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# 4 Guideline on clinical investigation of medicinal products in 5 the treatment of epileptic disorders

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


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

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# Executive summary

The present document is a third 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 EMA and ICH guidelines, which may apply to these conditions and patient populations.

The main changes to the existing guideline include incorporation of the new classification / definitions of seizure types and epilepsies, the acceptance of add-on studies in support of a monotherapy claim on a case-by-case basis, the inclusion of new sections on neonates and status epilepticus and other changes related to paediatric developments.

This Guideline provides assistance for the development and evaluation of medicinal products for the treatment of epilepsy in adults and children. 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.

# 1. Introduction (background)

Epilepsy is a brain disorder defined by spontaneous recurrence of unprovoked seizures, i.e. seizures not provoked by transient systemic, metabolic or toxic disorders. It constitutes a vast ensemble of diverse clinical conditions which differ by age of onset, type of seizures (only one or several type(s) in an individual patient), aetiological background, including genetic predisposition, prognosis and response to treatment, that entail neurobiological, cognitive, psychological and socioeconomic burden.

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 1000 subjects.

Clinically recurrent seizures are the primary marker of epilepsy. The classification of seizure types has been revised in 2017 by the International League Against Epilepsy (ILAE). The classifiers are type of onset, behaviour descriptors (e.g. tonic, autonomic, etc.) and level of awareness (see Annex I).

In addition to the type of seizures, the classification of epilepsies has been revised among three levels, i.e. seizure type, epilepsy type, and epilepsy syndrome embedded within an aetiology and co-morbidity framework (see Annex II). The diagnosis of an epilepsy syndrome involves the finding of a cluster of seizure types, electroencephalogram (EEG) and imaging features that may share genetic characteristics. Many of the epilepsies are age-dependent and are accompanied by comorbidities e.g. motor deficits, impaired neurodevelopment, and behavioural problems.

Epileptic encephalopathies refer to conditions where the epileptiform activity contributes to the development of cognitive and behavioural impairment.

Focal onset seizures, related to a focal brain dysfunction, occur in approximately 60% of cases and include symptomatic (lesion defined), probably symptomatic (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 and development. 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. Consequently, an earlier

initiation of the appropriate treatment may yield a better prognosis. 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 into adulthood (e.g. West syndrome or “Benign” epilepsy with centrotemporal spikes).

Status epilepticus is a condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. Persisting neuronal damage may occur with variable outcome. Severe status epilepticus has a high mortality rate. A new diagnostic classification system of status epilepticus has been proposed by the ILAE with four axes i.e. semiology, aetiology, electroencephalography seizures, correlated or not with clinical seizures, and age.

Antiepileptic drugs (AEDs) are the main treatment option of seizures. Approximately 60% of newly diagnosed patients become 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 treatment related adverse reactions.

New AEDs have been developed in the last two decades with the aim of improving the benefit/ risk balance of existing AED therapy. The evaluation of a new AED is traditionally performed as adjunctive therapy in patients already receiving at least one concomitant AED. Typically, in these studies 20 to 40% 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, few patients become seizure-free, which is the ultimate goal of treatment. Differences exist in the efficacy and tolerability profiles of AEDs depending on seizure type and epilepsy syndrome. A given compound may for instance improve one type of seizure type but worsen another.

The AEDs may have different spectra of efficacy:

- In terms of seizure types, most AEDs are effective against focal seizures and focal to bilateral tonic-clonic seizures. 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 medicine's spectrum of effectiveness is important when considering trials in newly diagnosed patients, even though the precise syndrome and seizure types may not have been defined at the time of treatment initiation.

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 prognostic value, in particular for paediatric patients.

# 2. Scope

This Guideline provides assistance for the development and evaluation of medicinal products for the treatment of epilepsy in adults and children. 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 and relevant guidelines

This Guideline has to be read in conjunction with the introduction and general principles (4) and Part I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant adopted European 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 E11CPMP/ICH/2711/99 and addendum 07/2017 (R1) Clinical Investigation of Medicinal Products in the Paediatric Population
- EC/87/013 Pharmacokinetic studies in man.
- EMA/CHMP/EWP/147013/2004 Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population
- EC 2008 "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population"
- EMA/CHMP/458101/2016 Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling 5 and simulation
- EC/90/022 Clinical testing of prolonged action forms, with special reference to Extended Release Forms
- CPMP/ICH/378/95 Note for guidance on dose response information to support drug authorisation
- EMA/CHMP/QWP/805880/2012 Rev. 2.Guideline on pharmaceutical development of medicines for paediatric use
- 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 application with 1. meta-analysis; 2. one pivotal study
- EMA/CHMP/158268/2017 Guideline on clinical development of fixed combination medicinal products

- EMA/199678/2016 Reflection paper on the use of extrapolation in the development of medicines for paediatrics

# 4. Patient selection

## *4.1. 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.

The seizure type, epilepsy type, epilepsy syndrome and aetiology of the subjects included in the studies should be clear. This should allow an evaluation of (lack of) differential effect of the new medicine by the seizure type, epilepsy type, epilepsy syndrome and aetiology. 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.

## *4.2. Selection of the seizure type and epilepsy syndrome*

Usually, focal seizures in adults is the first seizure type that is evaluated in clinical development plans, since they are the most frequent and a substantial percentage (approximately 30%) of them are not well controlled or treatment resistant. Efficacy needs to be evaluated for focal seizures and focal to bilateral tonic-clonic seizures separately.

It is however highly desirable to explore efficacy in other epilepsy syndromes/seizure types. Non-clinical 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 whole range of seizure types/epilepsy syndromes observed in humans.

Efficacy in seizure types or epilepsy syndromes should be explored separately (e.g. idiopathic generalised epilepsies, refractory focal epilepsy, West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, myoclonic-astatic epilepsy). Evaluation requires analysis of the efficacy of an agent on the different seizure types present in the given condition (e.g. spasms, generalised tonic-clonic, absences, myoclonic, tonic or atonic seizures).

Inclusion of subjects can be seizure type based within a given syndrome (e.g. primary generalised tonic-clonic seizure in Juvenile Myoclonic Epilepsy) or seizure type based across different syndromes (e.g. generalised-onset tonic-clonic seizure in Idiopathic Generalised Epilepsy and Lennox Gastaut syndrome) or it can be 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 disabling 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 in epileptic encephalopathies is claimed, efficacy should be shown for neurodevelopment, cognition, socialisation, EEG and not only on seizures.

# 5. Assessment of efficacy

## *5.1. Efficacy criteria / treatment goals*

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

### 5.1.1. Add-on trials

In add-on trials, the period over which seizure frequency is measured should be pre-defined (e.g. the number o*f* seizures per 4 weeks). Two important variables should be specified in the protocol. The primary endpoint should be 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.

The proportion of seizure-free patients is a very important variable. The cumulative change from baseline in seizure frequency should also be presented.

A time to event approach (e.g. time to pre-randomisation monthly seizure count) may be considered. An advantage of this design would be that the duration of the study is reduced. However, the underlying assumption that the seizure risk within a patient is constant over time, i.e. no clustering occurs, will need to be justified. In addition, the methods used to handling missing data would need to be very carefully considered. Further, reducing the time in the study or allowing change of treatment after an event makes an assessment of maintenance of effect, tolerability to treatment and safety more difficult as the exposure will not be equal across different treatment groups. Therefore, CHMP scientific advice is recommended, if a time to event approach is planned. Moreover such study design is not recommended as the sole study design in the clinical development plan as in addition, potential exacerbation of seizures (e.g. by 25 % or more) and the appearance of new seizure types should be assessed.

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, absence of spasms and hypsarrhythmia in the West syndrome). These and the secondary variables should allow full investigation of the distribution of change in seizure frequency after treatment. In neonates a reduction in seizure burden may by based on the assessment of video/electroencephalographic neonatal seizures (ENS) (See section 8.2.2). In younger children, from 1 month to less than 4 years, EEG or video/EEG may complete and evidence the clinical manifestation of seizures, in particular subtle clinical seizures can be confirmed when correlated with EEG.

### 5.1.2. Monotherapy trials

In monotherapy trials (adults and children):In newly or recently diagnosed patients, the primary efficacy variable should be based on the probability of patients remaining seizure free for at least six months (excluding the dose titration period). The trial should have a minimum duration of one year in order to assess safety and maintenance of efficacy.In conversion to monotherapy studies treatment retention time may be an acceptable primary outcome variable.

### 5.1.3. Add-on and monotherapy trials

Secondary efficacy variables applying to both add-on and monotherapy trials may concern:

a) 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.: $n^{th}$ seizure) should be justified by the applicant.

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

c) Patient reported outcomes, scales measuring social and working capacity if validated.

d) 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.

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

### *5.2. Methods to assess efficacy criteria*

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 using diaries. 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.

## 6. Study design

### *6.1. Non-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. 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 an anti-epileptogenesis effect 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.

### *6.2. Pharmacology studies*

#### 6.2.1. Pharmacokinetics

The PK of the new medicinal 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 6.2.3 and 6.3.2). 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. These data may be helpful in developing a PK/PD model in support of the extrapolation of the study results.

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 with adult and children distinct cohorts, on sparse samples scavenge sampling approaches, minimising the number of samples and the number of patients recruited). The model(s) selected for assessing PK/PD in the paediatric population should be qualified and validated. Physiological based and/or pop PK/PD model(s) and simulation(s) could predict the initial dose and, updated, be useful to confirm the dose-regimen per defined age-subsets.

### 6.2.2. Pharmacodynamics

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 .

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 as well as in 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 and including a positive control.

### 6.2.3. 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 6.3.2.

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

## *6.3. Therapeutic studies*

### 6.3.1. Exploratory and dose finding 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 event approach 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.

For focal onset seizures, monotherapy in patients undergoing pre-surgical evaluation for refractory focal epilepsy may generate some short-term efficacy data which, however, are not relevant for longer term clinical use.

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

It is custom to titrate a new AED until an optimal effect is seen or until the maximal tolerated dose is reached or up to the maximal doses allowed. If the dosing schedule incorporates titration the additive value of increasing the dose for efficacy should be evaluated.

### 6.3.2. Confirmatory studies

As for trials in any disease area it is of critical importance to clearly specify the scientific question of interest that the trial seeks to address. The target of estimation, including specification of how to account for intercurrent events to reflect the scientific question of interest, will need to be pre-specified and well justified given the therapeutic situation and scientific objective under consideration. Intercurrent events of particular interest in this setting are discontinuation or modification of treatment received, including the use of other AEDs. It is recommended to include this topic in requests for Scientific Advice.

**Add-on studies**

Traditionally, the initial evaluation process for a new AED involves the evaluation of its efficacy in reducing the frequency of seizures or seizure burden, in patients who continue to have seizures despite therapy with an adequate regimen of appropriate drug(s).

Add-on studies however may 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 (PK) interactions, pharmacodynamic (PD) 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, -with plasma levels being 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 target of estimation and efficacy analysis plan should consider in advance how to deal with patients with and without dose modifications of their concomitant AED products. Add-on studies should be large enough to allow concluding that the effect is consistent regardless of background AED.

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.

The pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design.

The studies 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.

Efficacy endpoints should be based on the changes in seizure frequency between the treatment maintenance phase and the baseline period excluding the titration period (see section 5.1). Efficacy first should be evaluated for all seizure types. Consistency of the effect per seizure type (focal, generalised, unknown onset) should be part of the secondary analyses. A meta-analysis of several add-on studies if predefined may be considered (see also section 5.3. Statistical analysis).

In epilepsy syndromes where different seizure types may co-exist, emphasis may be on improvement of the most invalidating seizure types where it might be accepted that concomitant seizure types might not improve or even worsen. This will be subject of the benefit-risks assessment. A prerequisite is that it should be predefined and justified in the study protocol what would be acceptable.

Given the add-on setting, the number of possible AEDs combinations is large. An evaluation of a (potential) different effect of the test drug depending on the background AEDs - whether or not they are enzyme inducers - is expected for both efficacy and safety. The studies should be large enough to allow concluding that the effect is consistent regardless of background AED.

*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 carefully documented preferably by monitoring 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 their target dose which is subsequently maintained during the whole maintenance period (see section 6.3.1).

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 7.

*Long term Efficacy/Safety*

Long-term data should be generated by continuation of add-on studies or by conducting open label extension studies in order to assess absence of tolerance on the long term alterations in the therapeutic effect over time and maintenance of safety. Treatment retention rate is recommended as a global indicator of clinical effectiveness. A one year study duration is considered the minimum.

**Conversion to monotherapy**

Some add-on studies may be designed to generate data on conversion to monotherapy in patients with multiple-drug treatment in an open label extension phase. In conversion to monotherapy trials, in which it is expected that patients who fail study treatment will switch to an alternative regimen, treatment retention time may be a useful outcome variable. The availability of conversion to monotherapy data, as well the lack of these data, is informative for the prescriber as it facilitates the decision to attempt secondary monotherapy or not in an individual subject. Therefore, these data or the absence thereof will be incorporated in the SmPC.

**Monotherapy studies**

Placebo controlled monotherapy trials in epilepsy are in general not feasible. However placebo controlled trials in subjects where it is not clear whether an AED should be started could be considered, especially when a benign safety and tolerability profile has been shown e.g. in the add-on setting.

Monotherapy trials traditionally have been active controlled trials of one year duration in newly or recently diagnosed patients, with the primary efficacy variable being the proportion of patients remaining seizure free throughout the duration of the randomised trial period. In practice, seizure recurrence in these trials has been low, so that the majority of the patients remain seizure free for the duration of the trial. These trials therefore often lack or have limited assay sensitivity.

On a case by case basis, it may be justified that a monotherapy trial is not necessary to support a monotherapy indication. Factors to be taken into account would include, among others, known characteristics of the class of AED including documented mechanism of action, results of trials in the add-on setting such as magnitude of effect, known PK/PD relationship, type of seizures wherein a product is effective and/or consistency of efficacy of the new compound when added to different classes of other AEDs.

Where the mechanism of action of a new AED may work by augmenting the efficacy/effectiveness of another AED and hence where the new AED might not have substantial efficacy on its own, monotherapy trials are likely to be required if a monotherapy indication is sought. This would not necessarily always be the case when the mechanism of action is novel but the evidence from available non-clinical and clinical data would need to be persuasive to support the claim that the new AED would be efficacious on its own. CHMP scientific advice is recommended in such situations.

Where required, monotherapy trials should be randomised, double-blind, active controlled non-inferiority trials comparing the test treatment to an acknowledged and well justified standard AED at an optimised dose. Specific measures are necessary to ensure assay sensitivity i.e. including subjects with a high seizure frequency at baseline or extension of the duration of follow-up.

However, it is problematic if the trial recruits patients who have a low likelihood of seizure recurrence as the trial is likely to lack assay sensitivity to detect clinically relevant differences in efficacy between treatments. Therefore patients should have characteristics that make them more likely than the general monotherapy population to have at least one seizure during the trial period. The following types of patients could be suitable:

- Newly or recently diagnosed patients with high baseline seizure frequency.
- Patients on monotherapy with insufficiently controlled seizures willing to convert to an alternative monotherapy in preference to adding a second AED.
- Patients with focal onset seizures without focal to bilateral tonic-clonic seizures who accept occasional seizures on monotherapy in preference to AED polypharmacy.

Although the type of patients described above may not be entirely representative of patients receiving monotherapy extrapolation of efficacy to the more responsive forms is considered possible.

The most appropriate trial objectives and efficacy measures will depend on the trial population. In newly or recently diagnosed patients previously untreated with an AED an appropriate primary efficacy endpoint would be the proportion of patients who experience a seizure during the randomised period of the trial. A non-inferiority margin should be justified a priori by the applicant.

The duration of the trial should be sufficient to achieve a sufficient proportion of patients with events (seizures) for a sensitive analysis and may be different depending on the seizure type and epilepsy syndrome. Follow-up of individual patients should be at least one year from randomisation 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.

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

**Monotherapy-safety**

The safety in the add-on setting is not representative for the safety profile of the same product used in the monotherapy setting. Therefore safety data under monotherapy should be generated e.g. open

label data of at least one year to collect additional safety information. In principle this may be done post-approval unless the safety profile observed in the add-on setting suggests that the benefit risk in the monotherapy setting may be different. Randomised comparative studies with retention rates as a global indicator of an overall favourable benefit-risk balance should be considered.

### 6.3.3. Statistical analyses

The analysis of efficacy will usually be based on all randomised patients analysed as randomised, i.e. the intent to treat (ITT) principle, and the period when patients are established on a fixed dose of either the study product or placebo/comparator i.e. the maintenance dose. Regardless of what happens to patients during the titration phase (e.g. discontinuing or otherwise modifying dose of randomised treatment, using other AEDs, or discontinuing from the trial) they should not be excluded from the analysis.

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. Sensitivity analyses should be pre-specified to assess the influence of the modelling assumptions on the results.

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 may be taken into account in supportive analyses. The use of concomitant anti-epileptic medicines should be summarised and the differential effect on efficacy of different AEDs used in combination with the investigational agent should be evaluated and discussed.

For the evaluation of less frequent seizure types (e.g. focal to bilateral tonic-clonic seizures), efficacy in epilepsy syndromes, and differences in efficacy in seizures of different aetiology, individual studies are not expected to have adequate statistical power to establish a treatment effect. Efficacy in these seizures may be evaluated by a meta-analysis of individual studies. Such (meta) analysis is expected to be covered in a separate protocol and statistical analysis plan in advance, including a plan to investigate consistency of the effects observed across separate studies to establish the validity of the analysis.

### 6.3.4. 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.

**Epilepsy syndromes**

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.

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 medicinal product, identifying those that may be candidates is a key point. Exploratory strategies are recommended to identify one of these syndromes as candidate to one randomised controlled trial with a new compound. It is recommended

to enter 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.

On a case-by-case basis a more focused, tailored approach may be an option if based on the understanding of the mechanism of action as well as the available non-clinical and (adult) clinical data certain epilepsies/syndromes can be identified as promising target indications. Such approach should however not jeopardise the identification of a possible benefit in other epilepsies/syndromes for which no or insufficient data exists.

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.

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

**Status epilepticus**

Status epilepticus is an acute medical and neurological emergency that is potentially life-threatening and requires prompt diagnosis and treatment. Status epilepticus may be defined as a transient condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures. Two time points are of relevance, i.e. the time point when treatment should be considered started and the time point when the status should be controlled in order to prevent structural damage. This differs per type of status epilepticus (e.g. tonic clonic status epilepticus, absence status epilepticus). Trials in status epilepticus should have clear criteria for rescue treatment, including specifying time points by which treatment should be initiated depending on the seizure type.

Three situations should be considered: treatment of the acute status epilepticus, prevention of recurrence of status epilepticus and (super) refractory status epilepticus. For each condition both the trial design and study endpoints are different.

*Treatment of the acute status epilepticus*

Trials of new medicinal products intended for the treatment of acute status epilepticus should normally be performed first in the controlled setting. Depending on the nature of the new product and the available clinical and/or non-clinical data, new medicinal products intended for the treatment of acute status epilepticus may be tested either as first line treatment (in early status epilepticus) or as second line treatment after standard treatment with a benzodiazepine has failed (in established status epilepticus). Stratification by prognostic factors is (e.g. aetiology) is recommended. Trials should be designed to show non-inferiority or superiority to an appropriate active comparator. For first line status

epilepticus treatment this would be an approved benzodiazepine. For trials in second line treatment, appropriate comparators could be intravenous (fos)phenytoin or phenobarbital. Persistent seizure cessation should be the primary endpoint.

For a medicinal product intended to be used by non-medically trained caregivers in an out of hospital setting, it is necessary to justify that the new product is suitable for administration by caregivers. The sample size should be sufficient to conclude that both the efficacy and safety (especially in relation to cardiorespiratory depression) of the new product can be expected to be non-inferior to products that are approved for this indication (e.g. buccal midazolam).

*Prevention of recurrence of status epilepticus*

This refers to the situation where the status is controlled but another AED is simultaneously given as an umbrella to prevent recurrence. Trials for new products for this purpose should have two arm designs intended to show non-inferiority or superiority to an appropriate active comparator e.g. phenytoin. Recurrence of seizures after the primary treatment of status epilepticus seizures is no longer effective (i.e. there is no carryover) is the primary endpoint.

*Refractory status epilepticus*

Refractory status epilepticus refers to ongoing seizures without recovering of consciousness to baseline, failing to respond to first line treatment with a benzodiazepine and second line intravenous anticonvulsant treatments such as phenytoin and/or phenobarbital. Refractory status epilepticus requires treatment with general anaesthesia, continued for 12−24 hours after the last clinical or electrographic seizure, in order to prevent or minimise neurological damage. Treatment is intended to reverse prolonged status epilepticus and prevent (further) structural damage. Whereas initial treatment is focused on seizure cessation and silencing the brain this is an intermediate endpoint as the ultimate goal is to prevent further neurological damage. Thus, for any new medicinal product studied in this setting, a functional outcome after weaning is recommended as the primary endpoint.

# 7. Safety aspects

## *7.1. Specific effects*

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.

## *7.2. Long-term effects*

Sponsors should continue to evaluate the test product after marketing in order to detect unusual effects, long-term adverse reactions 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.

## *7.3. Safety endpoints*

### 7.3.1. 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 an 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.

### 7.3.2. 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). In children impact on cognitive function needs to be addressed in short term pharmacodynamic studies. See section 6.2.2.

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. If the test agent or placebo is withdrawn, withdrawal symptom and dependence should be carefully evaluated. 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.

# 8. Studies in special populations

## *8.1. Studies in elderly patients*

### Efficacy in elderly patients

The incidence and prevalence of epilepsy increase 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 epilepsy, due to cerebrovascular accidents, neurodegenerative conditions including Alzheimer’s disease or brain tumour;
- An increased susceptibility to adverse effects despite the use of drugs at standard doses, especially on cognitive functions, vigilance and cardiovascular system;

- PK and/or PD 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 elderly patients should be included in the Phase III data base. A separate analysis between elderly patients, who may have suffered from epilepsy for years and those who developed epilepsy recently due to an underlying disease (e.g. stroke) should be presented as responses may be different.

**Safety in elderly patients**

Safety, especially with regards to 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 SmPC.

## *8.2. Studies in paediatric patients*

### 8.2.1. Development of AEDs in children

**Efficacy in paediatric patients**

Half of the epilepsies begin before the age of 18 years 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 and developing 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, and other epilepsies can arise. Moreover, epilepsy may affect the normal development of children in the broadest sense. The aetiology at baseline should be recorded.

In infants and very young children subtle seizures are more frequent and likely to be missed. Here video-EEG could be helpful and is recommended depending on the epilepsy syndrome or seizure type (See 8.2.2)..

For a claim of efficacy in the paediatric population several situations are distinguished warranting a different clinical development plan :

Focal epilepsies, idiopathic generalised epilepsies, as well as absences, myoclonic and/or generalised convulsive seizures, where the efficacy of AEDs is comparable in childhood and adulthood. With a few exceptions, focal epilepsies in children from 4 years of age may have a similar clinical expression to focal epilepsies as in adolescents and adults. For focal epilepsies, the results of efficacy trials performed in adults may be extrapolated to children and adolescents provided that the PK/PD relationship in adults is established and that the dose regime proposed in children and adolescents results in similar exposure levels as in adults in all age categories (4 to 18 years). This approach should be planned and pre-specified in an extrapolation development plan (See Reflection paper on the use of extrapolation in the development of medicines for paediatrics, EMA/199678/2016).

In the very young children (i.e. 1 month – less than 4 years) efficacy cannot be extrapolated given the uncertainty of the impact of the developing brain on the disease and response. Once efficacy has been shown in the older paediatric population, short term assessment of response by using video EEG monitoring only may be sufficient.

For epilepsies/seizure types which are specific to children (e.g. West syndrome, Dravet syndrome, Doose syndrome and Lennox Gastaut syndrome), efficacy should be shown based on randomised controlled trials. PK modelling may be useful for the estimation of the dose in children that leads to similar exposure as observed in the adult studies.

In case an effect on epileptogenesis is claimed it should be shown that the effect on seizures translates in an improved neuro-motor development. This would require long term comparative data. As this is a developing area of research CHMP scientific advice is recommended.

**Safety in paediatric patients**

Generally, from the safety point of view, preferably 100 children should be treated by the study drug and followed for at least one year. Moreover, short term and long-term studies should be designed to detect possible impact in the neurodevelopment, motor development, cognition, behaviour, growth, endocrine functions and puberty. In addition health-related quality of life may be assessed. Assessment scales should be validated by age and by language. 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)]. Prospective disease based registries (per paediatric epilepsy syndromes or symptoms) may be helpful and are encouraged.

### 8.2.2. Development of AEDs in Neonates

Newborns with multichannel video-EEG-proven and/or clinical repeated seizures or who are at high risk of seizures, such as with hypoxic ischemic encephalopathy, stroke or intracranial haemorrhage should be considered for inclusion in clinical studies, with birth gestational age of 34/35 weeks to less than 28 days of post-natal age. Lower gestational ages are to be included only if the new medicine has already been investigated in term age.

Multichannel (8 minimum) continuous video-EEG is needed to exclude artefacts, to identify minor clinical seizures or infra-clinical seizures and to evaluate the frequency, duration and severity of the seizures. The duration of EEG should be sufficient to ensure the adequate recording of seizures. At least one central reader should confirm the video-EEG recordings evaluated by the local physician, with epileptiform discharges/seizures to be distinguished from artefacts. The correlation with clinical signs or not should be investigated.

Aetiologies could be diverse (including cerebral malformations), with genetic causes, and should be carefully considered based on the anticipated mode of action and efficacy as well as PK and safety. Single aetiology trials versus trials in patients with multiple seizures aetiologies should be discussed considering confounders versus feasibility and generalisability. Single aetiology trials may be more appropriate for confirmatory trials. In addition, seizure severity is to be considered. Therapeutic hypothermia treatment potentially impacts drug PK, efficacy and safety, and should be balanced across treatment arms if applied.

Randomised comparative studies are recommended. Historical controls, if proposed, will need to be justified, including a predefined matching by age and condition, using comparable standard of care and diagnostic tools.

According to scientific recommendations, electroencephalographic neonatal seizures (ENS) are defined as lasting at least 10 seconds. The seizure burden is to be defined as a duration of activity on EEG in a defined timespan, which could be severe (> 50% seizure activity in 30 minutes) and non-severe. The evaluation period should last for at least 24 hours and continue until the patient is seizure-free for a

defined period, at least of 24 hours. For neonates with clinical motor seizures at baseline, the clinical signs of the seizure should be evaluated in addition to EEG.

The primary outcome in a drug efficacy trial in neonates should be a reduction in seizure burden, the extent of which should be justified, e.g. at least 50% or 80% in seizure burden (minutes/hour) from baseline period, in defined periods according to the severity of ENS. Premature drop-outs of treatment, subjects who switch to rescue medication should be counted as non-responders. A superior efficacy in seizure reduction for the active drug should be demonstrated by a pre-defined and justified relevant difference between study drug and comparator groups, which shall also inform sample size planning."

The secondary outcomes should include the need of rescue medication and other clinical measures (feeding, vision, etc), with neuroimaging before neonatal intensive care unit discharge (structural magnetic resonance imaging with a central reader) to evidence the structure of the brain.

The minimal follow-up period within the clinical study should be 30 days after final study drug intake, to evaluate the persistence of the effect, which should include routine EEG.

Long term assessment of central nervous system (CNS) function requires at least 24 months, including neurodevelopmental disability. Depending on data already available this may be done post-approval. More precisely, evaluation of cognitive and neuro-motor function beyond the major disabilities requires follow-up to at least pre-school age and the use of standardized age appropriate instruments. Protocolised prospective disease-specific registries are recommended for long-term outcome at least up to 2-5 years.

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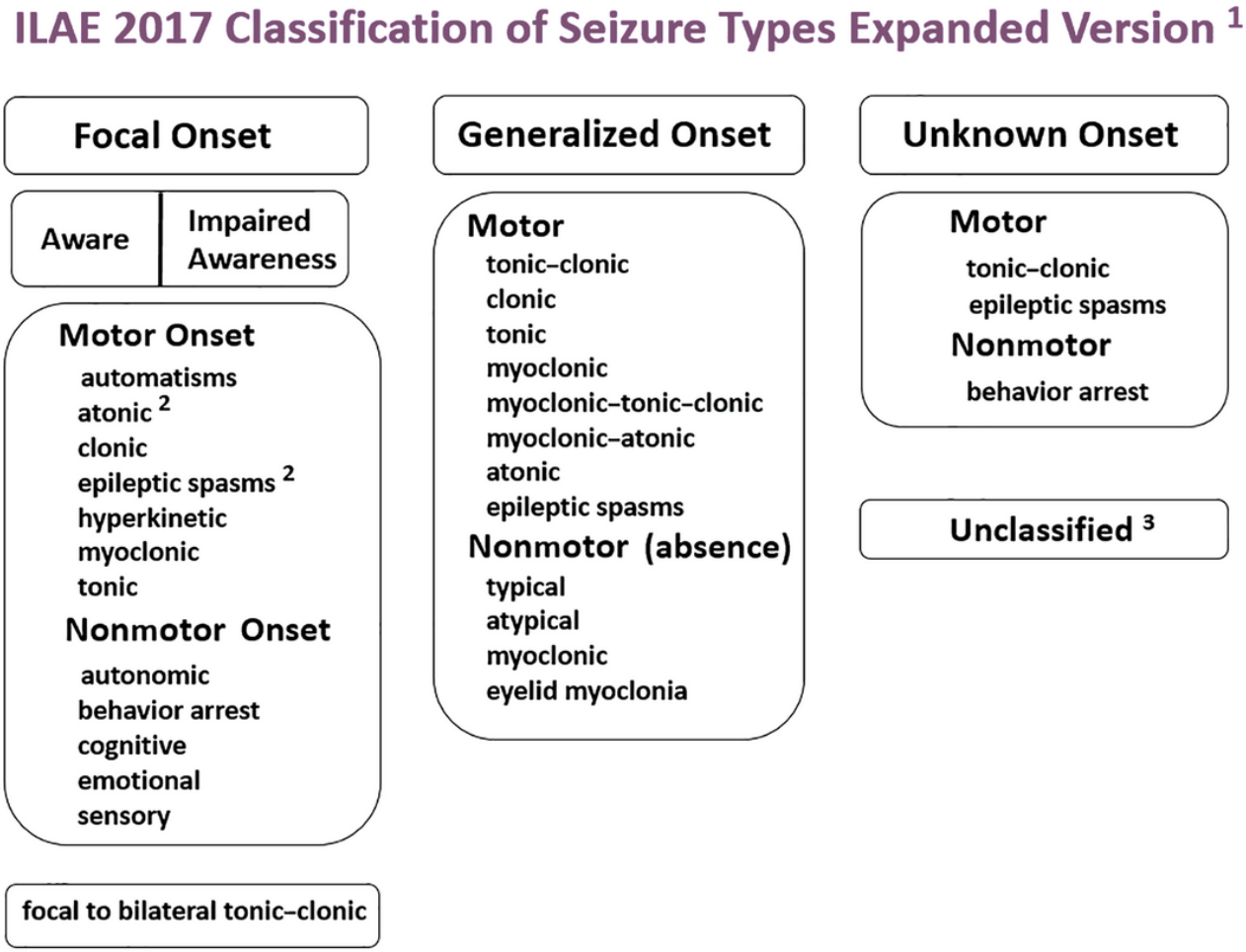
# ANNEX I

**Expanded ILAE 2017 operational classification of seizure types (based on Fisher et al., Epilepsia, 2017)**




[1] Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms of Fisher et al.

[2] Degree of awareness usually is not specified.

[3] Due to inadequate information or inability to place in other categories.

964 **Conversion table of old to new ILAE seizure classifying terms based on Fisher et al.,**
965 **Epilepsia (2017)**

| Old Term for Seizure<br>The most important are in bold | New Term for Seizure [choice] (optional common descriptor) |
|---|---|
| **absence** | **generalized absence** |
| absence, atypical | generalized absence, atypical |
| absence, typical | generalized absence, typical |
| akinetic | generalized/focal/onset unknown atonic |
| astatic | generalized/focal/onset unknown atonic |
| **atonic** | **generalized**/focal/onset unknown **atonic** |
| aura | focal aware |
| clonic | generalized /focal/onset unknown clonic |
| **complex partial** | **focal with impaired awareness** |
| convulsion | [focal/generalized/onset unknown] motor [tonic-clonic, tonic, clonic], focal to bilateral tonic-clonic, tonic-clonic unknown onset |
| dacrystic | focal [aware or impaired awareness] emotional (dacrystic) |
| dialeptic | focal impaired awareness |
| drop attack | generalized/focal/onset unknown atonic |
| fencer's posture | focal [aware or impaired awareness] motor (tonic) |
| figure-of-4 | focal [aware or impaired awareness] motor (tonic) |
| freeze | focal [aware or impaired awareness] arrest |
| frontal lobe* | focal |
| gelastic | focal [aware or impaired awareness] emotional (gelastic) |
| **grand mal** | **generalized tonic-clonic, focal to bilateral tonic-clonic, tonic-clonic unknown onset** |
| gustatory | focal [aware or impaired awareness] autonomic (gustatory) |
| **infantile spasms** | **generalized/focal/onset unknown epileptic spasms** |
| **Jacksonian** | **focal aware motor (Jacksonian)** |
| limbic | focal impaired awareness |
| major motor | generalized tonic-clonic, focal to bilateral tonic-clonic |
| minor motor | focal motor, generalized myoclonic |
| **myoclonic** | **generalized myoclonic** |
| neocortical* | focal aware |
| occiptal lobe* | focal |
| parietal lobe* | focal |
| partial | focal |
| **petit mal** | **generalized absence** |
| **psychomotor** | **focal with impaired awareness** |
| Rolandic | focal aware motor |
| salaam | generalized/focal/onset unknown epileptic spasms |
| secondarily generalized tonic-clonic | focal to bilateral tonic-clonic |
| **simple partial** | **focal aware** |
| supplementary motor | focal motor tonic |
| Sylvian | focal motor |
| **temporal lobe*** | **focal aware / with impaired awareness** |
| **tonic** | **generalized/focal/onset unknown tonic** |
| **tonic-clonic** | **generalized tonic-clonic, focal to bilateral tonic-clonic, tonic-clonic of unknown onset** |
| uncinate | focal [aware or with impaired awareness] sensory (olfactory) |

* Anatomical classification may still be useful for some purposes, for example in evaluation for epilepsy surgery.

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# ANNEX II

**ILAE Framework for Classification of the Epilepsies (based on Scheffer et al., Epilepsia Open, 2016)**