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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS**  
**(CPMP)**

**POINTS TO CONSIDER:**  
**THE ASSESSMENT OF THE POTENTIAL FOR QT INTERVAL**  
**PROLONGATION BY**  
**NON-CARDIOVASCULAR MEDICINAL PRODUCTS**

During its May 1996 meeting, the CPMP decided to convene an ad-hoc group of experts to address preclinical and clinical testing of compounds to identify QT prolongations and documentation to provide reassurance concerning the safe clinical usage of such products. The outcome of this work is presented in the present document. Since scientific knowledge in this field is developing rapidly, this document will need to be revised accordingly to keep pace with this ongoing development.

## **THE ASSESSMENT OF THE POTENTIAL FOR QT INTERVAL PROLONGATION BY NON-CARDIOVASCULAR MEDICINAL PRODUCTS**

### **INTRODUCTION**

During its May 1996 meeting, the CPMP decided to convene an ad-hoc group of experts to address preclinical and clinical testing of compounds to identify QT prolongations and documentation to provide reassurance concerning the safe clinical usage of such products.

Medicinal products that prolong the cardiac repolarisation have been associated with a specific, potentially fatal polymorphic ventricular tachycardia termed torsade de pointes (TdP). This tachycardia is usually observed in the setting of a prolonged QT interval, is often initiated following extrasystolic pauses and is identified by the continuously twisting appearance of the QRS complex in the 12 lead ECG. Additional risk factors that are thought to predispose to this proarrhythmic effect include cardiac disease, congenital long QT syndrome, hypokalaemia, hypomagnesaemia, bradycardia and concurrent administration of other medicinal products known to prolong QT interval. Apart from some cardiovascular medicinal products that are well recognised to be proarrhythmogenic in certain circumstances, there are a number of other therapeutic classes of compounds that have been known to cause serious and potentially fatal proarrhythmias. These include, amongst others, psychotropic agents, H1 antihistamines and antibiotics. The association of non-cardiac medicinal products with the potential to prolong the QT interval and induce TdP has significant implications for the future development of medicinal products.

This document provides a number of recommendations for future applicants involved in the development of non-cardiovascular medicinal products to help identify this effect and assess the associated clinical risk this may present. Certain medicinal products may be exempt if justified e.g. monoclonal antibodies, blood products etc. Scientific knowledge in this field is developing rapidly and this 'Points to Consider' document will need to be revised accordingly to keep pace with this ongoing development. Clinical development of cardiovascular medicinal products has been addressed elsewhere in specific CPMP guidelines.

This document should be read in conjunction with other CPMP guidelines, particularly those relating to pharmacokinetics, drug interactions, use of drugs in the elderly, drugs intended for long term administration and population exposure for safety assessment.

### **PRECLINICAL STUDIES**

As part of the safety assessment of any new active substance (NAS), a series of preclinical studies are performed to characterise its general pharmacodynamic properties and toxicological activities. Cardiovascular safety pharmacology studies and repeat dose non-rodent toxicity studies, typically in the dog, form part of this evaluation. Such studies should be robust and generally include measurements of heart rate, blood pressure and ECG (especially QT interval) as well as description of T and U waves morphologies and the occurrence of any arrhythmias over a range of escalating doses. ECG recordings during these studies should be standardised and they should be performed in 6 leads recorded at 50 mm/second. The pharmacokinetic profile of the drug should be considered in the study design.

In addition, *in vitro* electrophysiological studies should now be undertaken as part of this screening programme. These studies should be conducted prior to first use in humans and they should be carried out in suitable preparations, using physiologically relevant conditions (e.g. normal electrolyte concentrations). It is recommended to use an adequate number of preparations from an appropriate species, e.g. rabbit, guinea pig, dog or pig, but other species may be used as long as it is ensured that the ion channels in the tissue used correspond to those contributing to repolarisation in human cardiac tissue. Preparations that have been used most frequently include papillary muscle and Purkinje fibres.

Using appropriate stimulation frequencies, these studies should carefully explore the reverse rate dependency of an effect on action potential duration (APD). Furthermore, the drug concentrations tested should be justified and should cover and well exceed the anticipated maximal therapeutic plasma concentrations and take into consideration other aspects of pharmacokinetics of the NAS such as possible interactions etc. The effect of the drug on APD at 90% repolarisation (APD<sub>90</sub>), appearance of early after-depolarisations and subsequent triggered activities are particularly relevant in the context of proarrhythmic prolongation of QT interval. Effects on APD<sub>30</sub> and APD<sub>60</sub> may provide additional qualitative information. Additional parameters to be reported include membrane potential, amplitude and V<sub>max</sub> (upstroke velocity).

The results from these *in vivo* and *in vitro* studies are considered to reliably elucidate the potential of the NAS to prolong the QT interval.

If these *in vitro* and *in vivo* studies do not show a potential for prolongation of the QT interval, it appears reasonable to proceed to studies in healthy volunteers provided all other normal safety requirements are met. However, if there is evidence of QT interval prolongation, change in T wave morphology, increases of APD or induction of early after-depolarisations, additional animal studies and/or *in vitro* electrophysiological studies are recommended, either before or in parallel with early clinical studies. In some cases, further development of the NAS may not be justified.

These additional studies are valuable in assessing the potential of the NAS to prolong QT interval and/or induce early after-depolarisations and TdP during its clinical use. They also provide an opportunity of investigating the risk factors for TdP that cannot adequately be studied *in vivo* in humans. Such risk factors include hypokalaemia, myocardial ischemia, bradycardia, and concurrent administration of other drugs known to prolong the QT interval. In any such investigation, comparison should be made to marketed compounds known to affect the APD and QT interval, using (where possible) compounds having structural similarities to the NAS and/or having similar therapeutic indications.

Further *in vitro* testing should be considered to identify the subtype of the ionic channel(s) involved and effects at other cardiac receptors should be explored. Comparative studies assessing the effect in an appropriate animal model for TdP should also be considered. To facilitate the interpretation of the *in vitro/in vivo* preclinical findings and their clinical relevance, it may be necessary to take into account additional characteristics of the NAS e.g. the extent of its protein binding, lipophilicity, volume of distribution and myocardial binding.

Whenever the main metabolite(s) in humans have been identified, a carefully reasoned assessment should be made whether these metabolites should be evaluated for their proarrhythmic potential. The role of enantiomers of a racemic drug should be characterised.

## CLINICAL STUDIES

### Methodological Issues

The clinical studies should be of appropriate design (preferably placebo-controlled cross-over studies) and duration. The electrocardiographic effects should be evaluated by cardiologists experienced in such evaluations.

Special attention should be paid to the methodology used to record and measure the QT interval. A standard 12 lead recording is recommended with manual reading and interpretation of the traces obtained in accordance with generally accepted methodology suggested by the American Heart Association (*See References*). Measurements of QT interval and QT dispersion should be assessed as the mean of 3-5 beats. The U wave should normally not be included when QT interval is measured. Often, however, the T wave and the U wave merge to produce morphologically bizarre changes in the T wave. Since a significant proportion of repolarisation is present in the terminal half of this bizarre T wave, the end of the T wave may have a higher amplitude. In such cases, it may be more appropriate to include the U wave when measuring the QT interval.

Changes in the T wave morphology and/or the occurrence of U wave constitute important warning signs and they may precede the occurrence of TdP. Drug-induced changes in the T wave morphology and/or the occurrence of U waves must be attached the same significance as prolongation of the QT interval.

At present, automatic ECG readings are generally not considered sufficiently accurate or reliable and readings from Holter recordings and standard ECG do not sufficiently correlate to be of value. Particular attention should be paid to the timing of the measurements. These should ideally coincide with, as far as is practical, the maximum expected plasma peak of the NAS (parent drug and /or the most significant metabolites as appropriate) or when the maximum concentration of a NAS in the target cell could be expected. To enable effects at low concentrations to be distinguished from those at high concentrations, these ECG measurements should be done before as well as after the peak levels. When measuring plasma concentrations, enantioselective methods may be needed to investigate the role of various enantiomers in case of a racemic NAS. The possibilities of a clinical interaction between the parent drug and its significant metabolite(s) should be considered.

Both mean changes and individual data should be adequately tabulated and reported. Parameters of particular interest are PR, QRS and QT intervals. The latter should be presented uncorrected (with corresponding heart rate) and corrected by square root (Bazett-QTcB). QT dispersion is increasingly thought to be important and the effect of the drug on this parameter also needs to be characterised. Changes in T wave morphology and appearance of a U wave should be specifically noted.

A number of studies have shown that QT interval duration exhibits a high degree of intra-individual variability which makes a strict definition of normal and abnormal values difficult. In the absence of any drug or disease, QTc interval values (msec) after Bazett's correction which are considered to be normal and prolonged are shown below:

	Adult Males	Adult Females
<b>Normal</b>	<430	<450
<b>Borderline</b>	431-450	451-470
<b>Prolonged</b>	>450	>470

Basic research is still needed to better understand the relationship between the QT interval and TdP. Notwithstanding the absence of clinical data allowing a more categorical statement regarding potential clinical risks, the following values are suggested as a general guide for consideration on "signal" values for QT measurements. The values given are individual changes, mean values for study populations should not be used.

1. QTcB changes relative to baseline measurements

- Individual changes less than 30 msec are generally thought unlikely to raise significant concerns about the potential risk of an NAS inducing arrhythmias including TdP.
- Individual changes between 30-60 msec are more likely to represent a drug effect and raise concern about the potential risk of an NAS inducing arrhythmias including TdP.
- Individual changes greater than 60 msec raise clear concerns about the potential risk of an NAS inducing arrhythmias including TdP.

2. Absolute QTcB value

- QTcB or at low heart rates, uncorrected QT interval values greater than 500 msec raise clear concerns about the potential of an NAS to induce arrhythmias including TdP.

3. QTcB dispersion across a 12 lead ECG.

Baseline dispersion is generally estimated to be approximately 40-60 msec. Although QT dispersion is at present investigational, the following changes in an individual subject should raise a concern about the potential of the NAS to induce arrhythmias including TdP:

- Dispersion greater than 100 msec.
- A change in dispersion of more than 100%.

The signals from the above parameters should also be considered collectively when evaluating their significance for any NAS under investigation. While changes in QTcB relative to baseline or in QTcB dispersion indicate a drug effect, an absolute QTcB value has greater prognostic significance. At low heart rates, it is the uncorrected QT interval that is thought to have a greater prognostic significance.

**A. NAS with no preclinical findings indicating QT interval prolongation.**

Lack of evidence of QT interval prolongation during the preclinical studies of an NAS needs to be confirmed during initial clinical studies in normal volunteers/patients. The design of these studies will be dependent on the pharmacokinetic/ pharmacodynamic profile of the NAS in question. If a significant metabolite not produced in animals is detected in human, additional preclinical investigation should be performed e.g. *in vivo/in vitro* studies to evaluate the potential of the metabolite(s) to prolong the QT interval or interfere with cardiac ion channels. ECG data should be generated in at least 100 volunteers/patients (including both genders) in early Phase I/II studies paying attention to issues relating to:

- dose - concentration - effect relationship
- steady state plasma levels

- gender effects
- age effects
- metabolic capacity

Drug-drug interactions may occur and it should be considered in this phase whether the drug should be tested together with other medicinal products for potential cardiac effects.

Depending on the strength of the preclinical signal, these studies should include the use of inhibitors or inducers, as appropriate, of the metabolism of the NAS under development.

In the light of the present scientific knowledge, if neither the preclinical testing nor the early clinical testing shows any electrophysiological effects, the likelihood of the NAS showing important proarrhythmic effects during its clinical use, is considered remote.

If this early clinical testing signals a potential for an NAS to produce QT interval prolongation in humans, additional *in vitro* electrophysiological investigations (previously described) are indicated despite earlier negative findings.

#### **B. NAS with preclinical findings indicating QT interval prolongation**

An NAS that shows preclinical evidence of action potential prolongation and/or QT interval prolongation needs a more extensive and carefully designed clinical testing programme to evaluate the relevance of these signals. Early clinical testing as described in the previous section should be performed in at least 200 volunteers / otherwise healthy patients. However, the actual number of patients may be influenced by the strength of the signal observed preclinically and/or during early clinical testing.

If QT prolongation or other electrocardiographic effects are observed in these early studies, it is recommended that ECG measurements be taken in all patients included in the clinical development programme. ECGs should be recorded prior to drug intake and at steady-state plasma levels of the drug and/or its metabolites. In addition, plasma potassium levels should be measured at the same time as part of the routine laboratory data collection. The introduction of Holter monitoring should also be considered at this stage in order to determine if QT prolongation complicates into arrhythmias, T-wave/ U-wave morphological changes and other types of secondary effects. For drugs showing preclinical evidence of an effect on QT interval, this monitoring should be performed before the administration of the drug as well as during its administration until well past T<sub>max</sub>. If effects such as syncope or arrhythmias are observed in some patients these should be followed up more intensively using Holter monitoring or other diagnostic measures to further characterise these effects where possible. Special attention should be paid to ensure that Phase II/III studies include the likely at-risk groups e.g. females, the elderly, patients of different metabolic phenotypes and patients with concomitant diseases e.g. renal or hepatic impairment. Depending on the target population for the clinical use of the drug, patients with cardiovascular disease, with and without diuretic treatment, should generally also be included in these studies if careful ethical and scientific considerations justify such a decision.

### **Regulatory Implications**

The overall risk benefit assessment of an NAS that prolongs QT interval will depend on consideration of the following factors:

- The frequency and magnitude of the QT changes observed and related adverse events detected in the clinical programme.
- The safety risks presented by the drug relative to its therapeutic potential.
- The availability of clinically effective alternatives with a more favourable safety profile.

Detailed consideration of these factors will enable a final decision regarding the licensing of a medicinal product and where appropriate, the conditions for clinical use to be included in the SPC.

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