February, 16, 2019

Submission of comments on 'Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders' (CHMP/EWP/566/98 Rev.3)

Comments from:

Name of organisation or individual
Institute for Quality and Efficiency in Health Care (IQWiG) Im Mediapark 8 D-50670 Köln Germany

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	IQWiG appreciates the opportunity to comment on the draft guideline. In recent years, IQWiG has evaluated several new antiepileptic drugs approved for combination treatment. A common experience from these evaluations is that the pivotal studies for this indication are consistently inappropriate to support the treatment decision of patients with epilepsy. This is due in particular to artificial restrictions in the comparison group, although therapeutic options are still available for the patients included. In addition, the studies are usually short and not focused on collecting patient-reported outcomes (quality of life and functional outcomes). Therefore, IQWiG recently participated in a workshop hosted by The German Chapter of the ILAE (Deutsche Gesellschaft für Epileptologie, DGfE). This workshop discussed how studies for combination therapy should be designed in the future to better inform patient treatment. Other participants of the workshop included patient representatives, representatives of the G-BA (the German decision-making body) and representatives of the pharmaceutical industry. Key points from this workshop are outlined in the specific comments on the text of the draft guidance in section 2. In addition, we refer to the comments of the DGfE on behalf of the workshop participants.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
187		Comment: It is important to recruit groups of patients for trials who need new AED the most and who may, therefore, have the greatest benefit from new drug developments. The cohorts investigated in former AED studies were frequently not representative for the total patient population who need new antiepileptic medication. This was due to over-restrictive exclusion criteria. Especially persons with frequent comorbidities like psychiatric conditions and related co-medications, mental handicaps and elderly patients who presently represent the largest patient population are frequently excluded. These restrictive inclusion and exclusion criteria contributed to the impression that the results of many AED trials have no or only limited relevance for the real-world treatment of epilepsy as discussed above. Therefore, it is recommended to open future trials also to patient groups which have the highest need for and who will be the biggest user group of new AED in clinical routine, including difficult-to-treat persons with intellectual disabilities or other comorbidities as well as the elderly. Proposed change (if any): After line 187 insert a new section as follows: "It is recommended to open future trials to patient groups which have the highest need for new AED in clinical routine, including difficult-to-treat persons with intellectual disabilities	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		or other comorbidities as well as elderly people.”	
216-225 and 252-262 and 389-390		Comment: There are major concerns regarding a complete lack of progress in the consideration of adequate outcome parameters for add-on trials of AEDs in recent years. A major point of criticism is the current use of the “responder rate” as primary outcome parameter. There is no evidence that a response based on a reduction of seizure frequency by 50% is a patient-relevant outcome parameter. The commission of the ILAE on outcome assessment has accordingly stated already in 1998 that a ≥50% reduction may not reflect functional or QoL improvements, does not adequately forecast real-world drug performance, and will leave most patients unable to maintain daily activities and thus dissatisfied (Baker et al. 1998). Several alternative options for outcome assessment are available. We particularly encourage accepting outcome parameters that reflect the impact of benefits and harms of treatments. We propose to include seizure freedom, seizure severity and retention rate as primary outcome measures, which should be accompanied by functional outcomes and QoL. Proposed change (if any): • Change line 216 as follows: “The assessment of efficacy should be based primarily upon ~~seizure frequency / occurence~~ seizure freedom, seizure severity and retention rate. These endpoints	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		should be accompanied by functional outcomes and measurements of quality of life (QOL).” • Delete lines 218-225; insert new paragraphs at the beginning of “5.1.1. Add-on trials” as follows: “In add-on trials, it is important to choose endpoints that reflect the impact of the new drug on benefits and harms for the patients. Therefore, the primary endpoint should either be the proportion of seizure-free patients or the retention-rate. An endpoint that validly depicts the severity of seizures may also be considered as primary outcome. For endpoints measuring the severity of seizures, CHMP scientific advice is recommended. Regardless of which endpoint is chosen as the primary endpoint, these endpoints (seizure freedom, seizure severity and retention rate) should always be presented. In contrast, endpoints that do not reflect seizure freedom, retention rates or severity of seizures (e.g. 50% reduction in seizure rates, cumulative change from baseline in seizure frequency) are not recommended. In addition, functional outcomes and quality of life should always be chosen as secondary outcomes.” • Change section “5.1.3. Add-on and monotherapy trials” accordingly. • Change lines 389-390 (“Efficacy endpoints should be based on...”) accordingly.	
362-426		Comment: Active comparators are important also in add-on trials. Good	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		examples for active comparator AED trials represent the widely accepted and well recognized SANAD studies (Marson et al., 2017a,b). In both trials, patients were randomized to several AEDs, titration was carried out at the discretion of the study physician, and AEDs were successfully compared to each other using the retention rate over a study period of several years in an unblinded fashion. In analogy to this design, future studies on adjunctive AEDs could compare a new drug to approved AEDs after failure of first-line AED with known low potential for pharmacokinetic interactions, like levetiracetam. An alternative approach could be a trial design which compares a study drug to one out of several predetermined active comparator compounds (‚best medical treatment') in a randomized but unblinded fashion. Prior to randomization, the study physician would have to define the active comparator for the individual patient. This approach would allow comparing new adjunct AEDs independently from the baseline compound and taking into account individual patient characteristics. Proposed change (if any): The current type of add-on studies should no longer be recommended (currently, patients in the comparator group have to continue their previous therapy plus placebo, although this previous therapy has been unsuccessful). The section on add-on studies should therefore be revised with the aim of primarily requiring active comparator trials. As an active	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		comparison, either a change to a defined combination therapy or "Physician's choice" (with selection of the therapy before randomization) should be recommended.	
427-430		Comment: Epilepsy is a chronic disease with attacks which may occur irregularly over periods of months and years. The study period should, therefore, be long enough to generate clinically meaningful results. This is usually the case with study periods of at least 12 months. During this period, adaptation of AEDs should be possible, as it is in clinical practice. Otherwise, the results of regulatory trials will be much less applicable to clinical practice. Proposed change (if any): *Maintenance period*<br~~In the maintenance period the test and concomitant products should be kept stable whenever possible.~~ The maintenance period should last at least 12 months~~weeks~~ in order to establish that efficacy is not short lasting. In addition, during this period AEDs should be adapted according to individual efficacy and tolerability and according to the SPC of the AEDs.	

Please add more rows if needed.