24 June 2010
EMA/611366/2009
Committee for Medicinal Products for Human Use

Overview of comments received on 'Guideline on Clinical Investigation of Medicinal Products in the treatment of epileptic disorders' (CHMP/EWP/566/98 Rev.2)

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

Stakeholder no.	Name of organisation or individual
1	IFAPP = International Federation of Associations of Pharmaceutical Physicians
2	H. LUNDBECK A/S
3	EFPIA

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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No. *(see coverpage)*	**General Comment (if any)**	**Outcome (if applicable)**
1.	The guideline is well written and updated to most recent scientific evidence. We have no comments or suggestions to the guideline text and contents.	The comments are appreciated. **No action needed.**
2.	We welcome the opportunity to review this draft guideline. We find the consultation document to be useful and well written. However, we would like to take this opportunity to draw your attention to some points of general concern: • The draft guideline is vague as to when results from monotherapy studies should be available. To avoid delays in the availability of treatment to patients, it should be possible to initiate a monotherapy trial after one controlled add-on trial has shown efficacy.	As stated the clinical development plan of an anti-epileptic agent is not considered complete in absence of efficacy studies in monotherapy. Indeed preferably monotherapy studies should be started as soon as possible once efficacy in the add-on setting has been shown. However the timing (pre-/post marketing, after one or more add-on trials) can not be imposed. However the ideal situation will be mentioned in the text: *Preferably monotherapy studies should be started as early as the development of the medicinal product allows, in order to avoid an excessive delay in obtaining a marketing authorisation for monotherapy. See section 4.7 Conditions for registration.*
	• The draft guideline refers to the standard add-on trial design using reduction in seizure frequency and responder rate as primary outcome measures as the only acceptable design for a pivotal trial. Please consider including a discussion on other acceptable trial designs (e.g. time to n^{th} seizure as mentioned in section 4.5.5.2).	The time to n^{th} seizure is not considered a good primary endpoint in confirmatory add-on studies. The reason is that in refractory epilepsy seizures appear in clusters, patients are sensitive to change in treatment (i.e. seizures are more frequent at the start of treatment) and need a stabilisation period. Hence time to n^{th} seizure is not considered a good primary endpoint in confirmatory add-on studies. **No action needed.**
	We find a need to specify more precisely what level of experience would be expected before these medicines could be registered for use in children.	Given the limited experience with studies in children with epileptic syndromes except LGS and heterogeneity of epilepsies in children, no firm recommendation can be made

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		with respect to the design of the confirmatory studies except that they should be RCT. Details with respect to efficacy endpoints, duration of trials, relevant effect size, etc. differ per condition studied.
3.	EFPIA believe this guidance document is a very well written, reasonable document whose ease of reading is impressive. We wish to raise the following general comments, regarding some of the concepts presented in the draft guidance document. These general points are followed by other text-specific important comments presented in the draft guidance. In order to streamline the document, no editorial or typographical comments are provided. General Comments: • There is no guidance for other specific situations such as: prevention of epilepsy post-trauma, post-surgery, etc. It would be recommended to include any valid or probable biomarkers for epilepsy. This may include genotyping of patients, since mutations in genes coding for voltage-gated and ligand-gated ion channels are associated with generalised epilepsy and infantile seizure syndromes.	Prevention of epilepsy post-traumatic, post-surgery is not considered a separate indication. They fall under treatment of symptomatic seizures. It is noted that prevention might not be the most appropriate term here. For post-traumatic, post surgery patients anti-epileptic medication is given as they have a high probability of developing seizures. De facto these patients are considered to become epilepsy patients. This is treatment. For true prevention that is intervening in the epileptogenesis no recommendation can be made as the mechanism that lead to epileptic foci are largely unknown and there is not experience at all. **No action needed.** So far potential biomarkers in epilepsy further specify a patient population that may be selected. This would determine restrict the indication to the specific population. However it does not affect the design of the efficacy studies. **No action needed.**

2. SPECIFIC COMMENTS ON TEXT

So far specific comments as received from stake holder 3.

Line No.	Ref	Comment and Rationale; proposed changes	Outcome
105-108	3	**Comments:** "*These syndromes should be explored separately: idiopathic generalised epilepsies, symptomatic/cryptogenic generalised epilepsies, including some syndromes specific to childhood (e.g.: West or infantile spasms syndrome, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, etc...).*" Why not allow pooling in exploratory trials as is suggested for paediatric epilepsy (see lines 195-199).	The recommendation to explore the syndromes separately is consistent with the recommended approach at lines 195-199. **No action needed.**
111-113	3	**Comments:** "*Inclusion can be seizure type based within a given syndrome (e.g. primary GTC in JME for instance) or seizure type based across different syndromes (e.g. primary GTC in IGE and symptomatic generalized epilepsies, like Lennox Gastaut) or syndrome based*". This proposal is reasonable. However, the best approach would be to enrol the seizure type and also obtain accurate assessment of syndromic classification at enrolment. This approach may allow, although not powered to do so, for study results to support efficacy of the AED on the seizure type in specific syndromes. **Proposed change:** "*Inclusion can be seizure type based within a given syndrome (e.g. primary **Generalised Tonic-Clonic** seizure in **Juvenile Myoclonic Epilepsy** for instance) or seizure type based across different syndromes (e.g. primary Generalised Tonic-Clonic seizure in Idiopathic Generalised Epilepsy and symptomatic generalized epilepsies, like Lennox Gastaut) or syndrome based. **Given the rarity of some syndromes, it would be preferable to enrol by seizure type but also to carefully characterise syndromes at enrolment.**"*	Partly accepted. The message is that there is a choice between two approaches. The proposed addition would weaken this. However it may be added that in the first approach a careful characterisation of the population included is needed: *In the seizure type based approach the syndromes should be carefully characterised for further evaluation (see 4.4. statistical analysis).*
130-136	3	**Comments:** "*Therefore add-on trials should be conducted optimally in the presence of only one or two pre-existing AEDs, which plasma levels are kept stable within appropriate limits…*"	Not accepted The indication is not the issue here. The issue is that the more concomitant AEDs are given the more difficult it will be to disentangle the relative contribution of the new agent to the

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		Regarding add-on studies: the draft guideline recommends studying the drug candidate in only 1-2 other AEDs. There is no mention of the possibility of a more refractory indication. **Proposed change:** Please consider including a discussion on requirements for a claim of refractory epilepsy.	observed effect as the potential for PK/PD interactions increases. Further it is highly questioned whether the number of AEDs used is indicative for refractoriness and could be used for support of a more refractory indication. The etiology, syndrome type and medication history are more important.
131-133	3	**Comments: "***Plasma monitoring of cAES and test agent is required to exclude interference of PK interaction with the treatment effect*". Conducting plasma monitoring during a clinical trial would require taking repeated blood samples from patients. Although this monitoring is of value for AED with a narrow therapeutic index, its interest decreases for the more recent AEDs for which the difference between efficient vs toxic doses is more important. Hence, the decision to conduct plasma monitoring should be based on the nature of the AEDs. **Proposed change: "*Depending on the nature of the background anti-epileptic agents, ~~P~~plasma monitoring, including sparse sampling, of ~~cAES and~~ test agent (and background AEs if appropriate) ~~is required~~ can be considered to exclude interference of PK interaction with the treatment effect. Additional samples should be considered in the presence of ongoing adverse events"*	Not accepted. A broad or narrow therapeutic index is not at stake here. For instance lamotrigine has a broad therapeutic index but the interaction with oral contraceptives is clinically relevant. Referred is to the SPC of lamotrigine. Increases and decreases by 30-50% in plasma-levels of cAEDs in a patient matters and confounds the assignment of treatment effect to the test agent. Except when a PK interaction can be excluded based on separate PK studies the current text applies.
140-142	3	**Comments:** "*Once the efficacy of the new compound in combination with others has been determined and approved, it is important to evaluate the efficacy of the product in the monotherapy setting when given alone."* Waiting to start monotherpay trials until after the add-on therapy indication has been approved will cause significant delays in development of the AED and ultimately to its availability to the patient. It should be acceptable to initiate monotherapy trial after one controlled add-on trial has shown efficacy. **Proposed change:** "*Once the efficacy of the new compound in combination with others has been determined ~~and approved~~, it is important to evaluate the efficacy of the product in the monotherapy setting when given alone.*	Accepted. See also general comments stake holder 2, first bullet point.

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163-167 426-427	3	**Comments: "***Dose-response relationships from add –on studies in refractory patients may not be applicable to use in monotherapy. This is not only due to pharmacodynamic and pharmacokinetic interactions, but also the fact that most (newly) diagnosed patients have milder, more responsive forms of epilepsy. Therefore dose finding studies may have to be conducted separately in monotherapy settings."* *"Dose finding studies may have to be conducted in monotherapy settings (see section 4.2.3 Dosage)."* Due to the very low frequency of seizures in the newly diagnosed population, it would be challenging to carry out dose findings studies in monotherapy setting. In addition, once an effective dose range has been established for an AED, the ethical basis for using a lower dose in the population entering the monotherapy trials is questionable.	Partly accepted. Dose finding studies need to be conducted in monotherapy settings. However, it is considered acceptable to evaluate dose response relationship in the confirmatory monotherapy studies i.e. by a protocolised titration schedule where titration depends on treatment response (see Brodie MJ et al., Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology. 2007 Feb 6;68(6):402-8). This is clarified in section 4.5.5.3 heading monotherapy: *Dose finding studies may have to be conducted in monotherapy settings (see section 4.2.3 Dosage). A possible option for evaluating the dose response relationship would be a protocolised titration schedule where the up titration depends on treatment response.*
165	3	**Comments:** By definition newly diagnosed patients need not have milder forms of epilepsy. The difference is that the percentage of responders is naturally higher. Rewording should reflect that. The phrase assumes that there is a biological difference in epileptogenesis that relates to treatment responsiveness, whereas there are other variables that can influence response e.g. CNS penetration, metabolism of drug, etc. **Proposed change:** *Dose-response relationships from add-on studies in refractory patients may not be applicable to use in monotherapy. This may be not only due to pharmacodynamic and pharmacokinetic interactions, but also to the fact that* ***in*** *most (newly) diagnosed patient****s*** ***groups the percentage of responders is higher*** ~~***have milder, more responsive forms of epilepsy***~~*. Therefore dose finding may have to be conducted separately in monotherapy settings.*	Partly accepted, the text is adapted: *Dose-response relationships from add-on studies in refractory patients may not be applicable to use in monotherapy. This may be not only due to pharmacodynamic and pharmacokinetic interactions, but also to the fact that most (newly) diagnosed patient****s have*** ~~milder~~***, more responsive forms of epilepsy****. Therefore dose finding may have to be conducted separately in monotherapy settings.*

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168	3	**Comments:** Specific guidance should be provided for the development of drugs in epileptic encephalopathies. Given the large unmet need and the grim prognosis for these conditions, there could be a case for modifying the safety and efficacy criteria to allow for faster development of effective AEDs.	**Comments:** This is covered by the remark that *Compounds could be effective in age-dependent seizures/epilepsy syndromes but may be ineffective in adult seizure types. Therefore, developmental plans in these conditions may start at the same time in children (exploratory) and adults.*
169	3	**Comments:** *"Half of the epilepsies begin before the age of 20, and one fourth of these are intractable, having severe social and cognitive consequences."* It is recommended to adapt the statement to before the age of 18, which defines the paediatric population.	**Accepted** for pragmatic reasons
182-183	3	**Comments: "***In the very young children (e.g. 1 months -4 year), once efficacy has been shown in the elderly paediatric population, short term vEEG monitored trials may be sufficient."* Short term video monitoring would not be meaningful in testing an AED with a long titration (4 weeks or longer). In this case, an alternative design, such as randomized withdrawal, is needed. **Proposed change: "**In the very young children (e.g. 1 months -4 year), once efficacy has been shown in the elderly paediatric population, short term vEEG monitored trials may be sufficient. **However, when the test drug has a long titration (4 weeks or longer), the value of short term video monitoring will be limited. Hence, alternative design, such as randomized withdrawal, could also be considered**."	**Not accepted** This is not the point, the point is that provided there is evidence of efficacy in an elderly paediatric population, for the very young a vEEG based primary endpoint would be acceptable. For AEDs with a long titration this is not different as a vEEG based primary endpoint can be monitored in the maintenance phase.
187	3	**Comments:** It is stated that: *"Sufficient experience needs to be gained in these populations before a new medicinal product may be registered for these indications in children."* which is rather vague. **Proposed change:** Please specify / describe what is meant by sufficient experience.	The process is described in the paragraphs that follow.
After Line	3	**Comments:** It may be appropriate to include patients > 65 years of age who have suffered from epilepsy for years (i.e. as younger adults) in studies along with young adults.	**Comments:** This is covered by lines 226-229: An adequate number of geriatric patients should be included in the Phase III

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234			data base. A distinction may be made between elderly patients, who may have suffered from epilepsy for years or who developed epilepsy recently due to an underlying disease as response is different.
235 ff	3	**Comments:** The standard add-on trial design using reduction in seizure frequency and responder rate as primary outcome measures is presented as the only acceptable design for a pivotal trial. **Proposed change:** Please consider including a discussion on alternative trial designs, as e.g. mentioned in section 4.5.5.2. (time to nth seizure), that would be acceptable in this regard.	**Not accepted.** As stated earlier the time to nth seizure is not considered a good primary endpoint in confirmatory add-on studies. The reason is that in refractory epilepsy seizures appear in clusters, patients are sensitive to change in treatment (i.e. seizures are more frequent at the start of treatment) and need a stabilisation period. Hence time to nth seizure is not considered a good primary endpoint in confirmatory add-on studies.
249	3	**Comments:** *"in newly or recently diagnosed patients, the primary efficacy variable should be based on the proportion of patients remaining seizure free for at least six months (excluding the dose escalation period)…"* Seizure free is a very hard endpoint. Percentage of reduction in seizures is preferable, especially for exploratory Ph2 trials. One year duration is too long for POC studies. **Proposed change:** *"in newly or recently diagnosed patients, the primary efficacy variable should be based on the proportion of patients* ***with a clinically meaningful, predefined percent reduction in seizures*** ~~***remaining seizure free***~~ *for at least six months (excluding the dose escalation period)"…*	**Not accepted.** A monotherapy therapy indication should be based on freedom of seizures. It is acknowledged that an individual patient with refractory epilepsy, whose level of seizure control does not change by adding a second AED, may remain on monotherapy but this is clinical practice/patient management, not an indication. Likewise in conversion to monotherapy studies for an individual patient it may turn out that the level of seizure control remains the same on monotherapy as compared to combination therapy which would justify monotherapy in that particular patient. Again this is not considered an indication but clinical practice/patient management. Such information might be informative for patient management and therefore might be mentioned in the SPC but can not support a monotherapy indication. This is already covered in the guidance.
268	3	**Comments:** *"EEG pattern according to specific syndromes (i.e. Continuous Spike-Waves in Slow Sleep in children)"* Only when this is modifiable by AED – some situations have clinical	**Not accepted.** This is implicit as this variable is mentioned as a potential secondary endpoint i.e. providing supportive evidence for efficacy.

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		efficacy w/o modification. **Proposed change:** *"EEG pattern according to specific syndromes (i.e. Continuous Spike-Waves in Slow Sleep in children)**, only when this is modifiable by AED (some situations have clinical efficacy with or without modification).**"*	No changes are deemed necessary.
279-280	3	**Comments**: "*The analysis of efficacy should be based on the period when patients are established on a fixed-dose of either of the study product or placebo/comparator i.e. maintenance dose*." The above sentence is confusing as it implies that the analysis of efficacy should exclude patients who dropped out of the trial(s) during the titration phase which is against the ITT principle referred to in ICHE9. **Proposed change:** "*The analysis of efficacy should be based on **the ITT principle as referred in ICHE9 and focus** on the period when patients are established on a fixed dose of either the study product or placebo/comparator i.e. maintenance dose".*	**Accepted.** Changed accordingly.
316-320	3	**Comments**: "*The pharmacological effects on some parameters, such as cognition and/or memory and/or learning and/or sleep and/or psychological function and/or reaction time, should be studied in healthy volunteers, the general patient population and especially in children and elderly. Studies should include a positive control arm. Neuropsychological tests known to be sensitive to sedative / CNS depressive effects should be applied*." Regarding AEDs it is not clear what would constitute a "positive control". Many different tests are used in studies assessing the pharmacological effects of an AED on parameters such as cognition and/or memory and/or learning and/or sleep and/or psychological function and/or reaction time and if the product is shown to have an effect on one test, it may not be the case on another test. Hence, a "positive control" could be considered but it might not provide the right assay sensitivity for the cognitive profile specific to AED being tested. **Proposed change:** "*The pharmacological effects on some parameters, such*	**Not accepted.** The presence of a positive control is mandatory for assay sensitivity. It is acknowledged that there might be no universal positive control that covers all items. However depending on the main objective of the study a positive control may be chosen. It is not expected that all these factors can be evaluated in an all in one study.

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		as cognition and/or memory and/or learning and/or sleep and/or psychological function and/or reaction time, should be studied in healthy volunteers, the general patient population and especially in children and elderly. ***Due to the multiplicity of elements of the above listed parameters, studies may need to*** *include a positive control arm* ***when appropriate****. Neuropsychological tests known to be sensitive to sedative/CNS depressive effects should be applied.*"	
338	3	**Comments**: Given that certain diseases occur at higher rates in certain epilepsy syndromes, interactions with commonly used drugs may be appropriate. For example, methylphenidate (ADHD).	**Comment** This is agreed but considered covered by the last sentence of section 4.5.4 i.e. *Also the potential pharmaco-dynamic interactions with alcohol and CNS active products should be investigated*.
347	3	**Comments:** *"Potential interactions with contraceptive pill must be determined."* As some syndromes are specific for children or the elderly, it may not always be necessary. **Proposed Change:** *"Potential interactions with oral contraceptives must be determined****, if the AED is to be used in young adults or adolescents****."*	**Not accepted.** Children who successfully use an AED for a child specific syndrome may use this agent still when they become adolescents / adults.
460-462		**Comments**: "*For absences short term randomised placebo controlled withdrawal trials with EEG monitoring endpoints may be considered as proof of concept studies. It should be supplemented by long term randomised efficacy studies monitoring clinically and EEG freedom of absences."* There is an ethical issue of continuing the exposure to placebo over a long period of time during the long term randomised efficacy studies. Once efficacy has been established with randomized withdrawal, it should be acceptable, in the case of absence epilepsy, to allow continued treatment in an open label study with maintenance of effect verified over time with objective repeat EEG monitoring. **Proposed change:** "*For absences short term randomised placebo*	**Point taken and clarified.** It is acknowledged that long term exposure to placebo may not be justified. If a product is developed for absences, long term efficacy and safety data are needed. As long as there are good escape criteria a long term placebo controlled study, or randomised withdrawal study in absences is not considered unethical. This is clarified in the guidance.

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		controlled withdrawal trials with EEG monitoring endpoints may be considered as proof of concept studies. ~~***It should be supplemented by long term randomised efficacy studies monitoring clinically and EEG freedom of absences.***~~ ***Once complete seizure control has been demonstrated with EEG monitoring in a short term placebo control trial, it should be acceptable to allow continued treatment in an open label study with maintenance of effect verified over time with repeat EEG monitoring.****"*	
494-499	3	**Comments:** *"Data concerning potential withdrawal and / or rebound effects should be generated. A carefully monitored withdrawal evaluation should be performed in the add-on / monotherapy studies when the test agent and placebo are withdrawn."* Typically in the epilepsy trials the only patients who prematurely discontinue from the studied AED are those who did not show efficacy or have an adverse events: It would not be appropriate to complicate a primary study with a secondary process exploring different withdrawal rates. Too rapid a withdrawal of any AED is known to cause seizure exacerbation and thus AEDs are routinely discontinued by gradual withdrawal with the intent of avoiding precipitation of withdrawal seizures. The large majority of patients in placebo-controlled trials in epilepsy continue treatment by converting to open-label treatment.	**Not accepted.** This is a safety issue, not an efficacy issue. Patients where the product is withdrawn should be evaluated carefully for AEs in order to assess the occurrence of withdrawal symptoms or rebound. When performed in a blind manner the difference in AEs incidence during withdrawal is informative for agent related/non-agent related withdrawal events.
511-514	3	**Comments:** *"Long term comparative observational studies in children are of great potential interest children in order to disentangle long term effects of the disease and the potential undesirable effects of the medicinal products on e.g. cognitive functions. The design of the longitudinal studies will need to take into account the influence of age on cognition."* The cognitive capacities are affected by both the age of the patient and the underlying disease. Hence, this factor should also be taken into account in the design of the longitudinal studies. **Proposed change:** *"Long term comparative observational studies in children are of great potential interest children in order to disentangle long term effects of the disease and the potential undesirable effects of the*	**Accepted**

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		medicinal products on e.g. cognitive functions. The design of the longitudinal studies will need to take into account the influence of age ***and underlying disease*** *on cognition."*	
532	3	**Comments:** *"The development of non-oral formulations is recommended."* Whilst EFPIA is pleased to see this in writing, please consider discussion of some general principles relevant to alternate formulation development for AEDs. For instance, most formulations are approved on BE for Cmax and AUC. For AEDs, Cmin is also relevant and these general principles should be stated.	**Not accepted.** Bio-equivalence is not at the scope of this document. Referred is to the upcoming revision of the bioequivalence guidance.