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Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of hypertension

Draft

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Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

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Guideline on clinical investigation of medicinal products in the treatment of hypertension

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Executive summary

This is the 4th revision of the Guideline on clinical investigation of medicinal products in the treatment of hypertension. The main aim of the 4th revision was to include more comprehensive guidance on the collection of long-term safety data and to clarify in which situations outcome studies might be required in order to detect potential long-term effects on mortality and morbidity.

1. Introduction (background)

There is a continuous increase of cardiovascular risk associated with increasing levels of blood pressure (BP): the higher the BP, 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. The elevations in SBP are more important than DBP not only for diagnosis and therapy but also for prognosis.

The dividing line between ‘normotension’ and ‘hypertension’ is arbitrary and might vary with age. 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

- aetiology: essential or primary hypertension vs. secondary hypertension;
- severity: according to WHO/ISH, JNC 7 or ESC/ESH guidelines;
- type: systolic, diastolic or both;
- effects of treatment.

2. Scope

Guidance is provided on the design of clinical studies considered to be of relevance for the evaluation of antihypertensive drugs. The main aim of the current revision was to include more comprehensive guidance on the collection of long-term safety data and to clarify in which situations outcome studies might be required in order to detect potential long-term effects on mortality and morbidity. Every effort should be undertaken to include a study population that mimics as far as possible the target population including high-risk patients with co-morbidities and concomitant medications. Different safety aspects should therefore be evaluated in a dataset representative of this population. In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new drug increases the risk of damage in any of the target organs normally affected by elevated BP (in particular the cardiovascular system and the kidneys).

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles and Annex I to Directive 2001/83 as amended and with the following guidelines:

- Dose-Response Information to Support Drug Registration (ICH E4)

- Statistical Principles for Clinical Trials (ICH E9)

- Choice of Control Group in Clinical Trials (ICH E10)

- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A)

- Pharmacokinetic Studies in man (3CC3A)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Reporting the Results of Population Pharmacokinetic Analyse (CHMP/EWP/185990/06)
- Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005)
- ICH topic E7 Studies in Support of Special Populations: Geriatrics Questions and Answers (EMA/CHMP/ICH/604661/2009

In addition, all pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

4. Assessment of efficacy criteria

4.1. Blood pressure

The goal of treating hypertension is to prevent morbidity and mortality associated with high BP. Reduction in BP 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 5.3 and 8.2).

4.2. 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 SmPC that beneficial effects on mortality and cardiovascular morbidity are unknown.

4.3. 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, target organ damage 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 (all cause or CV) remains to be established. Thus, these endpoints are considered of supportive value. Specific studies are only mandatory when specific claims are made or when there are suspicions of a detrimental effect.

5. Methods to assess efficacy

5.1. Blood pressure

BP lowering effects of anti-hypertensive therapy should be documented as the pre-/post-treatment reduction of BP. SBP is the preferred efficacy variable whilst DBP is a mandatory secondary end point. Other secondary endpoint effects on response criteria can also be assessed. Arbitrarily, response criteria for antihypertensive therapy include the percentage of patients with a normalisation of BP (reduction SBP <140 mmHg and DBP <90 mmHg) and/or reduction of SBP ≥20 mmHg and/or DBP

≥10 mmHg. Results obtained should be discussed in terms of statistical significance and in relation to their clinical relevance. BP 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 BP at trough which is defined as the residual effect at the end of the dose interval. The peak effect is the maximum BP reduction (at steady state) identified in each patient compared to baseline following repeated BP measurements across a dose interval. All measurements should be performed under standardised conditions and with the patient in the office, in the same position at the same time of day when repeated measures are performed and ambient room temperature should be as similar as possible. 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:

a) Sphygmomanometry

Measurements with a calibrated sphygmomanometer are the standard method to determine BP in the setting of pivotal trials. If not available, another device may be used which is calibrated carefully in proportion to a mercury sphygmomanometer. Use of 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 SBP differ by more than 5 mmHg, additional readings should be obtained until stabilisation has occurred with difference between these two readings within this limit. BP should be checked in both arms, at least once. BP should be recorded in the arm with the higher pressure; if differences between arms 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. BP should be measured in either supine or sitting position or both. Additional measurements of standing BP 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 posture should be adopted for at least 5 minutes before measurement, and when standing BP is measured, the subject should be standing for at least 1 minute before measurement. BP 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. BP measurement during exercise may provide supportive evidence for efficacy.

b) Intra-arterial measurements

Intra-arterial measurement of BP has been used in phase II studies to investigate the relation between dose, magnitude 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 fully evaluated. Thus, intra-arterial measurement of BP can be regarded as a valuable method in initial therapeutic studies. It is not considered to be widely applicable in the setting of clinical pivotal studies.

c) Non-invasive ambulatory blood pressure monitoring

As ambulatory blood pressure monitoring (ABPM) provides a better insight to blood pressure changes during everyday activities, ABPM is strongly recommended for the evaluation of new antihypertensive agents, although there are insufficient data to accept ABPM as the sole basis for efficacy in an approval process.

The recorders used must fulfil international acknowledged validation procedures (e.g. AAM-IBHS). Repetitive investigations should be performed on a comparable (work-) day using the same equipment every time throughout the study.

Readings should be done with sufficient frequency. Time intervals should be short enough to get meaningful and reliable results at day and during night-time. The measurement intervals should be justified in the protocol. It is important that certain issues such as circadian variation, drop in night time pressure and time for highest vs. lowest pressure are assessable.

A certain minimum of readings/24 hours have to be evaluable. The number of evaluable readings must be sufficient to enable a proper assessment. It is suggested that in day-time 2 readings and during night-time 1 reading hourly may provide an appropriate database. Other approaches, if properly justified and validated, may be accepted. Readings should cover time before drug intake. Measurements within one hour and two hours after wake up, respectively, are recommended. At least 8 measurements should be included between 18 and 24 hours after drug intake. Analysis of the results could be performed in several ways, but it is recommended that mean values (± SD) for day- and night-time periods should be analysed separately. Special analysis could be performed to assess trough-to-peak ratio, early morning rise, drop in night-time pressure etc.

d) Automatic self (home) measurement

Self (home) measurement of BP with the help of automatic devices has been advocated as an alternative approach to better characterise a patient's BP level and to estimate the effect of antihypertensive treatment, also in case of treatment cessation. However, as stated for ABPM, there are insufficient data to accept self (home) measurement of BP as the sole basis for the evaluation of efficacy in clinical studies.

Validation of the device used is necessary.

5.2. Target organ damage

Compared to ECG and chest radiography, echocardiography combines a higher sensitivity for left ventricular hypertrophy (LVH) with a more precise assessment of the degree of LVH (i.e. as a continuous variable reflected by magnitude of LV mass). Tissue Doppler myocardial imaging and echo tracking events can be used to study left ventricular (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. Renal function could also be assessed by estimated glomerular filtration rate (eGFR) calculated by means of properly evaluated equations. 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 para aminohippurate (PAH clearance) and inulin can be used as alternatives. Fundoscopy 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.

5.3. Morbidity and mortality

When conducting mortality and morbidity trials special emphasis should be placed on the effects in certain populations such as elderly patients and subjects with co-morbidity e.g. diabetic patients. Patients above 75 years of age will need special attention. The evaluation of cardiovascular morbidity should especially take into account sequelae of severe organ damage (e.g. myocardial infarction, heart

failure, stroke, renal insufficiency), and respective therapeutic interventions (e.g. co-medication, need for bypass surgery or coronary angioplasty). When planning an all-cause mortality study, further distinction should be made with regard to cardiovascular mortality and sudden death. Adjudication regarding causes of death and morbidity will be necessary.

6. Selection of patients

6.1 Study population

Generally, the study population will depend on aetiology 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 SBP and DBP. 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 studies and an add-on study design may be more appropriate here. Attention should be placed on ethnic peculiarities and concomitant illnesses (e.g. diabetes mellitus, renal disease). Salt intake and other non-pharmacological measures possibly impacting BP levels should be identified, recorded and (ideally) kept constant during the trial duration for all trials.

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

7. Study 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 currently receiving antihypertensive therapy who are to be included should be withdrawn from current existing treatment during a wash-out. The time needed for wash-out will depend on the half-life of the agent(s) used and time taken for the BP to return to pre-treatment levels. This will be variable but may take weeks to months. Patients with markedly elevated BP readings may require a continuous underlying antihypertensive drug therapy, thus making an add-on design appropriate.

Allocation of an individual patient to a study drug should only be performed if the baseline BP is stable. Initial elevated readings should be confirmed on at least two subsequent visits during one to several weeks. A run-in period of at least 2, sometimes as long as 4 weeks is essential before commencing a clinical trial of a new antihypertensive agent. A prolonged run-in period may be necessary to avoid bias due to the regression-toward-the-mean phenomenon.

7.1 Pharmacodynamics

These pharmacodynamics (PD) studies should include evaluations of tolerability, duration of action, haemodynamic parameters (e.g. stroke volume, pulmonary capillary wedge pressure, systemic vascular resistance), heart rate (e.g. assessed via Holter monitoring), 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 orthostatic reactions, (intra)cardiac contractility, impulse formation and conduction, especially repolarisation (i.e. QT/QTc intervals), diastolic LV function, myocardial oxygen consumption, and coronary and regional blood flow. Which tests ought to be performed depend on the drug and its characteristics and the chosen tests should be justified by the Applicant.

7.2 Pharmacokinetics

Special pharmacokinetic (PK) studies should be performed in the elderly and, depending on the route of elimination, in patients with varying degrees of renal dysfunction and/or hepatic dysfunction.

7.3 Interactions

Interaction studies can provide information which may help to define the position of the new drug in the therapeutic schemes (i.e. treatment algorithms) 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 of hypertension. 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 formal PK and PD interaction studies should be performed if results of clinical trials or the PK and PD properties of the drug give reason to assume/suspect specific interactions (see *NfG on the Investigation of Drug Interactions [CPMP/EWP/560/95]*).

7.4 Therapeutic studies

a) Therapeutic exploratory studies

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. 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. It is also essential to demonstrate the added contribution of each dose chosen.

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 to the 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 mono-therapy or combined with underlying therapy.

b) Therapeutic confirmatory studies

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 by time (tachyphylaxis).

Careful consideration should be given to the results in those patients who fail to complete the study per protocol (e.g. drop-outs due to adverse events or lack of efficacy).

Drug therapy in the main dose-response studies should last at least 3, preferably 6 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.

7.5 Studies in special populations

The efficacy studies should include patients reflecting the target population. Generally these will mainly include patients with mild to moderate essential hypertension, but a certain proportion of patients with (very) severe hypertension should be enrolled as appropriate. The sample size depends, among others, on the target variable and its variance. Subgroup analyses for gender, race, age, etc. are desirable in order to demonstrate consistency across groups. However, these are unlikely to lead to indications in specific subgroups when no effect is demonstrated overall. Dose schedules should be clearly defined for elderly patients and those with various risk factors.

7.5.1. Elderly

There is a special need for data in elderly patients, including specific PK studies, dose-response curves and clinical data. Target BP targets might differ with age, particularly for age over 80. A reasonable number of elderly patients (>65 years, >75 and > 85 years, respectively) should be included in the therapeutic confirmatory studies. The number of subjects 75 years and older included in (pivotal) trials should be sufficient to assess both efficacy and safety in this group.

8. Safety aspects

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug events/reactions, dropouts, deaths while on therapy and clinical laboratory results.

8.1. Specific effects related to mechanism of action

Special efforts should be made to capture potential adverse events that are characteristic of the mechanism of action and the PD properties of the class of products being investigated. This may include the following effects:

8.1.1 Hypotension

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

8.1.2 Rebound hypertension

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

8.1.3 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.

8.1.4 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.

8.1.5 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, 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 central nervous system (CNS)-effects (dizziness, blurred vision, syncope and TIA), especially in the elderly.

8.1.6 Effects on concomitant diseases

Concomitant diseases (or co-morbid conditions) of specific interest include diabetes mellitus, renal impairment, 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. From a safety perspective, it is expected that the new agent does not have significant adverse events or deleterious effects on other pathologies.

8.1.7 Effects on concomitant risk factors

As concomitant risk factors are often present at the same time, effects on glucose and lipid metabolism should be evaluated with special attention.

8.2 Long-term effects on mortality and morbidity

The target population for BP lowering agents includes to a large degree patients with co-morbidities and concomitant medications. Different safety aspects should therefore be evaluated in a dataset representative of this population. In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new drug increases the risk of damage in any of the target organs normally affected by elevated BP (in particular the cardiovascular system and the kidneys).

8.2.1 Type of studies

The complete development program will be taken into account in order to detect potential signals that may suggest an increased risk for other rare adverse events including cardiovascular (CVS) risk and renal toxicity. The following general elements should be considered:

- Non-clinical data

Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects, including CVS risk, should be conducted and provided as an instrumental element of the safety evaluation. Animal studies should focus, amongst others, on athero-thrombotic findings, fluid retention, BP, renal function, electrolytes homeostasis, cardiac functionality, repolarisation and conduction abnormalities (pro-arrhythmic effects), as outlined in ICH Guidelines (e.g. S7A and S7B). If the drug is developed in the paediatric population the *Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)* should be considered.

- Clinical data

There are two important aspects to consider in terms of detecting signals of adverse events; the overall size of the database and the time needed to detect the signal.

An overall plan for the detection and evaluation of potential adverse events, including justification of the size and duration of the studies with respect to the possibility of detecting safety signals, should be prospectively designed early during the clinical development, optimally by the time of phase II studies. While the relevant ICH document provides a general guidance on the requirements of safety databases, a wider exposure is likely to be necessary commensurate with the target population for the medicinal product to refute the suspected safety issues. This program should take into consideration key elements of the primary and secondary pharmacology as well as key toxicological findings from non-clinical studies.

Two approaches are conceivable:

- A pooled, patient level meta-analytic approach to safety events. In such cases the size of database, as well as the mean duration of the studies, are expected to be adequate to detect signals for serious and uncommon events;
- As an alternate approach or when there is suspicion of an adverse CVS signal (from the database), a specific long-term controlled outcome study with at least 18 – 24 months follow-up (depending on the characteristic of a drug and baseline risk of the studied population) would be expected as part of the clinical development program of BP lowering agents at the time of submission of the MAA.

The safety evaluation should include a prospective definition of adverse events, particularly CVS safety outcomes of interest that is common for all phase II-III studies, facilitating pooled analysis strategies. Furthermore, applicants should foresee a consistent central adjudication system for all predefined CVS and other adverse events of interest during the phase II-III program. Detailed statistical analysis plan for the pooled CVS safety data should be prospectively designed.

8.2.2 Study Population

In the development program, every effort should be undertaken to include a study population that mimics as much as possible the target population, regardless whether a meta-analytic approach or a specific study approach is used. In either case, an adequate number of high risk patients such as elderly patients, including patients over 75 years, subjects with other CVS risk factors (e.g. diabetes, hyperlipidemia), high risk for CVS complications and confirmed history of ischemic heart disease and/or congestive heart failure should be included in the clinical development. Detailed clinical information allowing a proper characterisation of the baseline characteristics, including ischemic heart disease and congestive heart failure, for patients enrolled in controlled studies must be collected and summarised. Every effort should be made to include geriatric patients using concomitant therapies and with co-morbidities in the pre-marketing clinical development program.

8.2.3 Safety outcomes

Concerning CVS events, the emphasis will be on major CVS events (MACE [major adverse cardiac event]: CVS death, non-fatal myocardial infarction and stroke) but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. It is important to ensure that these are adjudicated events. Other events such as revascularisation and/or worsening of heart failure can also be evaluated.

Clinically relevant changes in cardiac function should be evaluated (e.g. by echocardiography) if there is an indication of a detrimental effect on cardiac function.

Other safety outcomes should be chosen based on the known safety profile of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.

Use of relevant terms for coding AEs should be properly defined and harmonised across clinical development, allowing an efficient analysis of safety.

8.2.4 Evaluation of results

For medicinal products belonging to a well-known class (and mechanism of action) a careful evaluation of the available medical literature together with the absence of pre-clinical and clinical signals of increased CVS risk may lend some support to a meta-analytic approach provided there is no product specific signal from the database. If a benefit or at least absence of harm in terms of CVS risk has been shown with the other agents in the class and product specific differences in the off target effects between agents are unlikely this may reduce the need for a specific outcome study.

An integrated safety analysis with specific focus on CVS safety (i.e. with adjudicated pre-determined MACEs) should be submitted at the time of MAA for any drug. An appropriately powered CVS safety assessment, e.g. based on a dedicated CVS outcome study, should be submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/ mechanism of action or has emerged from pre-clinical/ clinical registration studies.

Independently on whether a meta-analytic approach or a specific outcome study approach is used, due consideration should be given to the range of analyses presented as in the field of signal detection no single approach to the analysis of data is sufficient to guarantee that relevant signals can be captured.

The overall results of this safety program should be discussed in terms of internal and external validity and clinical justification of the safety outcomes. Acceptability of the data presented will be decided based on its overall quality, the point and interval estimates obtained for the calculation of specific risks, including CVS risk, and the reliability of these estimations. A summary of what is known about CVS risk should be proposed for the SmPC.

Indications of increased risk of certain adverse events or unacceptable lack of precision are important concerns and may trigger the request for additional specific long-term outcome trials to exclude an unacceptable increase in CVS or other identified risks associated with the new agent. The risk management plan should cover identified and potential safety issues. Detailed guidance on Risk Management Plans (RMPs) are relevant here.

9. Fixed combinations (FDCs)

9.1 General remarks

Combination therapy in hypertension is commonly applied to improve efficacy and/or safety as compared to the respective mono-therapies. 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 dose combination (FDC);

- 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 FDC, 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~~ for the mono-components.

9.2 The clinical development of a fixed combination

In the situation where a combination has not yet been demonstrated to be safe and efficacious, the positive benefit/risk of the joint application of the mono-components should be demonstrated by means of one or more studies with appropriate design and dose-response data. Initially, a factorial design should preferably 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 FDC could be tested in patients with insufficient response.

The results of the factorial 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 FDC should be given as 1) first line therapy in patients receiving previously neither of the substances 2) second- or third-line therapy in non-responders to the mono-components, and 3) substitution therapy in patients adequately controlled with the individual products, given concurrently, but as separate tablets at the same dose level as in the intended FDC.

Any FDC should not raise new safety concerns other than encountered with the mono-components. Special attention should be paid on dose-dependent side effects, including “first dose hypotension” and symptoms and signs of organ damage (e.g. renal dysfunction) initially (e.g. 1-2 weeks) and after each dose step. Attention should also be paid to serum electrolyte levels. Particular caution is necessary in patients at higher risk for orthostatic hypotension for example those with diabetes mellitus, autonomic dysfunction, and elderly patients.

9.2.1 First line therapy

In this situation the FDC is considered for patients receiving previously neither of the substances. The FDC may contain either subtherapeutic doses, with doses lower than when given as monotherapy, or therapeutic doses, depending on the clinical justification for the combination.

9.2.1.1 Subtherapeutic doses

In this possible, although uncommon, situation the (fixed) combination of two antihypertensive agents contains a dosage lower than the respective lowest approved individual dosages for antihypertensive mono-therapy. In addition to showing at least similar efficacy to the lowest approved doses of the monotherapy, the primary aim of developing a low-dose FDC is a reduction of adverse drug reactions in particular dose-dependent adverse events (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 are normally treated with antihypertensive mono-therapy 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.

The following minimum requirements have to be met if first-line therapy is claimed for a fixed low-dose combination.

1) Demonstration that each substance 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 BP lowering effect 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. 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 FDC of interest should still be based on the pair-wise comparisons described above.

2) Demonstration of at least similar efficacy to the lowest approved doses of each monotherapy compound

It is necessary (but not sufficient) that the BP lowering effect of the low dose FDC is better or at least similar, i.e. at least not inferior to the effect of the lowest approved dosage of each component. The inclusion of a placebo arm in this study is helpful to establish external validity of the trial and underline these claims.

3) 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:

There should be a trend towards better safety regarding the low-dose FDC as compared to each component administered at the lowest approved dosage.

9.2.1.2 Therapeutic doses

In this situation the (fixed) combination of two or more antihypertensive agents contains a dosage in accordance with approved individual dosages for antihypertensive mono-therapy. According to current recommendations, the primary aim of initiating antihypertensive therapy with a FDC would be to achieve the BP (BP) goal in a more timely fashion, which may be more convenient and simplify the treatment regimen. In many hypertensive patients the treatment goals for BP cannot be achieved by one drug alone. This has been shown in several large trials, especially in the group of patients with higher initial BP (≥160/100 mmHg or >20/10 mmHg above goal) or with risk factors for cardiovascular events. Therefore, recent hypertension guidelines recommend that initial therapy with two or more drugs may be used in these patients. In addition, the use of multidrug combinations may produce greater BP reduction at lower dosage of the component agents, resulting in fewer side effects.

On the other hand, a too rapid and/or too strong reduction in BP may lead to orthostatic hypotension, renal dysfunction and cerebral hypoperfusion. Last but not least, the indiscriminate use of FDC as first line option may lead to unnecessary drug use.

Patient selection

Appropriate patient selection is the key point and it is recommended that the Applicant thoroughly justifies that the patients considered for a first line FDC have a low chance to be adequately treated with mono-therapy or by a combination in sub-therapeutic doses. Furthermore, the Applicant should show that the risk for CVS events among the included patients is sufficiently high to justify that treatment is initiated with more than one drug. The inability to reach the preset goal is influenced by many factors such as initial BP levels, target BP, concomitant diseases, target organ damage and older age. Therefore, only patients with at least moderate or severe hypertension and/or at high risk for CVS disease are regarded to fit into the category with a high risk for inadequate BP control on mono-therapy. The Applicant should also take into account demographic peculiarities, like age and gender, and concomitant illnesses, as indicated in section 4 of this document. In order to properly assess the real value of the FDC as first line therapy, it is highly recommended that the pivotal body of evidence comes from studies conducted in treatment-naive patients fulfilling the recommendations outlined

above.

Demonstration of the blood-pressure effect of the substances

Requirements for therapeutic exploratory studies will vary depending on what substances are used in the FDC. The following situations are possible:

1. All substances are well known and the joint application of the two components has proven to be efficacious, safe and thus clinically useful.

Relevant studies should be available, either as original studies or on the basis of the literature to document the benefit/risk of the combination and the doses used. In this case, in particular when the FDC is already available for the second-line indication, one therapeutic confirmatory study could be sufficient to demonstrate its benefit in terms of obtaining a more rapid and at least comparable blood pressure lowering effect compared to the dose titrating regimen of the free combination.

When all substances are known and the value of the combination of the mono-components has been documented sufficiently, in particular when the FDC is already available for second-line indication, long term safety demands could be satisfied to a large extent by historical data. The completed studies should, however, supply a large enough sample for safety assessments and a safety extension may be necessary. This could be performed with an open label design and/or comparative studies with other FDC.

2. One or all substances are not well known and/or the efficacy and safety of the joint application have not been established

In this case the benefit of the combination will need to be explored further, similar to the general requirements for a FDC, before proceeding to the therapeutic confirmatory study. This will normally include a factorial study with comparison between the mono-components and the FDC.

Design of the therapeutic confirmatory study

The therapeutic confirmatory study should demonstrate that the use of the FDC as initial therapy is safe and provides a more timely blood pressure control as compared to a strategy initiated with monotherapy and subsequent addition of further substances. It should be a parallel arm study to compare the antihypertensive effects of the standard regimen of initiating and titrating one agent before adding and titrating the second, with the new regimen of titrating the FDC. As the FDC (substances X and Y) will normally consist of at least two ascending dosages, the effect of the lower dose combination will be studied during the first treatment period and compared with the full dose of X and/or Y (the mono-components) at the end of this period. At the end of this period, in non-responders, dose should be doubled in the FDC arm and the second drug (X or Y, one or the other) should be added in the mono-therapy arm(s). Subsequently, all treatment arms should be studied for the second treatment period and compared at the end of this period. Dose-titration steps may be necessary in all arms to obtain the required dosages at the end of each treatment period that should be of sufficient duration to allow a reliable treatment effect. Ultimately, the number of treatment periods will depend on the number of ascending dosages of the FDC. A low number of patients reaching the target BP on monotherapy in the add-on arm is expected in an appropriately chosen target group.

With such an approach it is expected that the mean reduction in BP and the success rate in both arms will be similar when patients have been uptitrated to the maximal target dose. Based on demonstration of non-inferiority of the BP lowering effect of the FDC as compared to the second-line approach the key parameter for evaluation of efficacy is “time until achieving target BP”. Such an endpoint is in accordance with the primary aim to achieve the BP goal in a more timely fashion. The clinical relevance of the time gained remains to be demonstrated for the target group of patients. Alternative approaches, if properly justified, may be acceptable, provided that the gain obtained with the FDC as initial strategy

is adequately documented as stated above.

Safety in those patients that could be successfully treated with mono-therapy but receive a FDC in a first line approach should be addressed.

9.2.2 Second- or third-line therapy

A FDC may be considered when response to one or more of the mono-components is insufficient. The following strategies in conducting confirmatory clinical studies should be considered.

Add-on therapy

Depending on the indication claimed (*see addendum*) at least one or two pivotal clinical study/-ies should be performed in a population of patients whose blood pressure cannot be normalised with one or all of the mono-components. A statistically significant and clinically relevant additional BP reduction of the combination should be demonstrated in patients who did not respond adequately to standard therapeutic doses of one or more of the mono-components. Dose-titration will usually be indicated. Current clinical practice recommendations for the treatment of high BP do not recommend forcing the dose of a single antihypertensive before considering the combination of two or sometimes even three drugs. Therefore, it is not necessarily expected that the dose of the single agent is up-titrated beyond the regular maintenance dose before the second or third agent is added. In any case, the selected upper dose-titration level of each component 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 SBP and DBP, but it would be optimal, if such a trial could show a statistically significant improvement in response rate (i.e. applying a BP threshold of <140/90 mmHg) for the FDC, 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 BP levels are stable before the second drug is added to the medication. In special situations, in particular for triple combinations, an alternative study design may be appropriate.

Parallel group comparisons

A parallel comparison of the combination with the individual components using the same therapeutic doses with the demonstration of statistically significant superior efficacy of the combination and no additional safety concerns outweighing the additional benefits of the FDC can be supportive for the proof of efficacy. Comparison with another FDC may also provide supportive data in the benefit/risk assessment.

In some cases (e.g. the FDC 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 relevantly 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.

9.2.3 Substitution therapy

In this situation the FDC of two or more antihypertensive agents is intended for patients adequately controlled with the individual products, given concurrently, but as separate tablets at the same dose level as in the combination. The primary aim is to reduce the number of tablets the patient has to take, which may potentially enhance adherence to therapy.

Requirements

Requirements will vary depending on which substances are used in the FDC.

The following situations are possible:

1. All substances are well known and the joint application of the two or more components is already in widespread use in the proposed dosage strengths, has proven to be efficacious and safe and thus clinically useful.

This situation includes those cases where the requirements for granting a first line indication (therapeutic doses) or an add-on indication are fulfilled. Moreover, this approach may also be acceptable for combinations of drugs for which a wide therapeutic experience is available (e.g. 5 years or more), provided there is a good plausibility and that the pharmacological rationale for the use of both drugs in combination is adequately justified. Provided that the respective data are thoroughly and reliably documented, a well founded bibliographical data analysis may be helpful in reducing the amount of clinical trials to be performed. In this case comparative PK data are needed, demonstrating that the two components of the FDC do not affect each other's PK patterns. Showing bioequivalence of the components in free combination with the FDC is the pivotal aspect in this setting.

2. One or all substances is/are <u>not</u> well known and/or the efficacy and safety of the joint application have not been established

In this case, original clinical data on efficacy and safety for the combination are required. In addition to the bioequivalence study comparing the drugs in free combination with the fixed dose, the benefit/risk of the combination will need to be explored further, before a substitution indication can be considered. This will normally include clinical studies showing efficacy and safety of the FDC as well as factorial studies for the dose-response assessments. These studies should demonstrate significant additional BP reduction of the combination and that the mono-components contribute to the effects. An add-on study in non-responders should be considered in when clinical use in a substitution indication may not be clearly differentiated from a second- or third line add-on use. This may be the case when the majority of patients is not already on long term combined treatment with the individual monocomponents, but will be treated de novo with combinations containing at least one component that is not well known. Long term safety data will also be needed. Specific attention should be paid to the doses, as used in the fixed combination tablet.

10. Addendum

FIXED COMBINATION ANTIHYPERTENSIVE MEDICINAL PRODUCTS IN SECOND LINE THERAPY

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

1. Indication

It was concluded that, provided sufficient evidence is included in the application, the second line indication for FDC 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 nonresponders 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.