European Medicines Agency

London, 18 October 2006
Doc. Ref. CHMP/EWP/426093/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE REVISION OF THE GUIDANCE ON FIXED COMBINATION MEDICINAL PRODUCTS IN THE TREATMENT OF HYPERTENSION

AGREED BY EFFICACY WORKING PARTY	3 July 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 October 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2007

This guideline replaces guideline CHMP/EWP/358529/2006.

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KEYWORDS	*arterial hypertension, fixed dose combination, first-line indication*

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1. INTRODUCTION

In the majority of patients with arterial hypertension blood pressure (BP) goals cannot be achieved by one antihypertensive drug alone. E.g. in the ALLHAT trial less than 30% of the patients were effectively treated with monotherapy. For many patients a stepwise approach either starting with on substance or with a fixed low-dose combination is adequate. However, especially in the group of patients with higher initial blood pressure the responder rate to monotherapy is remarkably lower. At the end treatment with two concomitant medications is not sufficient in many of these patients and 3 or more substances are required (e.g. Dunlay et al., 1995, Cifkova et al., 1999, Oparil S, 1999). It may be advantageous for some of these patients to initiate the treatment with a fixed combination in the therapeutic range of the components and thereby to more rapidly achieve BP goals.

Regulatory background: A first line indication for fixed combinations in therapeutic doses is not specifically covered by regulatory guidelines. The *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1)* refers to fixed combination products in a second-line indication and to a first line indication in sub-therapeutic doses of the two components. According to the *NfG on fixed combination medicinal products (NfG/CPMP/EWP/240/95, 1996)* in general an improvement of the benefit/risk assessment is required, either due to addition or potentiation of therapeutic activities or due to counteracting adverse reactions. In special instances a simplification of the therapy which improves patient compliance may justify the use of a fixed combination. On the other hand difficulties in individualizing the therapy and the addition of different adverse reactions are among the disadvantages to be considered.

Patients with severe hypertension are the most likely target group for a first line fixed dose combination. Most of them require a combination therapy since only about 5 – 25% of these patients can be sufficiently treated with a monotherapy (e.g. Dunlay et al., 1995; Oparil S., 1999). Accordingly the *JNC 7 report* states that most patients with "stage 2" hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg) will require a combination therapy. Initial therapy with 2 drugs should be considered when blood pressure is more than 20/10 mmHg above goal. The *2003 ESH/ESC Guideline* recommends that drug therapy should be started gradually either with monotherapy or with a "low dose" combination, irrespectively of initial blood pressure levels. There is no recommendation on special patient groups to be considered for a first line combination therapy. The term "low dose" as used in this *ESH/ESC Guideline* covers both sub-therapeutic and low therapeutic doses of the mono-components. This is in contrast to the *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1*) that explicitly refers to "sub-therapeutic" doses.

Recently an increasing number of applications for marketing authorisation and national scientific advises were filed for a first line indication of fixed dose combinations in the treatment for arterial hypertension.

Moreover, a number of regulatory precedents indicate that there is a need for clarification on the regulatory requirements for the licensing of new doses of existing fixed combinations of antihypertensives. This revision should cover situations where the new proposed doses are within or out of the accepted therapeutic range for the mono-components.

2. PROBLEM STATEMENT

Two types of applications are conceivable: A first-line application for a fixed dose combination already approved for a second line treatment and an application for a combination not approved yet.

Accordingly the guidance paper should distinguish between additional requirements in the former case and the whole clinical program in the latter.

Target population
Patients to be considered for a first line fixed dose combination should have a low chance to be adequately treated with monotherapy or by a combination in sub-therapeutic doses. This may be influenced e.g. by initial blood pressure levels, target blood pressure, non-pharmacological measures, concomitant diseases or age. In general, only patients with at least moderate or severe hypertension are regarded to be eligible.

Efficacy parameter and requirements on study designs
The same parameters for efficacy are regarded relevant that are outlined in the *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1)*. However, the studies have to prove that an *a priori* identifiable target population cannot be adequately treated by an appropriate dose of one of the mono-components. Possible study designs are to be discussed and to be outlined in the guideline. It is conceivable that the pivotal study is a parallel group comparison between a) a first line fixed combination and b) an add on therapy starting initially with an adequate and justified dose of one of the mono-components. The assessment of responder rates, defined as patients achieving the target blood pressure, is of major importance. Responder rates with a monotherapy should be very low after an adequate time (e.g.<5%) in the study population. On the other hand the first line fixed dose combination should show a statistically significant and clinically relevant additional effect. The term “clinical relevance” has to be discussed in this context: Change in systolic BP and diastolic BP vs. responder rate in terms of BP reduction or achieving target blood pressure.

Dose finding:
Dose selection should be justified preferably by a multifactorial study as outlined in the *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1)* for a second line indication. However, in patients with severe hypertension a placebo arm and low dose monotherapy may not be justifiable for ethical reasons. It has to be defined whether a multifactorial study in patients with mild to moderate hypertension may be sufficient for the selection of a dose in the pivotal study in patients with (moderate to) severe hypertension or whether additional data are necessary (e.g. an add on study in the target group).

Safety aspects
A positive benefit-risk ratio has to be shown for the total population in comparison to an add-on second line approach. In the small subgroup of patients treated with the combination but actually requiring only a monotherapy the first line combination should not raise safety concerns. In addition to the safety requirements outlined in the *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1)* particular caution is necessary in patients at risk for orthostatic hypotension as those with diabetes mellitus, autonomic dysfunction, and some elderly patients. Furthermore, special attention is necessary to patients that are at special risk after a marked initial reduction in blood pressure, e.g. elderly patients, patients with cerebrovascular or coronary artery disease.

3. MAIN TOPICS TO BE ADRESSED

Guidance on the following issues should be given:

Characterisation of the target population
Concomitant diseases and additional indications
Requirements for the design of studies for dose finding and pivotal studies
Primary and secondary efficacy endpoints
Safety analysis
Requirements for the licensing of new doses of existing fixed combinations of antihypertensives

4. RECOMMENDATION

It is proposed to revise the *NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 1)* and to add a chapter on the first line indication of fixed combination products in therapeutic doses.

5. PROPOSED TIMETABLE

It is anticipated that a first draft document is available for discussion at the EWP by March 2007.

6. RELEVANT REFERENCES

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