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DRAFT

REFLECTION PAPER ON GENDER DIFFERENCES IN CARDIOVACULAR DISEASES

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I. INTRODUCTION

Cardiovascular (CV) disease, primarily coronary heart disease, is a major cause of death in the world and also an increasing problem in developing countries. This is the case for both males and females, however, over the past decades a substantial decrease in the number of deaths from cardiovascular diseases has been observed. Mortality rates have declined almost linearly for ischaemic heart disease, stroke, and total CV diseases between 1970 and 2000 in Western Europe. This decrease is observed in both men and women. Although not fully quantified, new and more intensive therapeutic approaches in general, and pharmacological interventions in particular, have played an important role in this achievement

Heart disease in women has recently been addressed by the European Society of Cardiology in their "Women at Heart" initiative. This initiative aims at highlighting the growing burden of cardiovascular disease in women and to promote improved treatment of women at risk of cardiovascular disease in clinical practice. The understanding of potential differences between men and women regarding the manifestation of CV disease is of importance for the improvement of the clinical management of CV diseases and has implications for the development of new cardiovascular drugs.

This paper tries to echo the growing interest amongst the scientific community on the gender-related differences in CV disease manifestations by reviewing the current regulatory situation and highlighting the importance of a careful attention to this topic in the development of new cardiovascular drugs.

II. CURRENT REGULATORY STATUS

Current regulatory recommendations requires that patients entering clinical trials should reasonably well represent the population that later will be treated by the drug, as subpopulations may respond differently to a given drug treatment. This clear statement is fully applicable to the representation of gender in clinical trials, and as such is widely reflected in a number of EMEA clinical guidelines and ICH documents. The adequate representation of both males and females in clinical studies for the development of drugs has been specifically discussed in the ICH Gender considerations in the conduct of clinical trials. Moreover, in the cardiovascular field, several CHMP-EWP documents highlight the importance of an appropriate representation of women in regulatory clinical trials.

The differences between the proportion of men and women included in clinical trials in cardiovascular diseases are in general explained by the fact that women present with cardiovascular diseases at a 5-10 years older age compared to men.

According to investigations preformed by regulatory bodies in recent times, women are, in general, adequately represented in clinical trials reflecting gender prevalence of the disease studied (Surveys conducted by FDA in 1983, 1989 and 2001, by the General Accounting Office in 1992 and 2001, Review by EMEA of pivotal trials for products filed 2000-2003).

III. GENDER-RELATED DIFFERENCES IN CARDIOVASCULAR DISEASES

It is recognized that there are gender differences regarding the disease presentation, occurrence of more severe disease in women in certain age groups, differences regarding prevalence related to age, which will affect co-morbidity and there are also findings suggesting that the underlying mechanisms of disease might be gender-specific. Thus, gender-related differences in the lipid profile, hormonal status and influence of menopause, body composition, etc. might make the clinical presentation, the interpretation of the diagnostic findings and prognosis of similar clinical conditions to differ between

sexes. Examples of this are the diagnostic performance of commonly used diagnostic cardiovascular tests that might differ between genders in their ability to correctly identify a cardiovascular condition. The poorer prognosis in women with stable angina pectoris combined with significant coronary artery stenosis detected on angiography also could signal a gender difference that could to be taken into consideration.

In a recently published consensus paper the European Society of Cardiology (3) emphasises that the design of clinical trials should take into consideration that they should provide answers to questions related to possible gender differences. Inclusion of a sufficient proportion of elderly patients in pivotal clinical trials could increase the number of included females. By doing so, not only more women would be included but, and more importantly, a greater number of elderly patients would be participating.

The safety issue requires careful attention. Gender-specific data on the safety are scarce. Post hoc analysis of some trials showed that women in the actively treated group have a higher mortality than women receiving placebo, an effect not observed in men.

IV. REGULATORY EXPERIENCE

Importantly, in the assessment of an application for marketing authorisation, results based on gender (as for other subgroups) are always scrutinized in order to detect the need for specific recommendations. This includes a thorough assessment of pharmacokinetic data as well. It is recognized that these gender specific evaluations to some extent are based on extrapolations between males and females. However, this approach is based on a long regulatory experience.

Overall, women are considered to be adequately represented in the clinical development of new drugs in CV diseases, although there is a variable degree of representation, ranging from around 20% to slightly over 50%. Although the proportion of women in clinical trials has increased during the last decade, they are still not represented, at least in certain clinical trial, to an extent that their age specific disease prevalence justifies. This is particularly true for heart failure studies. Importantly, in some instances, the number of women in which primary and secondary end-points occur is lower than in men, which may have important implications for the assessment of their response to therapy.

V. CONCLUSIONS

In general terms, women are reasonably well represented in regulatory dossiers for cardiovascular drugs, although in some cases the proportion of women are at the lower limit of what could be considered acceptable. Although there seems not to be any major differences between men and women regarding efficacy on a group level, there is a lack of conclusive data on the magnitude of gender differences in response to cardiovascular therapies.

Both females and males are expected to be represented in cardiovascular clinical trial in a proportion that mimics the prevalence of the disease. The clinical database supporting the marketing authorisation application of cardiovascular drugs is expected to satisfactorily address potential gender related differences in terms of safety and efficacy, if not this may have regulatory implication and therefore this issue will continue to be a matter of attention.

VI. REFERENCES

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