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# COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

# NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF EPILEPTIC DISORDERS

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# CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF EPILEPTIC DISORDERS

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/560/95 Note for guidance on the investigation of interactions.

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

## 1. INTRODUCTION

Epilepsy which is defined by the recurrence of spontaneous/unprovoked seizures - i. e. seizures not provoked by systemic, metabolic or toxic disorders - constitutes a vast ensemble of very 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 varies from 4 to 8 per 1 000 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, partial or focal, which may become secondarily generalised, and unclassified seizures.

In addition to the type of the seizures, anamnestic, electroencephalographic, brain imaging and aetiological data allow definition of specific epileptic syndromes which are listed in the International Classification of Epilepsies and Epileptic Syndromes. Some of them are age-dependent. Partial epilepsies, related to a focal brain dysfunction, are the most frequent, approximately 60 % of cases and include idiopathic, symptomatic and cryptogenic 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

Antiepileptic drugs (AEDs) are the major therapeutic intervention. Approximately 60% of newly diagnosed patients are seizure-free on a single AED. It is thus estimated that about 40% of patients are not satisfactorily controlled, but there is another 25% suffering from significant adverse effects.

Recently introduced AED’s have been developed in order to improve the benefit risk/balance of the standard therapy. Of the recent new AED’s, all were evaluated in add on studies. Usually, 20 to 40 percent of patients obtained a 50% or greater reduction in the frequency of

seizures, as compared to baseline. In these studies, very few patients became seizure-free, which should be the ultimate goal. Some of these new AEDs have been licensed for monotherapy use. Although some of the newer AEDs may be better tolerated than established agents, overall, none of them has shown superior efficacy to the standard comparators in monotherapy.

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 generalised seizure types, primarily generalised tonic-clonic seizures for instance. For others, efficacy is restricted to two or only one type of seizures, for instance absence seizures.
- In terms of epileptic syndromes, it is important to know which aspects of the syndrome are covered by the new drug, since several seizure types may coexist in a given epileptic condition. On the other hand, a given seizure type may not show the same responsiveness in the various syndromes, particularly in certain age-dependent conditions.

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

## 2. SPECIFIC CONSIDERATIONS WHEN DEVELOPING AND LICENSING PRODUCTS FOR THE TREATMENT OF EPILEPTIC DISORDERS

### 2.1 Selection of the seizure type and epileptic syndrome

Usually, partial epilepsies represent the first target, since they are the most frequent, and a substantial percentage of them are not well controlled. Efficacy should be evaluated for all the seizure types present in this condition: simple partial, complex partial and secondarily generalised seizures. (see section 4).

It is important to explore the other epileptic syndromes. In this respect, the preclinical data, particularly the mode(s) of action and the results on experimental models, can help to build hypotheses on the agent's potential in clinical situations differing from partial epilepsies. These other 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 epileptic 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) The impact upon the other clinical features of the syndrome, cognitive outcome for example, should also be addressed.

The global antiepileptic efficacy of an agent in an epileptic syndrome can only be claimed when efficacy has been shown for all seizure types of the syndrome.

## 2.2 Specificity of clinical trials in epilepsy

### 2.2.1 Add-on studies

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

Add-on trials should be conducted optimally in the presence of only one or two pre-existing AEDs, whose dosage, whenever possible, should be kept stable. 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. If the test drug inhibits the metabolism of a concomitant AED, and thus increases its plasma concentration, the proof of efficacy of the test drug will require that the plasma concentrations of the concomitant drug(s) are maintained within appropriate limits.

However, it might be impossible to keep the concomitant medication unchanged 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.

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 whatever reasons (e.g. pharmacokinetic interactions, pharmacodynamic interactions, additive toxic effects). Therefore it may be difficult to disentangle the relative contribution of these changes superimposed on the true drug effect.

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

Therefore, once the efficacy of the new compound in combination with others has been determined, it is important to assess the efficacy of the product when given alone. Add-on studies, designed in such a way that data on conversion monotherapy may be generated, should be encouraged ( see paragraphs 2.2.2 and 2.4).

### 2.2.2 Monotherapy studies

The monotherapy studies are generally conducted in the following settings :

- Conversion to monotherapy in patients with multiple-drug treatment: these trials are carried out in patients undergoing an initial add-on phase with the test drug, and in whom subsequently the concomitant medication is gradually withdrawn. These designs reproduce well clinical practice, where physicians try to gain in safety and tolerability, while maintaining the same level of seizure control. They have however the disadvantages of methodological difficulties, in particular the potential confounding effects of co-medication withdrawal. The assessment of efficacy in this setting requires a randomised and controlled trial ( see section 5.5.4.)
- Monotherapy trials in newly or recently diagnosed patients: Before these trials are conducted, adequate evidence for efficacy and safety with the test drug in add on therapy must be available, since approximately two thirds of these patients can be well controlled with a standard treatment.
- Besides these two situations, monotherapy in patients undergoing presurgical evaluation for refractory partial epilepsy may generate some short-term efficacy data (generally no longer than two weeks), which may not be relevant for longer term clinical use (see section 5.5.2).

## 2.3 Dosage

The dossier should contain well-designed dose-finding studies in order to justify the dosages used in confirmatory clinical trials and dose recommendation in the SPC.

In clinical practice, in add-on as well as in monotherapy situations, it is recommended 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. Some of the trials should be as close as possible to these clinical principles . The dose range should be presented together with the related serum levels of the parent drug and its major (active) metabolites. The dose-response relationships from add-on studies in refractory patients may not be applicable to monotherapy use in newly diagnosed patients. 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 in monotherapy settings.

## 2.4 Conditions for registration

Overall, a step wise approach can be envisaged :

- The add-on indication may be granted on the basis of positive results of the confirmatory add-on trials.
- Some add-on studies may be designed to generate data on conversion to monotherapy. The availability of conversion to monotherapy data, as well the lack of these data, will be mentioned in the SPC.
- The monotherapy indication is usually granted when the efficacy and safety of the test drug has been proven in newly diagnosed patients. Other monotherapy situations will usually be supportive in this context.

## 2.5 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 types not seen in adults and the occurrence of seizures as part of specific epileptic syndromes. An epileptic 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 absence, myoclonic and/or generalised convulsive seizures, where the efficacy of AEDs seems to be comparable in childhood and in adult.
2) Seizure types specifically seen in childhood or seizure types specific within an epileptic syndrome seen in childhood (e.g. West, astatic-myoclonic epilepsy, Lennox Gastaut and Continuous Spike–Wave in Slow Sleep syndromes): Sufficient experience needs to be gained in this population before a new medicinal product may be accepted for these indications in children.

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 postmarketing 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.

Paediatric studies should be conducted as early as the development of the medicinal product allows, in order to avoid an excessive delay in obtaining a marketing authorisation for children compared to an adult marketing authorisation. It is recommended to implement the paediatric studies as planned in the clinical development plan after a potential benefit has been indicated in adult studies and before registration of the product in adults (see Guideline on clinical investigation of medicinal products in children)

### 2.6 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 patients may be different from those in younger adults for the following reasons :

- different aetiologies : Alzheimer or other neurodegenerative condition, brain tumour, cerebro vascular 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.

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). Moreover an adequate number of geriatric patients should be included in the Phase III data base. The potential impact of the drug, 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 other products frequently used in this age group. Depending on the data, specific efficacy and safety trials in this population may be needed. The results may be mentioned in the SPC.

## 3. ASSESSMENT OF EFFICACY

### 3.1 The assessment of efficacy should be based primarily upon seizure frequency :

- 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. 50% reduction). The other variable should be some parameterisation using the actual change in seizure frequency. 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

  a) in newly 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:

  a) In add-on designs: the proportion of seizure-free patients is a very important variable; the distribution of responders (seizure reduction < 50%, from 50% to 75%, and > 75%) should also be assessed.

  b) 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 enabling to assess failed efficacy (e.g.: nth seizure) should be justified by the applicant.

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

  d) Dose / efficacy studies based on drug blood level measurements.

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

  f) An additional secondary endpoint may be a composite rating scale wherein seizure frequency, seizure types, adverse events are weighted and expressed in one score. All scales should be thoroughly validated

### 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) 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. 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.

As the distribution of seizure frequencies may be 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 seizure type, baseline seizure frequency, seizure severity, epileptic 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 discussed.

For less frequent seizure types, individual studies may not have enough power to detect a true treatment effect. Efficacy in these seizures might be evaluated by a meta-analysis of individual

studies, provided that these studies are similar in design and that the meta-analysis was planned in advance in the product development plan.

## 5. STRATEGY AND STEPS OF THE DEVELOPMENT. METHODOLOGY OF THE CLINICAL STUDIES

### 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 epileptic syndromes the drug may be efficacious. It may be also predictive of a risk for certain adverse events. For instance some drugs have been specifically designed around a given mechanism : promoting GABA inhibition ; others constitute the extension of a preexisting 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.

### 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. 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 appropriate clinical and laboratory measures.

### 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 5.4). 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.

### 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 pivotal 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.

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

## 5.5 Methodology of clinical studies

### 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, when possible, International Classification of Epilepsies and Epileptic Syndromes.

For ethical reasons, the population selected for the initial clinical trials of AEDs should be patients with continuing seizures in spite of several attempts to control them with other appropriate anti-epileptic drugs, taken in monotherapy and in various combinations.

For newly diagnosed patients, the seizure type - and whenever possible the type of syndrome - should be well defined and the test drug should have shown efficacy in earlier add-on trials.

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, investigator). Training programmes for a reliable seizure recording are recommended.

### 5.5.2 Therapeutic exploratory studies

The purpose of this phase of the product development programme is to identify patients who may benefit from an 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 epileptic 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, who are subject to a pre-surgical evaluation programme may be included in these exploratory studies.

In the exploratory studies a reduction in the frequency of seizures and/or the time to first or nth seizure constitute the primary clinical 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.

### 5.5.3 Therapeutic confirmatory 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 become desirable.

Efficacy endpoints should be based on the changes in seizure frequency between the treatment phase and the baseline period ( see section 3.1)

The study should include a baseline period, a titration period, 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*

In this period, the baseline assessments are made. 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, should 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.

*Titration period*

In the titration period 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 adaptation of the concomitant anti-epileptic products may also be necessary due to interactions. It should be pre-defined in the protocol.

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 may be necessary 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.

Determination of plasma levels at this stage may be useful for correlating plasma concentration levels to efficacy and occurrence of adverse events.

*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.

At the end of the study, several additional data are important:

- Data concerning potential withdrawal and / or rebound effects: a carefully monitored withdrawal process could be performed wherein the test agent and placebo are withdrawn by a tapering off schedule and the occurrence of a rebound and withdrawal effects are evaluated.
- Long-term data: continuation or extension add-on studies are necessary to assess the maintenance of safety and absence of tolerance on the long term. A one-year duration is considered the minimum.
- Eventually data concerning conversion to monotherapy (see section 2.4)

### 5.5.4 Therapeutic confirmatory monotherapy studies

a) In newly or recently diagnosed patients: monotherapy studies should always 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.

Monotherapy studies might incorporate an initial titration phase. Patients should be titrated to a stable dose, which may be the individually determined optimal dose, the maximal tolerated dose or maximal allowed dose. Alternatively, in case of fixed dosages, it may be necessary 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 monotherapy.

The primary endpoint should be the proportion of patients becoming seizure free (see section 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.

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

Monotherapy studies using an established comparator are currently considered the best study design. This design may allow a better assessment of a genuine anti-epileptic effect, a safety assessment of the new compound and extrapolation of the observed findings to the majority of epilepsy patients. However, these trials may fail to show significant differences in seizure control between the various drugs, which may lead to the argument that remission rates could be related to the natural history of the disease rather than to efficacy of the administered drugs. To circumvent this problem, a number of innovative designs have recently been proposed in the scientific literature (see ICH E10). Their use should be justified by the applicant.

b) Conversion to monotherapy in patients with chronic epilepsy: trials should be randomised and controlled, and last for a minimum of 6 months. The choice of the control treatment should be justified by the applicant .

## 6. SAFETY ASPECTS

### 6.1 General considerations

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. The idiosyncratic or/and dose-dependent nature of the adverse events should be assessed as thoroughly as possible. All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of serious adverse events (including deaths) and adverse events leading to drop-outs.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self poisoning should be provided.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of products being investigated depending on the pharmacodynamic properties, the mechanism(s) of action and action on various receptor sites.

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 AED's, special attention should be given to metabolic and endocrine function, and also to the following types of possible adverse events:

#### 6.1.1 Neurological adverse events

Special attention should be given to the occurrence or exacerbation of neurological adverse events (e.g. those involving cognitive functions, thought processes, memory functions, emotional and behavioural reactions, gait, speech, coordination, nystagmus or lethargy).

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.

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 ophtalmological examination procedures.

### 6.1.2 Exacerbation of seizures

There is an increased awareness that AED's 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 try 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 overdosage; 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.

### 6.1.3 Psychiatric adverse events

Recording of behavioural/psychiatric adverse events should be clear and harmonised in its terminology. Specific attention should be paid to the occurrence of cognitive decline, psychotic, or depressive symptoms. Specific claims in this respect have to be based on appropriate studies.

## 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, information on pregnancies in women taking 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).