



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**NOTE FOR GUIDANCE ON  
CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS  
IN THE TREATMENT OF HYPERTENSION**

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Note: This revision concerns 'Fixed Combinations'.

# **CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF HYPERTENSION (CPMP/EWP/238/95)**

These Notes are intended to provide guidance for the evaluation of drugs in the treatment of hypertension. They should be read in conjunction with Directive 2001/83/EC, as amended, and current and future EU and ICH guidelines, especially those on

- (ICH) Studies in support of special populations: Geriatrics
- (ICH) The extent of population exposure to assess clinical safety of drugs intended or long-term treatment in non-life threatening conditions
- (EC) Biostatistical methodology in clinical trials
- (EC) Fixed-combination products
- (EC) Pharmacokinetic studies in man

They are intended to assist applicants in the interpretation of the latter with respect to specific problems presented by anti-hypertensive products.

## **1. INTRODUCTION**

There is a continuous increase of cardiovascular risk associated with the level of blood pressure: the higher the blood pressure, the higher the risk of both stroke and coronary events. Nonfatal and fatal cardiovascular diseases - including coronary heart disease, stroke and congestive heart failure - as well as renal disease and all-cause mortality increase progressively with higher levels of both systolic blood pressure (SBP) and diastolic blood pressure (DBP). At every level of elevated DBP, risks increase in association with elevation of SBP. Recent data underscore the importance of elevations in SBP, as well as in DBP for diagnosis and therapy.

The dividing line between 'normotension' and 'hypertension' is arbitrary and might vary with age. The current definition is that this line is the level of blood pressure above which intervention has been shown to reduce the risk. In the otherwise healthy adult population values below 140/90 mmHg are considered within the normal range and values of 140/90 mmHg and greater in the hypertensive range.

Hypertension may be classified according to

- etiology: essential or primary hypertension vs. secondary hypertension;
- severity: according to WHO/ISH or JNC V;  
type: systolic, diastolic or both;
- extent or progression (e.g. malignant hypertension) of target organ damage (heart, brain, eyes, vessels, kidney).

## **2. ASSESSMENT OF EFFICACY CRITERIA**

### **2.1 Blood pressure**

The goal of treating hypertension is to prevent morbidity and mortality associated with high blood pressure. Two classes of antihypertensives ( $\beta$ -blockers and diuretics) have been shown to reduce cardiovascular morbidity and mortality and they may be considered as 'gold' standards for the treatment of hypertension. Large morbidity/mortality studies are ongoing

with other antihypertensive agents, such as different types of calcium channel blockers, ACE-inhibitors, alpha-blockers and angiotensin II-antagonist and these studies will verify if there are differences between drug classes as regards reduction in morbidity/mortality. Reduction in blood pressure has usually been accepted as a valid surrogate endpoint in order to assess whether this goal can be achieved by an antihypertensive agent. Notwithstanding, even if an antihypertensive effect has been proven, a new antihypertensive agent is only acceptable for registration when there is no suspicion of a detrimental effect on mortality and cardiovascular morbidity (see 6.9)

## **2.2 Morbidity and mortality**

Positive effects on mortality and cardiovascular morbidity can only be evaluated properly in large-scale and long-term controlled clinical trials. Until the results are available, it should be specifically mentioned in the SPC that beneficial effects on mortality and cardiovascular morbidity are unknown.

## **2.3 Target organ damage**

Although the prognostic relevance of target organ damage of heart, brain, eyes, kidneys and blood vessels has not yet been fully evaluated in valid clinical studies, it is presumably and plausibly associated with morbidity and mortality; this holds particularly true for left ventricular hypertrophy and proteinuria/microalbuminuria. Trials on outcomes of antihypertensive therapy, monitoring progression and regression of organ damage may provide relevant information on the comparative effectiveness of a new antihypertensive agent, but the prognostic value of drug effects with regard to morbidity and mortality remains to be established. Thus, these endpoints are considered of secondary value and specific studies are only mandatory when specific claims are made or when there are suspicions of a detrimental effect.

# **3. METHODS TO ASSESS EFFICACY**

## **3.1 Blood pressure**

Blood pressure lowering effects of anti-hypertensive therapy should be documented as the pre-/post-treatment reduction of blood pressure. As a secondary endpoint these effects can also be assessed with respect to response criteria. Arbitrarily, response criteria for antihypertensive therapy include the percentage of patients with a normalisation of blood pressure (reduction SBP < 140 mmHg and DBP < 90 mmHg) and/or reduction of SBP  $\geq$  20 mmHg and/or DBP  $\geq$  10 mmHg. Results obtained should be discussed in terms of statistical significance and in relation to their clinical relevance.

Blood pressure should be measured frequently with emphasis on the maximum and minimum effects of the drug, i.e. before the next dose is given (peak-trough ratio). The main endpoint should be blood pressure at trough which is defined as the residual effect at the end of the dose interval. The peak effect is the maximum blood pressure reduction (at steady state) identified in each patient following repeated blood pressure measurements across a dose interval. All measurements should be performed under standardised conditions. Assessment of trough-peak ratio has to take into account methodological issues and a minimum value should be pre-specified (e.g. 50%) for the recommended dose range. The following methods are available:

### **ad a) Sphygmomanometry**

Measurements with a calibrated mercury sphygmomanometer are the standard. If not available, another device may be used which is calibrated carefully in proportion to a mercury

sphygmomanometer. Aneroid manometer is not recommended. Appropriate cuff size must be used to ensure accurate measurement. Both SBP and DBP should be recorded. The disappearance of sound (Korotkov phase V) should be used for the diastolic reading. Two or more readings separated by 2 minutes should be averaged. If the first two readings of DBP differ by more than 5 mmHg, additional readings should be obtained. Blood pressure should be checked in both arms, at least once. Blood pressure should be recorded in the arm with the higher pressure; if differences greater than 20 mmHg for SBP and 10 mmHg for DBP are present on 3 consecutive readings, the patient should be excluded from the study. Blood pressure should be measured in either supine or sitting position or both. Additional measurements of standing blood pressure are of value for evaluating postural changes and the risk of postural hypotension. No shift from one position to another should be made during the study. Supine or sitting should be for at least 5 minutes before measurement, standing should be for at least 1 minute before measurement. Blood pressure should be measured under standardised conditions, as nearly as possible at the same time each day, on the same arm, by the same personnel, with the same apparatus. Blood pressure measurement during exercise may provide supportive evidence for efficacy.

#### **ad b) Intra-arterial measurements**

Intra-arterial measurement of blood pressure has been used in phase II studies to investigate the relation between dose and height and duration of effect, to assess changes during exercise and to measure 24-hour efficacy. However, the method is complicated and the interpretation of the results is difficult since its prognostic value is not evaluated. Thus, intra-arterial measurement of blood pressure is not considered to be useful in the setting of clinical routine.

#### **ad c) Non-invasive ambulatory blood pressure monitoring**

As ambulatory blood pressure monitoring (ABPM) provides a better insight to blood pressure changes during every-day activities and is better standardised than casual readings, ABPM is required for the evaluation of new antihypertensive agents. The recorders used must fulfill international acknowledged validation procedures (e.g. AAMI/BHS). Recorders using auscultation and oscillometry as combined methods should be preferred since the numbers of errors can be reduced. Repetitive investigations should be performed on a comparable (work-) day using the same recorder. During daytime (06.00 hrs - 22.00 hrs) readings should be done at least at 15-minute intervals and during night-time (22.00 hrs - 06.00 hrs) at 30 minute intervals. For evaluation purposes at least 64 readings/24 hours have to be evaluable, including at least 52 readings during day-time and 12 readings at night. In day-time at least 2 readings and during night-time at least 1 reading/hour have to be available. Regarding the analysis of the results, mean values ( $\pm$  SD) for day- and night-time, periods should be evaluated separately. Special problems (e.g. trough-to-peak ratio, early morning rise) may be worked out by calculating hourly blood pressure or using time series analysis, respectively.

#### **ad d) automatic self (home) measurement**

Self (home) measurement of blood pressure with the help of automatic devices has been advocated as an alternative approach to better characterise a patient's blood pressure level and to estimate the effect of antihypertensive treatment, also in case of treatment cessation.

Validation of the device used is necessary.

### **3.2 Target organ damage**

Compared to ECG and chest radiography, echocardiography combines a higher sensitivity for LVH with a more precise assessment of the degree of LVH (i.e. as a continuous variable reflected by magnitude of LV mass). Vascular Doppler echography and echo tracking events

can be used to study LV diastolic function and arterial compliance. Changes in renal function can be assessed in terms of serum creatinine concentrations, 24-hour creatinine clearance and urinary protein excretion. The most objective method to assess renal blood flow and/or glomerular filtration rate is by using radio-isotopes, but this method is limited, among other reasons, by exposure to radioactivity. Clearance of PAH and inulin can be used as alternatives. Optic funduscopy can provide evidence about retinal arteries, retina, and papilla. Ultrasound of the large vessels and/or angiography can provide evidence of arteriosclerotic plaques or increased vascular mass or increased intimal-medial thickness.

### **3.3 Morbidity and mortality**

Special emphasis should be placed on the effects in certain populations (e.g. elderly patients, subjects with co-morbidity, e.g. diabetic patients). The very old (above 75 years) need a special attention. The evaluation of cardiovascular morbidity should especially take into account sequelae of severe organ damage (e.g. myocardial infarction, stroke, renal insufficiency), and respective therapeutic interventions (e.g. co-medication, need for bypass surgery or PTCA). When planning an all-cause mortality study, further distinction should be made with regard to cardiovascular mortality and sudden death.

## **4. SELECTION OF PATIENTS**

### **4.1 Study population**

Generally, the study population will depend on etiology and the type of hypertension for which the drug is intended. Studies for the evaluation of efficacy or safety of a new antihypertensive drug are mainly performed in patients with primary or essential hypertension of mild to moderate severity with elevated systolic and diastolic blood pressure. Patients of both genders should be included in studies in a balanced way. Patients with more severe stages of hypertension also need to be evaluated in add-on designed studies. Attention should be placed on ethnic peculiarities and concomitant illnesses (e.g. diabetes mellitus, renal disease). There is a special need for data in elderly patients, including specific pharmacokinetic studies, dose-response curves and safety data and the number of subjects above 60 years should be proportional to the frequency of prescriptions. Specific attention should be paid to people between 70 and 90 years of age. Salt intake and other non-pharmacological measures should be kept constant during the trial duration.

Patients with disorders causing secondary hypertension (e.g. pheochromocytoma, adrenal adenoma, renal artery stenosis) and isolated systolic hypertension should be studied separately, if the indication is specifically claimed. This also refers to the treatment of hypertension in pregnancy which should also take into account the obstetrical and pediatric aspects of the problem.

## **5. STRATEGY-DESIGN**

Studies involving the first administration of medicinal products for hypertension to man do not differ essentially from those dealing with other cardioactive medicinal products. Patients receiving antihypertensive therapy who are to be included should be withdrawn from treatment during a wash-out period. The time needed will depend on the half-life of the agent(s) used and time taken for the blood pressure to return to pre-treatment levels. The period will be variable but may take weeks to months. Patients with markedly elevated blood pressure readings may require a continuous underlying antihypertensive drug therapy.

Initial elevated readings should be confirmed on at least two subsequent visits during one to several weeks. A run-in period of 2, preferably 4 weeks is essential before commencing a

clinical trial of a new antihypertensive agent. An allocation of an individual patient to a study drug should only be performed if the basic blood pressure is stable.

### **5.1 Pharmacodynamics**

These studies should include evaluations of tolerability, duration of action, haemodynamic parameters (e.g. stroke volume, PCWP, SVR), heart rate (e.g. Holter), neurohumoral parameters (e.g. RAA-system, sympathetic nervous system) and renal function. Further studies - depending on the mechanism of action of the drug - may include evaluations of (intra) cardiac contractility, impulse formation and conduction, diastolic function, myocardial oxygen consumption, and coronary and regional blood flow.

### **5.2 Pharmacokinetics**

Special studies should be performed in the elderly and, depending of the way of elimination, in patients with varying degrees of renal dysfunction and/or hepatic dysfunction.

### **5.3 Interactions**

Interaction studies can provide information which may help to define the position of the new drug in the therapeutic schemes used in antihypertensive patients. Special attention should be devoted to potentially useful or unwanted interactions with other drugs which might be used alongside the investigational drug for combined treatment. These will be other antihypertensive agents of each of the major classes, but also other drugs which are likely to be used especially in the elderly patients. Special pharmacokinetic and pharmacodynamic interaction studies should be performed if results of clinical trials or the pharmacokinetic and pharmacodynamic properties of the drug give reason to suspect interaction problems.

### **5.4 Therapeutic studies**

#### **Evaluation of efficacy**

Dose-response studies should be randomised, placebo-controlled and double-blinded using at least 3 dosages to establish the clinically useful dose-range as well as the optimal dose. The dose schedule selected for pivotal studies must be justified on the basis of the results of the dose-finding studies in the target population. Dose schedules should be clearly defined for elderly patients and those with various risk factors. The results of the dose-response studies of a new antihypertensive agent should provide robust evidence of its efficacy as compared to placebo for each recommended dose.

Controlled trials with reference therapy should be performed aiming at demonstration of (at least) a similar efficacy/safety ratio of the drug under investigation in comparison to an acknowledged standard antihypertensive agent of the same and of other therapeutic classes. Placebo-controlled withdrawal phases can be introduced at the end of the study. A combination study with at least one other standard antihypertensive agent is mandatory.

Special attention should be paid to reduction of the antihypertensive effect (tachyphylaxis). Careful consideration should be given to the results of those patients who fail to complete the study per protocol (e.g. drop-outs due to adverse events or lack of efficacy).

#### **Patients**

The efficacy studies will mainly include patients with mild to moderate essential hypertension, but a certain number of patients with (very) severe hypertension should be enrolled as well. The sample size depends, among others, on the target variable and its variance. Subgroup analyses for gender, race, age, etc. are desirable. A distinction should be made between in- and out- patients.

## **Design and study duration**

The dose-response studies should preferably be designed as parallel group studies. Following a run-in period of 2, preferably 4 weeks, the comparative studies with reference agents should be double-blind and randomised. The dose should be increased according dosing rules expressed in the protocol, and at each dose level the duration of treatment should be long enough to estimate the effect of the respective dose. The parallel group design using fixed doses should be applied in some studies, instead of escalating doses. The investigational drug may either be given as monotherapy or combined with underlying therapy.

Drug therapy in the main dose-response studies should last at least 2 - 3 months in order to demonstrate efficacy in terms of the antihypertensive effect and each tested dose should be maintained over at least 4 weeks when more than one dose is used. Controlled studies with reference agents should last even longer up to 6 months, in order to allow a comparison with respect to adverse drug reactions as well.

## **6. SAFETY ASPECTS**

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug events/reactions, drop-outs and patients who died while on therapy. Long-term controlled studies may be necessary. Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided. Special efforts should be made to assess potential adverse effects/reactions that are characteristic for the class of drug being investigated. High-risk groups (e.g. elderly patients, patients with renal dysfunction or heart failure or coronary heart disease) require special consideration. Particular attention should be paid to the following specific side effects:

### **6.1 Hypotension**

This may be either symptomatic or asymptomatic. Special attention should be paid to orthostasis and first-dose phenomenon, especially at initiation of therapy or at increase of dosage.

### **6.2 Rebound hypertension**

Withdrawal phenomena, especially rebound hypertension, should be studied specifically.

### **6.3 Effects on cardiac rhythm**

This includes specifically (tachycardiac) pro-arrhythmic effects and effects on impulse-conduction. Depending on the particular pharmacodynamic properties of the drug, heart rate, ECG and Holter monitoring should be performed at frequent intervals throughout the study.

### **6.4 Pro-ischemic effects**

Coronary steal effects due to coronary vasodilation, together with potential hypotensive effects, may lead to angina pectoris and myocardial infarction. When suspected, this needs to be studied specifically.

### **6.5 Effects on target organ damage**

Data on blood chemistry, urine analysis and other general laboratory investigations should be submitted. Effects of alterations in regional blood flow in other organ systems, especially the kidney and heart and brain can be studied. Special emphasis should be placed on renal function, electrolyte homeostasis, and LVH. Depending on suspicion of ophthalmological

side effects, ophthalmological examination should be performed throughout the study. Special emphasis should be placed on cognitive functions and CNS-effects (dizziness, blurred vision, syncope and TIA), especially in the elderly.

#### **6.6 Effects on concomitant diseases**

Concomitant diseases include diabetes mellitus, renal diseases, ischemic heart disease, heart failure, cerebrovascular diseases and, more rarely, peripheral arterial occlusive disease. When specific claims are made, studies on hypertensive patients with concomitant diseases are required.

#### **6.7 Effects an concomitant risk factors**

As concomitant risk factors are often present at the same time, effects on glucose and lipid metabolism should be studied specifically.

#### **6.8 Immunological reactions**

Special attention should be paid to hypersensitivity reactions of the skin and other organs (especially liver, kidney, lung), changes in blood cells, and hepatitis.

#### **6.9 Long-term effects on mortality and cardiovascular morbidity**

Although the risk of cardiovascular morbidity and mortality is strongly associated with the degree of hypertension, the risk of cardiovascular disease is also determined by many other factors, which may also be affected to a different extent by antihypertensive therapy. Results of pharmaco-epidemiological studies have raised the issue whether, despite an equal blood pressure lowering effect, the influence of antihypertensive drug classes on (cardiovascular) morbidity and mortality may not be alike. Even negative effects have been suggested. Therefore, a sufficient cohort of patients of both sexes and all ages should be continuously exposed to the drug for at least one year. The available data on mortality and cardiovascular morbidity from the clinical trial program should be thoroughly analysed, taking also into account preclinical data and the results obtained from other drugs of the same antihypertensive class and other classes as well. A new antihypertensive agent is only acceptable for registration if there is no suspicion of a detrimental effect on cardiovascular morbidity and mortality. Otherwise, additional studies to clarify the drug effect on these parameters are mandatory

### **7. FIXED COMBINATIONS**

#### **7.1 General remarks**

Combination therapy in hypertension is commonly applied to improve efficacy and/or safety as compared to the respective monotherapies. Mono-substances for the treatment of hypertension are generally combined in a fixed manner if:

- the combination of the individual components is plausible since complementary modes of action exist which result in additive antihypertensive effects, or a reduction of ADRs;
- efficacy and safety of the individual components have been proven in confirmatory clinical studies;
- the individual suitable dosage ratio evaluated in confirmatory clinical trials with the free combination has corresponded with that of the fixed combination;



- the joint application of the two components has proven to be efficacious, safe and thus clinically useful.

In order to obtain a marketing authorisation for a fixed combination, it is mandatory to prove that each active component in the scheduled dosage independently contributes towards the positive evaluation of the combination drug. Concerning morbidity and mortality data the same requirements apply as to the monocomponents.

## **7.2 The clinical development of a fixed combination (Refer to the Addendum)**

Dose-finding studies are necessary for identifying the appropriate dosages of the components of a fixed combination. Preferentially, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their respective components and with placebo. Ascending dosages (e.g. in a range of dose equal or superior to two) of the fixed combination could be tested in patients with insufficient response.

The results of the dose-finding studies should be the basis for further, confirmatory, clinical trials. It is important that the clinical studies should be designed in accordance with the indication claimed and the wording of the indication must state clearly, whether the fixed combination should be used as first-line or as second-line therapy in hypertension.

### **7.2.1 Second-line therapy**

Usually, a fixed combination serves as a substitute for a free combination provided that a normalisation of blood pressure has been reached with the same doses of the individual components and the respective combination is well tolerated. Generally, the (fixed) combination should not be administered at the beginning of therapy.

The following strategies in conducting confirmatory clinical studies are acceptable, but it is mandatory that at least one pivotal clinical study is performed in a population of patients whose blood pressure cannot be normalised with monotherapy of one of the monocomponents, if this indication is claimed:

1. Add-on therapy: Add the second drug to non-responders to the first drug, and vice versa. Dose-titration will usually be indicated. It is necessary to demonstrate a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of either monotherapy. Current clinical practice recommendations for the treatment of high blood pressure do not recommend forcing the dose of a single antihypertensive before considering the combination of two drugs. Therefore, it is not necessarily expected that the dose of the single agent is uptitrated beyond the regular maintenance dose before the second agent is added. In any case, the selected upper dose-titration level of each component in monotherapy should be adequately justified. Furthermore, it is necessary to show that any additional safety concerns (incidence/seriousness/severity/outcome of adverse events/adverse drug reactions) do not outweigh the additional benefit of the combination.

In non-responders it is usually sufficient to show a clinically relevant and statistically significant superiority of the combination regarding the mean supine or sitting diastolic and systolic blood pressure, but it would be optimal, if such a trial could show a statistically significant improvement in response rates (blood pressure < 140/90 mmHg) for the fixed combination, as well.

Sufficient duration of time (consistent with the time-response course expected for each component of the combination) should be taken into account to ensure that blood pressure levels are stable before the second drug is added to the medication.

2. Parallel group comparison of the combination with the individual components using the same therapeutic doses: Demonstration of statistically significant superior efficacy of the combination and no additional safety concerns outweighing the additional benefits of the fixed combination.

Results of confirmatory dose-finding studies (e.g. using the factorial design) can also be supportive for the proof of efficacy.

In some cases (e.g. the fixed combination of two diuretics one of which is assumed to have a potassium-sparing effect) it can be mandatory to show a statistically significant and clinically relevant superior safety while accepting a comparable efficacy. In such a case the studies should primarily aim at safety and the indication should be worded accordingly.

### **7.2.2 First-line therapy**

The (fixed) combination of two antihypertensive agents in subtherapeutic dose (i.e. dosage lower than the respective lowest approved individual dosage for antihypertensive monotherapy) aims at the reduction of (dose-dependent) adverse drug reactions (taking into account the anticipated increased frequency of idiosyncratic reactions if the patient is simultaneously confronted with two antihypertensive agents new to him). Recognising that patients with (mild to moderate) hypertension normally are treated with antihypertensive monotherapy which usually will be titrated to the individually optimised dosage, in certain patients first-line therapy with a fixed low-dose combination could be considered. At least the following is required if first-line therapy is claimed for a fixed low-dose combination:

- 1. Demonstration that each substance (component) has a documented contribution within the (fixed) combination:**

It is necessary (but not sufficient) that the results of a valid clinical trial evaluating a fixed low-dose combination document a statistically significant and clinically relevant greater blood pressure lowering effect (e.g. > 2 mmHg with respect to sDBP) than placebo, whereas the difference to each component (same subtherapeutic low dose as in the fixed combination) given separately has to be at least statistically significant. In addition, the response rate on the low-dose fixed combination should exceed that on placebo by an amount which is statistically significant and clinically valuable.

If these objectives are addressed by means of a factorial design which includes groups of patients on additional doses and combinations of doses, then the conclusions regarding the low dose fixed combination of interest should still be based on the pair-wise comparisons described above.

- 2. Indication for a reduction of (dose-dependent) adverse drug reactions by the low-dose fixed combination as compared to the components in the lowest approved dosages:**

It is necessary (but not sufficient) that the blood pressure lowering effect of the low-dose fixed combination is similar, i.e. at least not inferior (e.g. decrease in mean sDBP < 2 mmHg lower than the active comparator) than those of the lowest approved dosage of each component. Moreover, there should be a trend towards better safety and response rate regarding the low-dose fixed combination as compared to each component administered at the lowest approved dosage. Accordingly, the inclusion of a placebo arm in this study is helpful to underline these claims.

## ADDENDUM

### FIXED COMBINATION ANTIHYPERTENSIVE MEDICINAL PRODUCTS IN SECOND LINE THERAPY

The three following relevant issues were identified regarding applications for fixed combination antihypertensives in second line therapy.

#### 1. Indication

It was concluded that, provided sufficient evidence is included in the application, the second line indication for fixed combination medicinal product mentioned under section 4.1. should read as follows:

*“Treatment of essential hypertension, <medicinal product Z> fixed dose combination (X mg /Y mg) is indicated in patients whose blood pressure is not adequately controlled on X or Y alone”*

#### 2. Posology

It was agreed that in section 4.2. Posology and method of administration" the two following recommendations should be included: *“Individual dose titration with the components can be recommended”* and *“When clinically appropriate, direct change from monotherapy to the fixed combination may be considered”*.

#### 3. Clinical trials requirements for second line indication

In the ‘Note for Guidance on clinical investigation of medicinal products in the treatment of hypertension’, two types of trials are discussed: trials in patients who are non-responders to the monotherapy, and trials in general population of hypertensive patients (including potential responders).

It was agreed that different trial requirements might be needed to support the three different following indications:

- 3.1 In order to support the indication "Treatment of essential hypertension, <medicinal product Z> fixed dose combination (X mg /Y mg) is indicated in patients whose blood pressure is not adequately controlled on X alone", at least one add-on trial to active treatment in non-responders to X should be carried out.
- 3.2 In order to support the indication "Treatment of essential hypertension, <medicinal product Z> fixed dose combination (X mg /Y mg) is indicated in patients whose blood pressure is not adequately controlled on Y alone", at least one add-on trial to active treatment in non-responders to Y should be carried out.
- 3.3 In order to support the indication "Treatment of essential hypertension, <medicinal product Z> fixed dose combination (X mg /Y mg) is indicated in patients whose blood pressure is not adequately controlled on X or Y alone", two add-on studies one in non-responders to X and one with non-responders to Y should be carried out.

In some cases where only one add-on clinical study in non-responders has been carried out, data from appropriately designed parallel group comparative studies of the combination with the individual components may support a broader indication in both categories of non-responders.