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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF EPILEPTIC DISORDERS

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF EPILEPTIC DISORDERS

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EXECUTIVE SUMMARY

The present document is a second revision of the existing guideline. It should be considered as general guidance on the development for 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 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, 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, allow a definition of specific epilepsy syndromes which are listed in the International Classification of Epilepsies and Epilepsy syndromes. Some of them are age-dependent. Brain imaging may add to the aetiological diagnosis.

Focal onset epilepsies, related to a focal brain dysfunction, occur in approximately 60 % of cases and include, symptomatic (lesion defined) cryptogenic (not lesion defined) and idiopathic forms. Generalised epilepsies 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.

Children also exhibit symptomatic and cryptogenic partial epilepsies as adults do. However, 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 partial epilepsy and for epilepsy syndromes (e.g. West syndrome/Infantile spasms, Dravet syndrome, myoclono-astatic epilepsy and Continuous Slow Waves during Sleep). Another major difference in paediatric and adult epilepsies is that several syndromes carry a grave mental prognosis due to the impact of epilepsy on cognitive functions the so-called epileptic encephalopathies. Some age-dependent epilepsy syndromes do not persist in adulthood e.g. most idiopathic partial epilepsy such as benign partial epilepsy.

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%

[1] The classification of seizure types is under revision. In this revision the appropriateness of the term "generalized" is under discussion (ILAE). Further the term partial is at discussion as the latter means incomplete. The term focal instead of partial appears to be preferred.

achieve freedom of seizure under with polytherapy. It follows that about 30% of the patients are not satisfactory 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 the existing AEDS therapy. Traditionally newer AEDs, all have been evaluated in add on studies in patients refractory to previous therapies. Usually, 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 giving placebo. However, very few patients become seizure-free, which is the ultimate goal. Differences exist in efficacy and tolerability profile depending of seizure 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 partial 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 of 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 in given age-dependant epilepsy syndromes 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 partial 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.

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 75/318/EEC and 83-5701EEC and current and future EC and ICH guidelines, especially those on:

- Studies in support of special populations.
- The extent of population exposure to assess clinical safety for products intended for long-term treatment in non life threatening conditions.
- (ICH-E8) General considerations for clinical trials.

- (ICH-E9) Statistical principles for clinical trials.
- (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 trial 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

They are intended to assist applicants in the interpretation with respect to specific problems presented by products in epileptic disorders

4. MAIN GUIDELINE TEXT

4.1. SELECTION OF THE SEIZURE TYPE AND EPILEPSY SYNDROME

Usually, partial epilepsies in adults represent the first target, since they are the most frequent, and a substantial percentage of them are not well controlled. Efficacy used to be evaluated for all the seizure types potentially present in this condition: simple partial, complex partial and secondary generalised seizures.

It is desirable to explore the efficacy in other epilepsy syndromes/seizure types as early as the development of the medicinal product allows (see also section 4.2.4 and 4.7). 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 differing from partial epilepsies 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, 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 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. A 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. The impact upon the other clinical features of the syndrome, EEG pattern or cognitive outcome for example may also be addressed and will be need to be addressed when claims are intended.

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 cAES 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 and approved, it is important to evaluate the efficacy of the product in the monotherapy setting when given alone.

4.2.2 Monotherapy studies

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 trial may be different depending on the seizure type and epilepsy syndrome.

For partial onset seizures monotherapy in patients undergoing presurgical evaluation for refractory partial epilepsy may generate some short-term efficacy data which however are not be 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 it 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.

4.2.4 Development of AEDs in children

Half of the epilepsies begin before the age of 20, 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 towards adulthood. Moreover, epilepsy in childhood may affect the normal development of children in the broadest sense.

Two situations can be described:

1) Partial 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. It is obvious that for a new agent for thid s condition efficacy and safety data are first generated adults before paediatric studies can be started.

   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

2) The epilepsies/seizure types which are specific to children (e.g. West, astatic-myoclonic 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 adult seizure type Therefore, developmental plans in these conditions may start at the same time in children (exploratory) and 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 this (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 open pilot studies including all types of paediatric epilepsy syndromes (whether common with adults or not), stratified by syndromes, they would permit to obtain initial information on population pharmacokinetics, and preliminary data on safety and efficacy. A further confirmation study will need to be performed in the candidate syndrome(s) identified in support of a claim.

For both situations the development of a child friendly formulation is required.

From the safety view point, approximately 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 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).

A specific dossier or a specific part of a complete dossier would be required for the compound to be registered in children. Usually, a complete dossier including kinetic, confirmatory controlled-studies and safety studies should be submitted before licensing. In this respect, a request for CPMP scientific advice may be considered by the applicant. Tolerability and short term safety data should also be made available.

4.2.5 Development of AEDs in the elderly

The prevalence of newly diagnosed epilepsy increases substantially after 65 years of age. Elderly patients, who may have suffered from epilepsy for years or may have developed epilepsy recently, should be considered differently.

Efficacy and safety of AED's in newly diagnosed elderly patients may be different from those in younger adults for the following reasons:

- dominance of symptomatic aetiologies: Alzheimer or other neurodegenerative condition, brain tumour, cerebrovascular accident,...

- an increased risk of toxic effects associated with use of standard doses of drug, especially regarding the impact on cognitive functions, vigilance and cardiovascular system;

- pharmacokinetic and/or pharmacodynamic interactions with other concomitant products frequently used in the elderly due to coexisting 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 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. See section 4.4.

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 for 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 during 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. One of these, 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 paediatrics studies the endpoint are in principle the same as for adults although other responder definitions are acceptable where justified (e.g. days without seizures 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 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). However 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, 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)

However, 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 should be based on the period when patients are established on a fixed dose of either the study product or placebo/comparator i.e. 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 modelling assumptions (e.g. normality of the distribution for an ANOVA) should be provided.

Factors known to interfere with outcome such as aetiology, seizure type, baseline seizure frequency, seizure severity, epilepsy syndrome should be taken into account in the primary 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 may not have enough power to detect a true treatment effects. Efficacy in these seizures should be evaluated by an overall-analysis of individual studies. Such (meta)analysis is expected to be covered in a separate study protocol and statistical analysis plan in advance.

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.

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 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 therapeutic range of the new agent and to

evaluate whether minor changes in the plasma concentration of the agent or its active metabolites are of clinical significance. Plasma concentrations should therefore be checked at the time of the assessments of efficacy as well as an undesirable effect is noticed.

In children the study of the influence of the maturation on the pharmacokinetics is of special importance as well as the limitation of invasiveness. Solutions of the limitations of invasive investigations in children should be looked for e.g. small blood samples drawn, population approaches on sparse samples, small number of samplings, smallest possible number of patients recruited …… etc.

4.5.4 Interactions

Pharmacokinetic in vitro and in vivo interaction studies should be performed in accordance with the guideline on interactions (CPMP 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 tests 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 contraceptive pill must be determined. Also the potential pharmacodynamic interaction 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 etiology 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 exploratory nature of this phase in the clinical development plan allows a variety of designs. Examples are randomised placebo-controlled cross-over studies, enrichment designs, controlled

studies in patients with refractory epilepsy subjected to a pre-surgical evaluation programme, 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 recording an increase in seizure frequency.

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 primary for all partial onset seizures (combination of simple partial seizures, complex partial seizures, secondary tonic clonic seizure). In addition, the efficacy for each of seizure subtypes should be evaluated. 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 new product and concomitant anti-epileptic products have to 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 of the epileptic diseases must be taken in account; for instance, patients in whom baseline seizure frequency differs substantially from their usual seizure frequency, may not be included.

Concomitant anti-epileptic product therapy 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 event observed may be attributed to the test agent or may also be explained by changes in plasma concentrations of the concomitant anti-epileptic agent.

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 whether 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 add-on studies in order to assess absence of tolerance on the long term and maintenance of safety. A 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).

Monotherapy studies should be randomised, double-blind positive 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 use. Given differences in efficacy profile of AEDs it should be excluded that no inferior treatment or insufficient dose is used. Stepwise fixed dose increments based on response may guarantee assay sensitivity.

The primary endpoint should be the proportion of patients becoming seizure free (see section 4.3.1). Overall the follow-up should be at least one year, for safety reasons and in order 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 were 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.

j) 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 claim as patients in conversion to monotherapy studies are not representative for patients receiving monotherapy i.e. newly or diagnosed patients who mostly have milder, 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 and will be mentioned in the SPC.

4.5.5.4 Specific cases

The development of anti-epileptic agents for indications in epilepsy other than partial seizures 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.

Specific epilepsy syndromes in children (i.e. Epileptic encephalopathies), in which specific 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 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.

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 epileptic patients exists.

4. 6. SAFETY ASPECTS

4.6.1 General considerations

Referred is to the relevant guidance's.

As for any other medicinal product, the occurrence of liver, blood , 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 eventuality should be taken into account in the design of clinical trials. This aggravation may consist of 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 mechanisms, 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 evoked. Such worsening potential, and the seizure types and/or syndromes concerned, should be identified as early as possible in the new drug development as it determines appropriate use of the product. i.e. 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 beneficial claims in this respect have to be based on appropriate studies.

Similarly, a special attention should be given for recording the occurrence of rebound seizures and/or behavioural changes after the new 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 subject 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 examination procedures.

4.6.2 Long term safety

Manufacturers and investigators would be well-advised, irrespective of any legal obligation, to continue to study new substances of this type 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 having taken 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 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.

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 although the clinical development plan of antiepileptic agent should not stop here.

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.

It is noted that the clinical development plan of an anti-epileptic agent is not considered complete in absence of efficacy studies in monotherapy, evaluation of effectiveness in other seizure types,

evaluation of efficacy in children, the development of a child friendly formulation and parental formulation. Depending of the product characteristics the absence of these should be justified or clinical development plan may need to be continued as part of post-approval commitments.

The development of non-oral formulations is recommended.

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