed. Moreover, if any change in the medicinal products' effect is observed during the selected treatment period the trial should be continued over a longer period until a stable condition is obtained. Since oral A.A. agents are likely to be administered for a long period of time, generally safety data on 300 - 600 patients for 6 months (or at least 100 patients for a minimum of one year) will be required.