23 June 2016
EMA/CHMP/345847/2015
Committee for Medicinal products for Human Use

Overview of comments received on ''Guideline on clinical investigation of medicinal products in the treatment of hypertension' (EMA/CHMP/29947/2013/Rev. 4)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Swissmedic, Swiss Agency for Therapeutic Products
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1. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
55	2	Comments: Please clarify the sentence "The elevations of SBP are more important than DBP not only for diagnosis but also for prognosis"	Accepted. The sentence amended accordingly.
85	2	Comments: Please confirm if it should read "analysis"?	Accepted. The spelling of the word corrected (“analyses”).
100	2	Comments: Please clarify if "positive" refers to a beneficial or deleterious effect, if the first is the intended meaning (as one could assume from reading the last sentence) this could be reworded as "beneficial".	Accepted. The text amended to more neutral direction.
113	2	Comment: Please consider mentioning measurement of central BP in the section on “Methods to Assess Efficacy”. Central BP is highlighted in the most recent 2013 ESH/ESC Guidelines for the management of arterial hypertension (Journal of Hypertension 2013, 31:1281–1357) because of both its predictive value for	Accepted. A new paragraph added of the topic (5.1.e)

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		CV events and the differential effect of antihypertensive agents compared to brachial BP. While not recommended for routine clinical use, it is of interest for mechanistic analyses in pathophysiology, pharmacology, and therapeutics.	
115-117	2	Comment: Please consider adding 24-hour ambulatory systolic BP as a potential primary endpoint. The importance of ABPM is evidenced by the recommendation in the most recent NICE clinical guidelines to offer ABPM to confirm the diagnosis of hypertension if clinic BP is elevated (NICE clinical guideline 127. Clinical management of primary hypertension in adults. National Institute for Health and Clinical Excellence, 2011).	Not accepted due to insufficient clinical data. The first paragraph of the section 5.1.c is however amended to clarify the issue.
129	2	Comment: Please clarify if “a minimum value" refers to the reduction of BP on treatment, i.e. the effect of the drug on BP?	Accepted. The sentence amended accordingly.
142	1	Comment: The wording is ambiguous because it might be interpreted as a reason to exclude patients from a running study.	Accepted. The sentence amended accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "....should be excluded from participating in the study."	
144	2	Comment: It would be helpful to have a definition of "postural hypotension"(a difference in mmHg between supine and standing) as this might be considered (and reported as) an adverse event.	Accepted. The definition of postural hypotension added in the end of the sentence.
145-146	2	Comment: Please consider adding that an additional standing BP measurement be measured 3 minutes after the assumption of standing position for elderly and diabetic patients and in other conditions in which orthostatic hypotension may be frequent or suspected, as recommended in most recent 2013 ESH/ESC Guidelines for the management of arterial hypertension (Journal of Hypertension 2013, 31:1281–1357).	Partly accepted. The text amended to clarify the issue.
173	2	Comment: It would be helpful to provide the rationale for this specific timing.	Accepted. Since the time after awakening will be anyway covered during the routine 24-25 hour ABPM period, the sentence is deleted.
175	2	Comment: It would be helpful to add a definition of the day- and night time periods and also to define what is the	Partly accepted. The text amended to clarify the issue.

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		recommendation of the analysis if the patient works in night shifts?	
179	2	Comment: Please clarify why should self-measurement be limited to the home? Wouldn't it be helpful to have Self-assessments at work where the BP might be higher?	The efficacy data of clinical studies using self-measurement of BP in other places than home are very scarce. No reason for text change.
179-183	2	Comment: Consider listing the specific conditions considered as clinical indications for out-of-office BP measurement for diagnostic purposes, such as suspicion of white coat hypertension, masked hypertension, or patients with considerable variability of office BP over the same or different visits. Home BP may provide useful information in clinical trial setting, in particular during washout period and during long-term follow-up periods. While not being the sole basis of evaluation, home BP may be a useful secondary endpoint.	Not accepted. The issues are in principle already covered in the current text. The more detailed information of the indications of out-of office BP measurements can be reviewed in the clinical hypertension guidelines (ESH, JNC, NICE etc.).
184	2	Comment: Please provide a definition of what will be considered as a "validated" device.	Accepted. A sentence added to clarify the issue.
185	2	Comment: Consider mentioning carotid-femoral pulse wave	Accepted. A sentence added to cover the issue in the end of the paragraph.

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		velocity as a means to assess aortic stiffness. Pulse wave velocity is highlighted as a diagnostic tool in determining target organ damage in the most recent 2013 ESH/ESC Guidelines for the management of arterial hypertension (Journal of Hypertension 2013, 31:1281–1357). Proposed change (if any):	
195	2	Comment: We would suggest considering as well cystacin C as it is not methodologically easy to use "inulin" in this respect. Proposed change (if any):	Not accepted. According to the increasing evidence, elevated cystatin C is not very specific to renal function. This variable is also elevated e.g. in patients with high age, chronic inflammation, obesity and vascular disease.
206	2	Comment: We would provide more details for this important subject. We are wondering if this means that a formal centralized adjudication is recommended. A reference justifying this recommendation would be helpful. This point should be clarified because of the important implications in the organization of clinical trials.	Accepted. The blinded, centralised adjudication of causes of death and morbidity has been the standard procedure used in pivotal trials already for a long time. The sentence is however amended to clarify the issue.
207	1	Comment: From our perspective, the term “adjudication” needs further specification. Proposed change (if any): “Blinded adjudication performed by an independent committee regarding	Accepted. Please see the Agency’s response above.

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		causes of death and morbidity will be necessary." See also Line 384	
211-213	2	Proposed change (if any): 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**/or** DBP.	Accepted. Text amended accordingly.
224-235	2	Comment: Considering the safety of patients, for studies enrolling moderate to severe hypertensive patients with previous treatment, it is suggested to allow a combined wash-out/run-in phase as long as the patients stay on the run-in drug long enough to reach a stable status. Proposed change (if any): To improve safety of the patients by allowing a combined wash-out/run-in phase	Not accepted. The combined wash-out and run-in period will not inevitably shorten the drug-free period since the long enough period with stable BP without medication (run-in) is however needed. The proposed problem is already covered in the sentence "Patients with markedly elevated BP readings may require a continuous underlying antihypertensive drug therapy, thus making an add-on design appropriate".
225-235	2	Comment: A run-in period of at least two weeks may not be appropriate in patients with high baseline BP values. The use of home BP monitoring during washout and run-in periods may be useful to confirm BP stability and monitor safety. Consideration should be given to combine washout and placebo run-in periods to avoid unnecessary prolongation of non-treatment for study patients.	Please see the response above.

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231	2	Comment: Baseline BP is mentioned Proposed change: Add that the baseline BP is obtained during the run-in period.	The whole paragraph deals with run-in period. No amendment necessarily needed.
262	1	Comment: A minimal dose should be identified. Proposed change (if any): “At least one of these doses should allow a minimal effective dose to be identified.”	The proposed change is in principle acceptable. However, the issue is already coveredin the current text: “…using at least 3 dosages to establish the clinically useful dose-range as well as the optimal dose”.. No further clarification needed.
282	2	Comment: We would suggest to add some indication of how these patients should be analyzed (e.g. last observation carried forward or other) would be helpful for a good planning of the clinical study design.	Since there is no methodological approach to be used in all situations, the broader discussion of the topic in this guideline is not possible. However, related to the issue, “the Guideline on Missing Data in Confirmatory Clinical Trials“ (EMA/CPMP/EWP/1776/99 2 July 2010, Rev 1) is proposed to be added in the section 3 of the GL.
283-285	2	Comment: In general, for most antihypertensives, the majority of the clinical effect is observed in 2-4 weeks, with full effect after 6-8 weeks. The 6-8 week treatment duration has been shown to be sufficient to demonstrate the differences in therapeutic effects between the investigational drug and a control. In addition, with a requirement for a washout/run-in period and a placebo treatment arm for 3 months, study patients will remain untreated for an extended period of time. A placebo control is considered important to quantify BP lowering effect	The safety issues will be taken into account in the design of the studies. The current proposed text in the guideline is not requiring a prolonged placebo-only period in subjects with moderate or severe hypertension. Also add-on therapy (standard therapy + placebo) is possible for these patients. No amendment of text proposed.
297-298	2	Comment:	Not accepted. The statement in the current guideline is similar

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		"There is a special need for data in elderly patients, including specific PK studies, dose-response curves and clinical data". It is not clear whether subgroup results of dose-response curves for elderly patients are acceptable. Is there any desired number of elderly patients for the dose-response curve? Proposed change (if any): Clarification.	with the one used in the "Lipid GL" (section 8.1). The issue is at least partly discussed in the document "ICH topic E7 Studies in Support of Special Populations: Geriatrics Questions and Answers (EMA/CHMP/ICH /604661/2009)", but no definitive answer is given. The exact sample size needed should be discussed with the regulatory agencies. Also the use of population PK analysis is possible.
298-301	2	Comment: "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". (1) In clinical practice it turns out that in a typical hypertension confirmatory study without an upper age limit patients >75 and even more patients >85 years of age are seldom if at all enrolled. Therefore the above mentioned criteria are hard to be met without including a bias into the study. Are other strategies than pivotal studies to assess efficacy and safety acceptable for the elderly >75 years of age, e.g. if no age dependency was shown in pre-Phase I or II studies? (2) A more concrete explanation of "sufficient to	Not accepted, because: 1) Hypertension is highly prevalent in elderly patients. Recruitment of patients (at least aged 65-85 years) should not be difficult also in pivotal studies. It is stated in the document "ICH topic E7 Studies in Support of Special Populations: Geriatrics Questions and Answers (EMA/CHMP/ICH /604661/2009)", that "it would usually be appropriate to include more than 100 geriatric patients in the phase 2 and 3 databases and include patients over the entire spectrum of the geriatric population". 2) The methods to assess the efficacy and safety of the treatment are similar across the all age-groups.

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		assess" could be helpful? Would a descriptive result be accepted as "sufficient"? Proposed change (if any): Clarification	
306	1	Comment: We discussed whether monitoring of liver enzymes / function should be included in this section Proposed change: e.g. "...renal and liver impairment..." (Line 332)	Accepted. Text amended accordingly (the text concerning renal impairment deleted, since already mentioned in the previous section 8.1.5)
317	2	Comment: we would recommend to look both tachycardia and bradycardia	Not agreed. Bradycardia is already covered by the term "effects on impulse conduction". No amendment of text needed.
340	2	Comment: Suggest that the section header be re-labelled since the contents go further than discussing mortality and morbidity alone but are a broader discussion on guidance for long term safety data. Proposed change (if any): Long-term effects on safety and morbidity and mortality	Not agreed, since the main heading of the section 8 is safety and also the topics covered in section 8.1 are included in the long-term safety aspects. No amendment of text needed.
374-376	2	Comment: According to the draft guideline: "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". What does "mean duration of studies" refer to? Is this related to the average patient exposure time over all Phase III studies? Does ICH E1A still define the minimal requirements	The section 8.2 of the GDL ("Cardiovascular safety") has now been extensively shortened. This section now refers to the just recently published "Reflection paper on assessment on cardiovascular safety profile of medicinal products" in terms of the further information of the requirements for the evaluation of cardiovascular risk. Specifically, the topic "duration of the studies" is discussed in the section 4.4 of the reflection paper. No further clarification needed.

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		(e.g. at least 100 patients for one year)? Proposed change (if any): Clarification	
430	2	Comment: It would be helpful to indicate what would be regarded as a “lack of precision” e.g definition of an upper limit for the 95% confidence interval for CV death would be helpful as it would help define the sample size for a morbidity-mortality trial.	Please see the previous response. The topic of the upper limit of the confidence interval is discussed in the section 4.6 of the reflection paper. No further clarification needed.
452	1	General Comment: To what extent can cardiovascular safety data be extrapolated from monotherapies to a new fixed combination? From our opinion, extrapolation is limited and specific mortality / morbidity data should be required for a new fixed combination.	The data requirements of a new FDC is highly dependent on the available clinical data of the concomitant use of the monocomponents of the FDC in the same target population (including morbidity and mortality). If case of well-established concomitant use of monocomponents, only PK data (interactions, BE) may be required to apply for MA.
454	2	Comment: The wording benefit/risk is used. In other parts (line 276) this reads efficacy/safety ratio. Proposed change (if any): Suggestion to harmonize	Accepted. The text amended for harmonisation.
530-533	2	Comment: The reason for using treatment-naive patients is not clear. With an appropriate washout and run-in period, previously treated patients should be able to qualify. Moreover is very difficult to find out a relevant number treatment naïve subjects	Taking into account the potential problems with safety in down-titration and stopping the antihypertensive treatment in patients with moderate or severe hypertension, the treatment-naïve patients is recommended as more appropriate target group. The prevalence of untreated hypertension is still unacceptably high (even in high-risk subjects) in many European countries. Therefore, the recruitment of patients should be possible.

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573	2	Comment: comparing efficacy of the two regimens. If the primary parameter for evaluation of efficacy is “time until achieving target BP”, it would seem appropriate not to impose a formal non-inferiority test on the comparison of regimens but rather summary statistics to show that the BP reductions are at least similar.	Accepted. The text amended accordingly.