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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

Agreed by CNS Working Party	June 2016
Adopted by CHMP for release for consultation	13 October 2016
Start of public consultation	25 October2016
End of consultation (deadline for comments)	31 January 2017

The proposed guideline will replace the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr).

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

Keywords	Seizures, epilepsy, anti-epileptic agents.

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1. Introduction

Epilepsy is a neurological disorder characterised by recurrent spontaneous/unprovoked seizures as the most dominant feature. The prevalence is estimated at 5-8 per 1000 subjects. Once diagnosed epilepsy is a life-long condition which has a major physical, psychological and social impact on patients. The clinical expression of epilepsy has a high variability depending on seizure types, epileptic syndromes, age, prognosis and response to treatment.

The current Guideline (CHMP/EWP/566/98 Rev.2/Corr) came into effect in August 2010. Recently a number of scientific advice procedures and several Paediatric Investigation Plans including modifications have been conducted for development programs on medicinal products for treatment of epilepsy indicating that there is a need for revision to further clarify the guidance provided.

2. Problem statement

Anti-epileptic agents may have different spectra of efficacy i.e. some anti-epileptics have a broad spectrum of efficacy whereas for others efficacy is limited to a specific seizure type. Data regarding efficacy and safety in various seizure types are therefore needed. Further, in epilepsy syndromes, it is important to know in which seizure types a product is effective and in which seizure types it is not effective or even harmful.

Hence, ideally, the clinical development plan of medicinal products intended for epilepsy treatment includes add-on studies, monotherapy studies, studies in children, and studies in epileptic syndromes and seizure types.

Most new anti-epileptic agents are initially developed and approved for the treatment of partial-onset seizures with or without generalised seizures as add-on to existing anti-epileptic treatment, in the adult population. Subsequent evaluation in e.g. other seizure types, epileptic syndromes, in children and the elderly or as monotherapy is often delayed. Preferably, the evaluation of the efficacy spectrum should continue and be started as early as the development of the medicinal product allows.

The need for evaluating the full efficacy spectrum of newly developed anti-epileptic agents should be highlighted and the way to foster further development needs to be re-visited. Also the guideline may be adapted according to the revised and ongoing terminology and classification of seizures and seizure syndromes (Engel 2006; Berg et al., 2010; Scheffer et al., 2016).

3. Discussion (on the problem statement)

The following critical aspects should be discussed in the update of the guideline:

Add-on studies

- Revision of the study design in the add-on setting e.g. validity and acceptability of a time to event approach as alternative endpoint and consequences for duration of the studies.
- Need and design of active comparative studies in the add-on setting.

Monotherapy studies

- Clarification of the type and breadth of evidence needed to support a monotherapy claim, i.e. study design (i.e. switching from one monotherapy to another), patient population, etc.

Special populations

- To which extent the results of adult studies can be extrapolated to children, i.e. for which conditions separate studies in children are required, under which conditions extrapolation from the results of adult studies may be possible and which data needs to be generated to support the extrapolation.
- Need for sufficient data in the elderly with newly diagnosed epilepsy as the benefit/risk profile may be different considering that the effect size may be smaller and subjects may be more sensitive to CNS adverse events.

Specific seizure types/epileptic syndromes

- Inclusion of status epilepticus section.
- Inclusion of neonatal seizures section.
- Need for separate studies and study design in epileptic syndromes and seizure types.

Miscellaneous

- Whether the revised classification of seizures and seizure syndromes is sufficiently established to include in the guideline.

4. Recommendation

The CNS Working Party recommends drafting a revision of the guideline on the clinical investigation of medicinal products for the treatment of epileptic disorder (CHMP/EWP/566/98 Rev.2/Corr) in line with the critical aspects discussed above.

5. Proposed timetable

It is planned to release for consultation the concept paper in Q4 2016 and a draft revised guideline document in 2017.

6. Resource requirements for preparation

The preparation of this guideline revision will involve the CNS Working Party and Paediatric Committee (PDCO). It is also planned to discuss the draft revision with the Scientific Advice Working Party and other relevant Working Parties and Committees.

7. Impact assessment (anticipated)

It is aimed that the guideline revision will be helpful to achieve consensus in the evaluation of antiepileptic agents by regulatory authorities in the European Union. Furthermore, it is expected, that the guideline revision will provide further guidance with respect to methodology, assessment tools and clinically relevant outcomes in epilepsy and thus would improve the quality and comparability of development programs for this therapeutic area by pharmaceutical companies.

8. Interested parties

Interested parties include learned societies and academia [e.g. International League Against Epilepsy (ILAE), European Neurological Society (ENS), pharmaceutical industry (e.g. EFPIA and others), the International Neonatal Consortium (ICH) and other regulatory agencies.

9. References to literature, guidelines, etc.

Note for guidance on clinical investigation of medicinal products in treatment of epileptic disorder http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500070043

Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004): http://www.emea.europa.eu/pdfs/human/regaffair/2414304en.pdf

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