EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 July 2010
CHMP/EWP/566/98 Rev.2/Corr
Committee for medicinal products for human use

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders

DISCUSSION AT THE EFFICACY WORKING PARTY	April 1998/September 1999
TRANSMISSION TO CHMP	October 1999
RELEASE FOR CONSULTATION	October 1999
DEADLINE FOR COMMENTS	April 2000
RE-SUBMISSION TO THE EWP	September 2000
ADOPTION BY CHMP	November 2000
DATE FOR COMING INTO OPERATION	May 2001
DRAFT REV. 2 AGREE D BY EFFICACY WORKING PARTY	January 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION REV. 2	January 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	July 2009
REV. 2 AGREED BY EFFICACY WORKING PARTY	January 2010
ADOPTION BY CHMP REV. 2	January 2010
DATE FOR COMING INTO EFFECT	August 2010
CORRIGENDUM	July 2010

This guideline replaces Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders CHMP/EWP/566/98 Rev. 1

KEYWORDS	Epilepsy, seizures, anti-epileptic agents

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Table of contents

Executive summary

The present document is a second revision of the existing guideline. It should be considered as general guidance on the development of medicinal products for the treatment of epileptic disorders and should be read in conjunction with other EMEA and ICH guidelines, which may apply to these conditions and patient populations.

The clinical development plan of anti-epileptic agents in partial epilepsy in the add-on setting is well-established. Current revision pays more attention to epileptic syndromes, need for studies in the paediatric population, need for monotherapy studies and other special cases.

1. Introduction (background)

Epilepsy which is defined by the recurrence of spontaneous/unprovoked seizures - i.e. seizures not provoked by transient systemic, metabolic or toxic disorders - constitutes a vast ensemble of diverse clinical situations which differ by age of onset, type of seizures (only one or several type(s) in an individual patient), aetiological background, resulting handicap, prognosis and response to treatment.

More than 50 million adults and children suffer from epilepsy world-wide. The two highest peaks of incidence are in children and in the elderly population (above 65 years). Prevalence estimates of epilepsy in the total population vary from 4 to 8 per l000 subjects.

Clinical recurrent seizures are the primary marker of the condition. They are of several types as classified in the International Classification of Epileptic Seizures, mainly: generalised onset, focal onset, which may become secondarily generalised and unclassified seizures.[1]

In addition to the type of the seizures, electroencephalographic monitoring allows a definition of specific epilepsy syndromes which are listed in the International Classification of Epilepsies and Epilepsy syndromes. Many are age-dependent. Brain imaging may add to the aetiological diagnosis.

Focal onset seizures, related to a focal brain dysfunction, occur in approximately 60 % of cases and include symptomatic (lesion defined), cryptogenic (no lesion detected but probably symptomatic), and idiopathic forms. Generalised seizures represent approximately 30 % of cases. They occur often in a non-lesional and genetic context; other cases are symptomatic or cryptogenic. In the remaining 10%, the classification is uncertain.

The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation. That is the case for the most frequent paediatric idiopathic partial epilepsies (e.g. benign epilepsy with centrotemporal spikes) and for epilepsy syndromes (e.g. West syndrome/Infantile spasms, Dravet syndrome, Lennox-Gastaut-syndrome, myoclonic-astatic epilepsy and Continuous Slow Waves during Sleep). Another major difference in paediatric and adult epilepsies is that some syndromes carry a grave prognosis for cognitive outcome due to the impact of epilepsy, the so-called epileptic encephalopathies. Focal non-idiopathic epilepsies in childhood may also have an important impact on cognitive development if not treated early and appropriately. Some age-dependent epilepsy syndromes do not persist in adulthood (e.g. West syndrome or Benign epilepsy with centrotemporal spikes).

Antiepileptic drugs (AEDs) are the main treatment option. Approximately 60% of newly diagnosed patients are seizure-free on a single AED (monotherapy). An additional 10%-20% achieve freedom of seizure with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition many patients suffer from significant adverse effects.

New AEDs have been developed in the last two decades with the aim of improving the benefit/ risk balance of existing AED therapy. Traditionally newer AEDs have all been evaluated in add-on studies in patients refractory to previous therapies. Typically, in these studies 20 to 40 percent of patients with focal epilepsy obtain a 50% or greater reduction in the frequency of seizures, compared to 2 to 25% of patients given placebo. However, very few patients become seizure-free, which is the ultimate goal. Differences exist in efficacy and tolerability profile depending on seizure

[1] The classification of epilepsies and seizure types is under revision (ILAE - International League Against Epilepsy). This includes a likely substitution of the term "partial" by "focal"as partial implies incompleteness.

type and epilepsy syndrome. A given compound may for instance improve one type of epilepsy/seizure type but worsen another one.

The AEDs may have different spectra of efficacy:

- In terms of seizure types, most AEDs are effective against focal seizures with or without secondary generalisation. Certain AEDs show a broader spectrum of efficacy, including focal and many generalised seizure types. For others, efficacy is limited to one or two seizure types, for instance absence seizures only.
- In terms of epilepsy syndromes, it is important to know on the one hand which (and how) seizure types associated with a given syndrome are affected by a specific medication. On the other hand, a given seizure type may not show the same responsiveness in the various syndromes, particularly in certain age-dependent conditions. Moreover, some AEDs may exacerbate some seizure types while being efficacious in coexisting seizure types.

The knowledge of a new drug's spectrum of effectiveness is important when considering trials in newly diagnosed patients. For many patients the precise syndrome and seizure types may not have been defined at the time of treatment initiation, and therefore, they can only be included when the test drug exhibits a broad efficacy spectrum.

Of note for most anti-epileptic agents the knowledge of their spectrum of effectiveness is limited considering that most clinical studies were performed in patients with focal seizures with or without secondary generalisation. Other seizure types have rarely been investigated in randomised controlled trials. Moreover, inclusion of patients in trials has usually been based on seizure type and not on epilepsy syndrome although the latter has a prognostic value.

2. Scope

The scope of this document is restricted to treatment of seizures in epileptic disorder although there are some remarks concerning non-seizure features of epilepsy syndromes. The guideline is intended to assist applicants in the interpretation with respect to specific problems presented by products in epileptic disorders.

3. Legal basis

These notes are intended to provide guidance for the evaluation of products in the treatment of epileptic disorders. They should be read in conjunction with the Directive 2001/83/EC and current and future EC and ICH guidelines, especially those on:

- ICH E7 CPMP/ICH/378/05 Studies in support of special populations.
- ICH E1 CPMP/ICH/375/95 The extent of population exposure to assess clinical safety for products intended for long-term treatment in non life threatening conditions.
- ICH-E8 CPMP/ICH/291/95 General considerations for clinical trials.
- ICH-E9 CPMP/ICH/363/96 Statistical principles for clinical trials.
- ICH E11 CPMP/ICH/2711/99 Clinical Investigation of Medicinal Products in the Paediatric Population
- EC/87/013 Pharmacokinetic studies in man.
- EC/90/022 Clinical testing of prolonged action forms, with special reference to Extended Release Forms
- EC/93/014 Dose response information to support product authorisation.
- CPMP/EWP/462/95 Clinical investigation of medicinal products in children.
- CPMP/EWP/83561/2005 Guideline on clinical trials in small populations.
- CPMP/EWP/560/95 Note for guidance on the investigation of interactions.
- CPMP/ICH/379/95 ICH Topic E 7 Studies in Support of Special Populations: Geriatrics

- CPMP/EWP/2330/99 Points to consider on validity and interpretation of meta-analysis, and one pivotal study

4. Main text

4.1 Selection of the seizure type and epilepsy syndrome

Usually, focal seizures in adults represent the first target, since they are the most frequent, and a substantial percentage of them are not well controlled. Efficacy needs to be evaluated for all focal seizures and secondary generalised seizures separately.

It is desirable to explore efficacy in other epilepsy syndromes/seizure types. Preclinical data, particularly the mode(s) of action and the results on experimental models, may be helpful to build hypotheses on the agent's potential in clinical situations although available animal models do not cover the range of seizure types/epilepsy syndromes observed in humans.

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, Dravet syndrome, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy, etc...). Addressing these epilepsy syndromes requires analysis of the efficacy of an agent on the individual seizure types present in the given condition, e.g.: spasms, generalised tonic-clonic, absences, myoclonic, tonic or atonic seizures (see section 4.2.4).

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 syndrome) or syndrome based. In the seizure type based approach the syndromes should be carefully characterised for further evaluation (see 4.4. statistical analysis).

Global antiepileptic efficacy of an agent in an epilepsy syndrome can only be claimed when efficacy has been shown for all seizure types of the syndrome or at least for the most severe and “invalidating” seizure types of the syndrome without any aggravation of the other seizure types. The impact upon the other clinical features of the syndrome, EEG pattern or cognitive outcome for example may also be addressed and will need to be addressed when claims are intended. Where an effect on the encephalopathic process itself is claimed, efficacy should be shown for cognition, communication, EEG and not only on seizure frequency.

4.2 Specificity of clinical trials in epilepsy

4.2.1 Add-on studies

The initial evaluation process for a new antiepileptic drug involves determination of its efficacy in reducing the frequency of seizures in patients who continue to have seizures despite therapy with an adequate dosage of appropriate drug(s).

Add-on studies however do not allow the full assessment of the anti-epileptic effect of a new compound. Interferences between the concomitant anti-epileptic products and the test product are common in add-on studies for various reasons (e.g. pharmacokinetic interactions, pharmacodynamic interactions and additive toxic effects). Therefore it may be difficult to disentangle the relative contribution of these changes superimposed on the true drug effect. The interaction potential should be taken into account regarding both directions, concomitant treatment versus test drug and test drug versus concomitant, pre-existing AED treatment.

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. Plasma monitoring of concomitant AEDs and test agent is required to exclude interference of PK interaction with the treatment effect. If it turns out to be impossible to keep the concomitant medication constant during the maintenance period, for instance due to additive adverse events, the efficacy analysis plan should consider in advance how to deal with patients with and without dose modifications of their concomitant AED products.

Also for safety it is often difficult to determine whether an adverse event can be attributed to the test-product, to changes in plasma concentration of the concomitant anti-epileptic products/active metabolites, a pharmacodynamic effect or to an additive toxic effect.

Once the efficacy of the new compound in combination with others has been determined, it is important to evaluate the efficacy of the product in the monotherapy setting when given alone.

4.2.2 Monotherapy studies

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 assessment of efficacy in this setting requires a randomised and controlled trial of sufficient duration (see section 4.5.5.3.) The duration of the trial may be different depending on the seizure type and epilepsy syndrome.

For focal onset seizures monotherapy in patients undergoing presurgical evaluation for refractory focal epilepsy may generate some short-term efficacy data which however are not relevant for longer term clinical use (see section 4.5.5.2).

Some add-on studies may be designed to generate data on conversion to monotherapy in patients with multiple-drug treatment. Such data cannot support a monotherapy claim but the availability of conversion to monotherapy data, as well the lack of these data, is informative and will be mentioned in the SPC.

4.2.3 Dosage

The dossier should contain fixed dose-finding studies in order to justify the dosages used in confirmatory clinical trials and dose recommendation in the SPC. The dossier should contain sufficient data on the plasma concentration of the new product (and active metabolites) and its relation to efficacy and safety.

In clinical practice, in add-on as well as in monotherapy situations, it is custom to titrate a new anti-epileptic drug until an optimal effect is seen or until the maximal tolerated dose is reached or up to the maximal doses allowed. If the dosage schedule incorporates titration the additive value of increasing the dose to efficacy should be evaluated.

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 patients have milder, more responsive forms of epilepsy. Therefore dose finding studies may have to be conducted separately in monotherapy settings. See section 4.5.5.3.

4.2.4 Development of AEDs in children

Half of the epilepsies begin before the age of 18 and one fourth of these are intractable, having severe social and cognitive consequences. Epilepsy in childhood differs from epilepsy in adults especially by the occurrence of seizures in a structurally and functionally maturing brain, the occurrence of seizure/epilepsy types not seen in adults and the occurrence of seizures as part of age dependent epilepsy syndromes. An epilepsy syndrome may persist or change in characteristics over time. Moreover, epilepsy may affect the normal development of children in the broadest sense.

Two situations can be described:

1) Focal epilepsies especially cryptogenic and symptomatic, and idiopathic generalised epilepsies, with absences, myoclonic and/or generalised convulsive seizures, where the efficacy of AEDs seems to be comparable in childhood and adulthood. Focal epilepsies in children older than 4 years old have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established.

In the very young children (i.e. 1 month – less than 4 years), once efficacy has been shown in the older paediatric population, short term assessment of response by using video EEG monitoring may be sufficient.

2) The epilepsies/seizure types which are specific to children (e.g. West syndrome, Dravet syndrome, myoclonic-astatic epilepsy, Lennox Gastaut Syndrome and Continuous Spike-Wave in Slow Sleep syndromes):

Sufficient experience needs to be gained in these populations before a new medicinal product may be registered for these indications in children. Compounds could be effective in age-dependent seizures/epilepsy syndromes but may be ineffective in seizure types occurring in adults. The minimal study duration should be discussed according to the specific characteristics of epilepsy syndromes as well as the outcome criteria.

Because not all of these conditions are likely to benefit from a new product, identifying those that may be candidates is a key point. It is recommended to enter these patients in exploratory add-on studies as soon as the dose for children has been established. These studies would ideally be large pilot studies including all types of paediatric epilepsy syndromes (whether common with adults or not), stratified by syndromes and/or age bands, they would permit to obtain initial information on population pharmacokinetics, and preliminary data on safety and efficacy. Results from such a trial should be interpreted with caution considering that multiple syndromes are being studied and hence that efficacy in any given syndrome may show particular promise by chance alone and has therefore to be confirmed by one or more randomised controlled trial for each indication pursued.

From the safety view point, a minimum of 100 children treated by the study drug should be followed for at least one year. Moreover short term and long-term studies should be designed to detect possible impact on brain development, learning, intelligence, growth, endocrine functions and puberty. Some of these studies may require continuation in the post marketing period. (See Guideline on clinical investigation of medicinal products in children (CPMP/EWP/462/95).

4.2.5 Development of AEDs in the elderly

The incidence and prevalence of epilepsy increases substantially after 65 years of age. Elderly patients who have suffered from epilepsy for years should be considered differently from those who developed epilepsy recently. Efficacy and safety of AED's in newly diagnosed elderly patients may be different from those in younger adults for the following reasons:

Predominance of symptomatic aetiologies: Alzheimer's disease or other neurodegenerative conditions, brain tumour, cerebrovascular accident;

an increased susceptibility to adverse effects associated with use of standard doses of drug, especially on cognitive functions, vigilance and cardiovascular system;

pharmacokinetic and/or pharmacodynamic interactions with other concomitant products frequently used in the elderly due to comorbidities.

Therefore it is important to determine whether or not the pharmacokinetic behaviour of the drug in elderly subjects is different from that in younger adults (see guideline ICH E7).

An adequate number of geriatric patients should be included in the Phase III data base. A distinction should be made between elderly patients, who may have suffered from epilepsy for years and those who developed epilepsy recently due to an underlying disease, as responses are different.

Safety, especially on cognitive function and on sedation in this age group should be evaluated. Interactions of the test product should also be assessed, especially with frequently used products in this age group where a PK/PD interaction is expected. Depending on the data, specific efficacy and safety trials in this population may be needed. The results, as well the lack of these data, are informative and will need to be mentioned in the SPC.

4.3 Assessment of efficacy

4.3.1 The assessment of efficacy should be based primarily upon seizure frequency / occurrence

In add-on therapy, the period over which seizure frequency is measured should be pre-defined (e.g. the number of seizures per 4 weeks). Two important variables should be specified in the protocol. The primary endpoint should dichotomise the data into responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency (e.g. a 50% reduction is commonly used). The other variable should be some parameterisation using the actual change in seizure frequency (See section 4.4).

In paediatric studies the endpoints are in principle the same as for adults although other responder definitions are acceptable where justified (e.g. days without myoclonic seizures in IGEs). These and the secondary variables should allow full investigation of the distribution of change in seizure frequency after treatment. In addition, potential exacerbation of seizures or appearance of new seizure types should be assessed (e.g.: by 25 % or more).

In monotherapy (adults and children)

a) 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). The trial should have a minimum duration of one year in order to assess safety and maintenance of efficacy.

b) in conversion to monotherapy a treatment retention time may be an acceptable primary outcome variable.

Secondary efficacy variables may concern:

c) In add-on designs: the proportion of seizure-free patients is a very important variable; the distribution of response (i.e. > 25% worsening, no-change -25%; 25%, by 25%-50%, improvement by 50%-75%, improvement > 75%) should also be assessed.

d) A treatment retention time, measuring the combination of failed efficacy and tolerability, enables to assess the global clinical effectiveness of the drug. The exit criteria defining failed efficacy (e.g.: nth seizure) should be justified by the applicant.

e) Seizure severity, including duration of seizure, warning symptoms or not, loss of consciousness, falls, injuries, post-ictal confusional state or neurological focal deficit, etc.

f) Dose / efficacy studies based on drug plasma concentration measurements.

g) Scales measuring social and working capacity, if validated.

h) An additional secondary endpoint may be a composite rating scale wherein seizure frequency, seizure types and adverse events are weighted and expressed in one score.

i) EEG pattern according to specific syndromes (i.e. Continuous Spike-Waves in Slow Sleep in children)

Such scales need a thorough validation.

4.3.2 Other methods to assess efficacy

The counts of clinical seizures represent the main marker of the expression of epileptic diseases, and thus of the efficacy of treatments. Usually seizure counts are recorded by the patient and/or care-giver. In cases of very frequent seizures, (e.g. absences) or seizures difficult to quantify clinically it is recommended to develop more precise tools of quantification of the seizure frequency such as quantitative EEG recordings or telemetry by video/EEG.

4.4 Statistical analyses

Reference is made to the ICH-E9 statistical principles for clinical trials.

The analysis of efficacy will usually be intended to demonstrate superiority based on the ITT principle as referred in ICHE9 and the period when patients are established on a fixed dose of either the study product or placebo/comparator i.e. the maintenance dose.

If the study population includes patients with unclassifiable seizures a careful follow-up of these patients should be made, and, if they can be classified later on, in a secondary analysis it should be evaluated if these patients have no influential impact on the outcome.

As the distribution of seizure frequencies are usually heavily skewed, careful consideration should be given to the parameterisation of the seizure frequencies and the choice of the primary analysis. Verification of any modelling assumptions (e.g. normality of the distribution for an ANOVA) should be provided.

The primary analysis of efficacy should be unadjusted except for factors used to stratify randomisation. Factors known to influence outcome such as aetiology, seizure type, baseline seizure frequency, seizure severity and epilepsy syndrome should be taken into account in supportive analyses. The use of concomitant anti-epileptic products should be summarised and the potential impact on efficacy evaluated and discussed.

For the evaluation of less frequent seizure types (generalized seizures), efficacy in epilepsy syndrome, difference in efficacy of seizures of symptomatic and cryptogenic aetiology, individual studies are not expected to have adequate statistical power to establish treatment effect. Efficacy in these seizures should be evaluated by a meta-analysis of individual studies. Such (meta) analysis is expected to be covered in a separate study protocol and statistical analysis plan in advance, including a plan to demonstrate homogeneity (consistency) of the effects observed across separate studies to establish the validity of a pooled analysis.

4.5 Strategy and steps of the development. Methodology of the clinical studies

4.5.1 Pre-clinical data

The neurobiological mode of action of the candidate antiepileptic drug may be important, since it may indicate in which seizure types and epilepsy syndromes the drug will be efficacious. It may be also predictive for the risk of certain adverse events. For instance some drugs have been specifically designed around a given mechanism: promoting GABA inhibition; others constitute the extension of a pre-existing family, with a more or less well-known preclinical profile. Other candidates which are the result of systematic screening may need identification of their mode(s) of action. The study of the efficacy profile should be done in several experimental models, including models of generalised epilepsies with absences. It is important to know if the drug in development displays anti-seizure activity only or if it has a potential for antiepileptogenesis as well.

In case of clinical development of antiepileptic drugs for all children, in particular for the age group below the age of 4 years, the potential neurotoxic effects of the agent in the developing rodent brain ought to be investigated.

4.5.2 Pharmacodynamic human data

There is no specific human pharmacodynamic model for studying anti-epileptic products. Consequently, as far as efficacy is concerned, the evidence which can be provided from pharmacodynamic studies is unclear. The photo-paroxysmal response on EEG or the study of effects on interictal EEG epileptic discharges may be considered however.

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.

Specific claims, e.g. psychostimulatory effects must be substantiated in controlled clinical trials especially designed for such a purpose, using both appropriate clinical and laboratory measures.

4.5.3 Pharmacokinetics

The pharmacokinetics of the new product should be thoroughly described. Absorption, bio-availability, protein binding, and route(s) of elimination (including metabolites and enzymes involved) should be characterised. These investigations are often closely related to those concerned with interactions (see section 4.2.1 and 4.5.5.3). The dossier should contain sufficient data on the plasma concentration of the new product (and active metabolites) with respect to efficacy and safety. This is in order to establish the reference range of the new agent and to evaluate the clinical significance of minor changes in the plasma concentration of the agent or its active metabolites. Plasma concentrations should therefore be checked at the time of the assessments of efficacy as well as at the time of significant undesirable effects.

In children the study of the influence of age and maturation on the pharmacokinetics is of special importance. It is important to limit the invasiveness of this type of experiment (e.g. drawing small blood samples, population approaches on sparse samples, minimising the number of samples and the number of patients recruited). The reliability and the precision of the estimates however, should not be compromised.

4.5.4 Interactions

Pharmacokinetic in vitro and in vivo interaction studies should be performed in accordance with the guideline on interactions (CHMP guideline), with special focus to the interaction between the test product and any anti-epileptic product given simultaneously in clinical practice.

The effect of the new anti-epileptic product on the pharmacokinetics of concomitant anti-epileptics to be used in the pivotal clinical studies should be known (and vice versa) before such studies start. Pharmacodynamic interactions expected to occur between the test product and any anti-epileptic product which is given simultaneously with the test product in clinical practice should be studied. See also section 4.2.1.

Potential interactions with the contraceptive pill must be determined. Also the potential pharmacodynamic interactions with alcohol and CNS active products should be investigated.

4.5.5 Methodology of clinical studies

4.5.5.1 Study population and selection of patients

Patients included in the clinical trials should be classified according to the International Classification of Seizures and International Classification of Epilepsies and Epilepsy syndromes.

For newly diagnosed patients, the seizure type, type of syndrome and aetiology should be well defined. If the study population includes patients with unclassifiable seizures at inclusion, a careful follow-up of these patients is recommended and, if they can be classified later on it should be checked that these patients have no impact on the outcome due to misclassification.

The inclusion and exclusion criteria in a trial should be such that the population is clearly defined and in accordance with the study objectives. The diagnostic criteria used should be mentioned in the protocol and justified by the company. Moreover, the seizure types studied must be clearly recognised by the subject who records the seizures (patient, relatives, and investigator). Training programmes for a reliable seizure recording are recommended.

4.5.5.2 Therapeutic exploratory studies

The purpose of this phase of the product development programme is to identify patients who may benefit from a new anti-epileptic product, to obtain initial information on safety and suitable therapeutic dose range and dosage regimen. These studies are also important for exploring the spectrum of efficacy of the test drug in a variety of seizure types and epilepsy syndromes. The designs of the exploratory studies should be sufficient to properly inform the decision of whether or not to proceed to confirmatory trials and, if so, the population and dose of experimental treatment to pursue.

The exploratory nature of this phase in the clinical development plan allows a variety of designs. Examples are randomised placebo-controlled parallel or cross-over studies, enrichment designs, controlled studies in patients with refractory epilepsy subjected to a pre-surgical evaluation programme, and open add-on studies among others.

In the exploratory studies a reduction in the frequency of seizures and/or the time to first or n^{th} seizure may constitute the primary criteria of efficacy. Changes in seizure pattern should also be measured. Special attention should be given to quantifying an increase in seizure frequency and the appearance of new seizure types.

Psychomotor performance should be recorded systematically in some studies, irrespective of whether or not it correlates with the anti-epileptic potential of the substance.

4.5.5.3 Therapeutic confirmatory studies

Add on studies

The pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design. As more anti-epileptics are approved for the add-on indication, comparative trials may be considered.

Efficacy endpoints should be based on the changes in seizure frequency between the treatment maintenance phase and the baseline period (see section 4.4). Efficacy should be evaluated primarily for all focal onset seizures. Secondarily generalized tonic clonic seizures should be analysed separately. This also may be done by a meta-analysis of several add-on studies if predefined. See section 4.4. Statistical analysis.

The study should include a baseline period, a titration period (when applicable), and a maintenance period. All changes in dosage of the test product and concomitant anti-epileptic products should be documented in detail.

Baseline period

Baseline seizure frequency should be sufficiently high and duration of baseline should be sufficiently long to detect decreases as well as increases in seizure frequency in the treatment phase. The spontaneous fluctuations in the frequency of epileptic seizures must be taken into account; for instance, patients in whom baseline seizure frequency differs substantially from their usual seizure frequency should not be included.

Concomitant anti-epileptic medication should be optimised and stable before the baseline is started. If a concomitant anti-epileptic product is stopped before the start of the trial, the washout period should be sufficient long to avoid PK/PD carry-over effects.

Titration period

In the titration period (when applicable) the dose of the test product may be increased up to the maximal tolerated doses or maximal predefined doses. The criteria of judgement of an optimal effect and intolerance should be carefully and unambiguously defined in the study protocol.

Dose adaptations of the concomitant anti-epileptic products may also be necessary due to interactions. It should be pre-defined in the protocol and monitored by plasma concentrations.

At the end of the titration period, patients should be on a stable dose, either the individually determined optimal dose or the maximal pre-defined dose.

It is recommended to study more than one dose arm in order to establish the lower end of the clinically effective dose range as well as the optimal effective dose. In these studies, patients should be titrated to a fixed dose arm which is subsequently maintained during the whole maintenance period. See section 4.2.3 Dosage.

In the add-on setting the determination of plasma concentrations is needed in order to verify whether the effect / adverse events observed may be attributed to the test agent or may also be explained by changes in plasma concentrations of the concomitant anti-epileptic agents.

Maintenance period

In the maintenance period the test and concomitant products should be kept stable whenever possible. The maintenance period should last at least 12 weeks in order to establish that efficacy is not short lasting.

Data concerning potential withdrawal and / or rebound effects should be generated. See section 4.6 Safety Aspects.

Long-term data should be generated by continuation or extension of add-on studies in order to assess absence of tolerance on the long term and maintenance of safety. One year study duration is considered the minimum.

Monotherapy studies

a) In newly or recently diagnosed patients

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 protocolled titration schedule where the up titration depends on treatment response.

Monotherapy studies should be randomised, double-blind active controlled trials aiming to demonstrate at least a similar benefit/risk balance of the test product as compared to an acknowledged standard product at its optimal dose. Given differences in efficacy profile of AEDs it should be excluded that an inferior treatment or insufficient dose is used. In monotherapy studies assay sensitivity might be a problem. A stepwise fixed dose increments based on response may be an option to guarantee assay sensitivity. The non-inferiority margin will need to be justified by the applicant.

The primary endpoint should be the proportion of patients becoming seizure free (see section 4.3.1). Overall follow-up should be at least one year, for safety reasons and to verify that the proportion of patients remaining seizure-free is not below the expected rates in this population.

Alternative monotherapy studies such as randomised delayed start trials and/or placebo-controlled trials in subjects where there is uncertainty whether an anti-epileptic agent should be started may be considered.

Plasma level monitoring may also be useful for correlating plasma concentrations to efficacy and the occurrence of adverse events.

b) Conversion to monotherapy studies

Trials should be randomised and controlled. The choice of the control treatment should be justified by the applicant.

Such data cannot support a monotherapy indication as patients in conversion to monotherapy studies are not representative for patients receiving monotherapy i.e. newly or diagnosed patients who mostly have more responsive forms of epilepsy. Therefore, conversion to monotherapy studies may be considered proof of principle studies. However the availability of conversion to monotherapy data, as well the lack of these data, is informative for patient management and will be mentioned in the SPC.

4.5.5.4 Specific cases

The development of anti-epileptic agents for indications in epilepsy syndromes other than focal epilepsy is encouraged. However, as trial experience is rare, in general no specific recommendation can be made. Some comments are made with respect to specific epilepsy syndromes in children, absences and status epilepticus.

In specific epilepsy syndromes in children duration of the different phases of the trial, specific end-points, and small population trial designs and analysis should be discussed according to the characteristics of a given syndrome. See section 4.2.4.

For absence seizures 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 clinical and EEG freedom from absences.. This preferably should be a randomised placebo control parallel group study with escape criteria. It might be complemented by a randomised withdrawal phase to establish benefits of continued treatment or a separate randomised withdrawal study. In the long term open label safety studies maintenance of effect may be verified over time with repeat EEG monitoring.

With respect to neonatal seizures no specific recommendations can be given as studies in neonatal seizures are scarce i.e. there is not much experience. A CHMP scientific advice may be considered if a product is developed specifically for neonatal seizures. Studies in status epilepticus are rare. However in stage 1 status epilepticus comparative clinical trials are considered an option. For stage 2 and 3 add-on study designs may be considered.

Of note, if a product is exclusively developed for a specific condition more safety data need to be generated as compared to products where safety data in patients with other epileptic disorders already exist.

4.6 Safety aspects

4.6.1 General considerations

As for any other medicinal product, the occurrence of liver, blood and skin disorders should be carefully monitored and documented in detail. In the case of AEDs, special attention should be given to metabolic and endocrine function, and also to the following types of possible adverse events:

4.6.1.1 Exacerbation of seizures

There is an increased awareness that AEDs can sometimes worsen epileptic disorders and this should be taken into account in the design of clinical trials. Aggravation may consist in increased seizure frequency, often for specific seizure types (e.g. absence or myoclonic seizures), or appearance of new seizure types. Efforts should be made to identify the causal mechanism, such as inappropriate choice of the drug regarding the seizure types or the syndrome of the patient; spontaneous fluctuation of the condition; intoxication with or without over dosage; modification of concomitant therapy. In the absence of explanation, a paradoxical reaction (which is when an AED appears to exacerbate a type of seizure against which it is usually effective) might be considered. The potential for seizure worsening, and the seizure types and/or syndromes concerned, should be identified as early as possible in the drug development as it determines appropriate use of the product, i.e. it may have labelling consequences.

4.6.1.2 CNS adverse events

Special attention should be given to the occurrence or exacerbation of CNS adverse events (e. g. those involving cognition, thought processes, memory, lethargy, emotional and behavioural reactions, psychotic or depressive symptoms, suicidal behaviour/ideation, disturbances of gait, speech, coordination, or nystagmus). Specific positive claims in this respect have to be based on appropriate studies. In children cognitive function needs to be addressed in short term pharmacodynamic studies. See section 4.5.2.

Similarly, special attention should be given to the occurrence of rebound seizures and/or behavioural changes after the test product is tapered off. 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. A randomised withdrawal phase with a quick and slow taper off schedule for both placebo and active study arms in subjects who will stop treatment may be very informative.

Visual functions, including visual field defects, have to be clinically investigated. If problems in this area are to be expected, it is necessary to study systematically the visual function by using adequate ophthalmological procedures.

4.6.2 Long term safety

Manufacturers and investigators would be well-advised, irrespective of any legal obligation, to continue to study the test product after marketing in order to detect unusual effects, long-term adverse reactions, alterations in the therapeutic effect over a long period and/or non-predicted interactions, possible exacerbation of seizures and information on pregnancies in women exposed to the test product.

The total clinical experience must generally include data on a large and representative group of patients (see EC, Guideline on population exposure).

Long term comparative observational studies in children are of great potential interest in order to disentangle the long term effects of the disease and the potential undesirable effects of the product on development depending on the mechanism of action of the product. The design of these longitudinal studies will need to take into account the influence of age and underlying disease on cognition.

4.7 Conditions for registration

Overall, a stepwise approach can be envisaged:

An add-on indication may be granted on the basis of positive results of the confirmatory add-on trials. However the clinical development plan of an anti-epileptic agent is not considered complete in the absence of efficacy studies in monotherapy.

The monotherapy indication will be granted when the efficacy and safety of the test drug has been proven in newly or recently diagnosed patients. Other monotherapy situations will be supportive in this context i.e. monotherapy withdrawal studies may be considered proof of concept studies but can not replace the need for monotherapy studies to support a claim in newly diagnosed epilepsy.

Studies evaluating the pharmacological effects of some parameters, such as cognition and/or memory and/or learning and/or sleep and/or psychological function and/or reaction time will be needed in the application dossier.

REFERENCES (scientific and / or legal)

1. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001 Aug 30;345(9):631-7.
2. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R. Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003723.
3. Posner EB, Mohamed K, Marson AG. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003032. DOI: 10.1002/14651858.CD003032.p
4. Tudur Smith C, Marson AG, Williamson PR. Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. Cochrane Database of Systematic Reviews 2001, Issue 4. Art. No.: CD001769. DOI: 10.1002/14651858.CD001769.
5. Muller M, Marson AG, Williamson PR. Oxcarbazepine versus phenytoin monotherapy for epilepsy. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003615. DOI: 10.1002/14651858.CD003615.pub2
6. Jette N, Hemming K, Hutton JL, Marson AG. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD001417. DOI: 10.1002/14651858.CD001417.pub2.
7. Castillo S, Schmidt DB, White S. Oxcarbazepine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2000, Issue 3. Art. No.: CD002028.
8. Chaisewikul R, Privitera MD, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant localization related (partial) epilepsy. Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD001901.

9. Pereira J, Marson AG, Hutton JL. Tiagabine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2002, Issue 3. Art. No.: CD001908.
10. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. Gabapentin add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 1999, Issue 1. Art. No.: CD001415.
11. Michael B, Marson AG. Clobazam as an add-on in the management of refractory epilepsy. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD004154.
12. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD001770.
13. Chadwick DW, Marson AG. Zonisamide add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001416.
14. Ramaratnam S, Marson AG, Baker GA. Lamotrigine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD001909.
15. Lozsadi D, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD005612.
16. Epilepsie, Richtlijnen voor diagnostiek en behandeling, Samengesteld door de Nederlandse Vereniging voor Neurologie en de Nederlandse Liga tegen Epilepsie, Herziene, tweede versie, januari 2006, Werkgroep Richtlijnen Epilepsie.
17. Martk Manford, Practical Guide to Epilepsy, 2003 Butterworth/Heinemann ISBN 0-7506-4621-7 .
18. Mpimbaza A, Ndeezi G, et al. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial.Pediatrics. 2008 Jan;121(1):58-64.
19. Baysun S, Aydin OF, et al. A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures.Clin Pediatr (Phila). 2005 Nov-Dec;44(9):771-6.
20. McIntyre J, Robertson S , et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005 Jul 16-22;366(9481):205-10.
21. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet. 1999 Feb 20;353(9153):623-6.
22. Epilepsy: State-of-art in the diagnosis and treatment – basic. Teaching course 3 11th Congress the European Federation of Neurological Societies, Brussels, August 25-28, 2007.
23. Epilepsy: State-of-art in the diagnosis and treatment – advanced. Teaching course 3 11th Congress the European Federation of Neurological Societies, Brussels, August 25-28, 2007.
24. French J. Historical control withdrawal to monotherapy . Epilepsy Research , Volume 68, Issue 1 , Pages 74 – 77.
25. Sachdeo R. Monotherapy clinical trial design. Neurology. 2007 Dec 11;69(24 Suppl 3):S23-7. Review.
26. Martin J Brodie, Steven C Schachter and Patrick Kwan. Fast Facts: Epilepsy, 2005 3th edition ISBN 978-1-903734-30-8
27. Arroyo S, Perucca E. Translating monotherapy trials into clinical practice: a look into the abyss. Epilepsy Behav. 2003 Oct;4(5):457-63. Review.
28. Wirrell E, Camfield C, Camfield P, Dooley J. Prognostic significance of failure of the initial antiepileptic drug in children with absence epilepsy. Epilepsia. 2001 Jun;42(6):760-3
29. Beydoun A, Kutluay E. Conversion to monotherapy: clinical trials in patients with refractory partial seizures. Neurology. 2003 Jun 10;60(11 Suppl 4):S13-25. Review.
30. Mohanraj R, Brodie MJ. Measuring the efficacy of antiepileptic drugs. Seizure. 2003 Oct;12(7):413-43. Review.
31. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006 Jul;47(7):1094-120. Review.

32. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Ninth Eilat Conference (EILAT IX). Epilepsy Res. 2009 Jan;83(1):1-43. Epub 2008 Nov 12.
33. Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Perucca E, Tomson T. Progress report on new antiepileptic drugs: a summary of the Eigth Eilat Conference (EILAT VIII). Epilepsy Res. 2007 Jan;73(1):1-52. Epub 2006 Dec 8.
34. Coppola G, Auricchio G, Federico R, Carotenuto M, Pascotto A. Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study. Epilepsia. 2004 Sep;45(9):1049-53.
35. SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1016-26
36. Pellock J. Antiepileptic drugs trials: neonates and infants. Epilepsy Res. 2006 Jan;68(1):42-5. Review
37. French JA, Pedley TA.Clinical practice. Initial management of epilepsy. N Engl J Med. 2008 Jul 10;359(2):166-76. Review.
38. McCorry D, Chadwick D, Marson A.Current drug treatment of epilepsy in adults. Lancet Neurol. 2004 Dec;3(12):729-35.
39. Sander JW. New antiepileptic drugs in praABctice--how do they perform in the real world? Acta Neurol Scand Suppl. 2005;181:26-9
40. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial.Lancet Neurol. 2008 Jun;7(6):500-6.
41. Pohlmann-Eden B. Issues when treating epilepsy in the elderly. Acta Neurol Scand Suppl. 2005;181:40-6
42. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ; Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology. 2007 Feb 6;68(6):402-8.
43. Holmes GL. Animal model studies application to human patients. nNeurology. 2007 Dec 11;69(24 Suppl 3):S28-32.
44. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006 Jul;47(7):1094-120. Review.
45. Glauser TA, Ayala R, Elterman RD, Mitchell WG, Van Orman CB, Gauer LJ, Lu Z; N159 Study Group. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. Neurology. 2006 Jun 13;66(11):1654-60
46. Cowling BJ, Shaw JE, Hutton JL, Marson AG. New statistical method for analyzing time to first seizure: example using data comparing carbamazepine and valproate monotherapy. Epilepsia. 2007 Jun;48(6):1173-8.
47. Marson AG, Williamson PR, Taylor S, Maguire M, Chadwick DW. Efficacy of carbamazepine and valproate as monotherapy for early epilepsy and single seizures. Neurology. 2006 Nov 28;67(10):1872-5.
48. Sachdeo R. Monotherapy clinical trial design. Neurology. 2007 Dec 11;69(24 Suppl 3):S23-7. Review
49. Dichter MA. Innovative clinical trial designs for future antiepileptic drugs. . Epilepsia. 2007;48 Suppl 1:26-30.
50. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008 Aug 12;5(8):e166. Review
51. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D; Medical Research Council MESS Study Group.Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005 Jun 11-17;365(9476): 2007-13.
52. Davis A, Pack A. Initial management of epilepsy. N Engl J Med. 2008 Dec 4;359(23):2499-500.

53. Garofalo E. Clinical development of antiepileptic drugs for children. Neurotherapeutics. 2007 Jan;4(1):70-4. Review
54. SANAD Study group.The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet. 2007 Mar 24;369(9566):1000-15
55. Faught E. Clinical trials for treatment of primary generalized epilepsies.Epilepsia. 2003;44 Suppl 7:44-50. Review.
56. Gilliam F. What we don't learn from clinical trials in epilepsy. .Epilepsia. 2003;44 Suppl 7:51-4. Review.
57. Schuele SU, Lüders HO. Intractable epilepsy: management and therapeutic alternatives. Lancet Neurol. 2008 Jun;7(6):514-24. Review
58. Sato S, White BG, Penry JK, Dreifuss FE, Sackellares JC, Kupferberg HJ. Valproic acid versus ethosuximide in the treatment of absence seizures. Neurology. 1982 Feb;32(2):157-63.
59. Perucca E, French J, Bialer M. Development of new antiepileptic drugs: challenges, incentives, and recent advances. Lancet Neurol. 2007 Sep;6(9):793-804. Review
60. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology. 2003 Jun 10;60(11 Suppl 4):S2-12. Review
61. Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord. 2007 Dec;9(4):353-412. Review
62. Faught E. Monotherapy in adults and elderly persons. Neurology. 2007 Dec 11;69(24 Suppl 3):S3-9. Review.
63. Sullivan JE 3rd, Dlugos DJ. Antiepileptic drug monotherapy: pediatric concerns. Semin Pediatr Neurol. 2005 Jun;12(2):88-96. Review.
64. M. J. Brodie, MD, E. Perucca, MD, P. Ryvlin, MD, E. Ben-Menachem, MD, H.-J Meencke, MD for the Levetiracetam Monotherapy Study Group* Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. NEUROLOGY 2007;68:402-408
65. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: considerations for a revisited strategy. Drugs. 2008;68(1):17-25.