CLINICAL INVESTIGATION OF MEDICAL PRODUCTS IN THE TREATMENT OF GENERALISED ANXIETY DISORDER, PANIC DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

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Clinical Investigation of Medical Products in the Treatment of Generalised Anxiety Disorder, Panic Disorder and Obsessive-Compulsive Disorder

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Additional Notes
This note for guidance is intended to assist applicants in the interpretation of Directive 75/318/EEC as amended with respect to specific problems presented by clinical investigations of medicinal products intended for the treatment of generalised anxiety disorders, panic disorders and obsessive-compulsive disorders.

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CLINICAL INVESTIGATION OF MEDICAL PRODUCTS IN THE TREATMENT OF GENERALISED ANXIETY DISORDER, PANIC DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

This note for guidance should be read in the light of the annex to Directive 75/318/EEC as amended; it is intended to assist applicants in the interpretation of this Directive with respect to specific problems presented by clinical investigations of medicinal products intended for the treatment of generalised anxiety disorders, panic disorders and obsessive-compulsive disorders.

1 INTRODUCTION AND FIELDS OF APPLICATION

Anxiety as a leading or accompanying symptom occurs in a variety of clinical conditions. Anxiety may occur as the main or only symptom in syndromes such as panic disorder, or as an associated symptom in major psychiatric illness (such as depressive illness), or as an accompaniment to somatic disease (e.g. myocardial infarction). Anxiety disorders may also follow persistent or transitional psychic conditions (e.g. post-traumatic stress disorder).

Anxiety thus may be regarded as a trait as well as a state variable. Treatment of anxiety disorders is an approach in which pharmacotherapy plays a role besides psychotherapeutic intervention techniques. The place and the choice of the measures depend on the specific diagnosis made in a particular patient.

At any rate, treatment of the underlying psychic or somatic disease or counselling in the psychosocial conflict is the first measure if ever possible.

Products which are used in the treatment of anxiety disorders cannot be classified as members of a single pharmacological class.

However, our experience with anxiolytic substances is mainly confined to benzodiazepines which have been widely used despite major concerns due to their dependency risks. There are efforts to replace those classical compounds by newer non-benzodiazepines where it is the hope that they might not present the problem of dependence.

Other compounds are being investigated in special anxiety conditions such as panic disorders or obsessive-compulsive disorders as well: tricyclic antidepressants, MAO-inhibitors and 5-HT reuptake inhibitors.

So-called major tranquillisers have also been recommended. However, their benefit-risk ratio has still to be explored in this indication, in particular concerning medium and long-term treatment, because of their adverse reactions (e.g. tardive dyskinesia).

This note for guidance is intended to assist investigators in clinical studies in the various anxiety conditions such as generalised anxiety disorder, panic disorder with or without agoraphobia, and obsessive-compulsive disorder independent of the class of product under investigation.
Since most of the products currently used in the treatment of anxiety disorders are not devoid of a dependence potential, new compounds have to be investigated with respect to this problem by specific procedures.

Concerning the preclinical considerations the reader is referred to the note for guidance on Clinical Investigation of Hypnotic Medicinal Products where detailed advice is given as to the animal models which can be used to explore the dependency potential of a new compound in animal models.

2. STUDIES IN CLINICAL PHARMACOLOGICAL MODELS (PHASE I)

Initial studies of a potential anti anxiety agent will follow the normal pattern (pharmacokinetics, pharmaco-dynamics, single and repeated dose tolerance) with the following special features:

2.1 Pharmacokinetics

Pharmacokinetic parameters should be investigated in elderly persons as well as in young adults. As an alternative approach to formal pharmacokinetic studies a population approach may be used if clinical assessments on tolerability and efficacy preclude overdosing and underdosing. However, as population approaches are still experimental, the use should be critically discussed in the Expert Report.

Special attention should generally be paid to:
- cumulation effects;
- effects of food intake and smoking on absorption and elimination;
- kinetic interactions (e.g. enzyme induction);
- activity of metabolites;
- pharmacokinetic variability due to genetic polymorphism;
- chiral active substances.

2.2 Pharmacodynamics

Onset, nature and duration of CNS effects may be documented by neurophysiological (EEG) measures or psychometric mood and performance tests (dose-effect-curves, time-effect-curves).

Again separate studies in elderly people are considered desirable.

EEG and pharmacopsychological laboratory studies even in healthy volunteers without symptoms of anxiety may be useful in investigating dose response-relationships and performing dose comparisons.

Studies in symptomatic volunteers may serve to generate hypotheses about the anxiolytic potential of a new compound in the human model. Trait models (volunteers with high vs. volunteers with low level of anxiety measured by specific questionnaires) as well as state models (experimentally inducing stress, panic or anxiety in otherwise healthy subjects,
provided that thorough information and a carefully worded written consent have been given, may both be useful for this purpose.

Special risks (e.g. unwanted sedation, amnesiac effects) should be investigated in appropriate models in healthy volunteers (including vigilance, reaction time, visomotor and attention tests, learning and memory tests after product intake).

3. Therapeutic studies (Phase II and III)

3.1 Patient selection

The patient selection criteria depend on the kind of disorder to be studied:

The nature of the patient's anxiety disorder should be classified according to an internationally acknowledged classification system, preferably DSM III-R or ICD-10, using the diagnostic criteria given therein.

Further descriptive parameters (duration and severity of the disorder) as well as a detailed history of the anxiety should be documented. In addition, cut-off scores, based on appropriate scales, may be used as inclusion criteria. It is essential that the inclusion criteria and reason for treatment with a pharmacological agent should be perfectly clear to the reader of the study report.

It is highly desirable that patient groups are as homogenous as possible for the dose finding and pivotal studies, although this may turn out as a problem because of possible overlaps in different anxiety disorders.

Special attention is required in order to take account of any concomitant depressive symptomatology.

History of alcohol or substance abuse should be an exclusion criterion, at least in phase II trials

If it is not used as an exclusion criterion in phase III trials, any history of alcohol or substance abuse should be documented appropriately.

3.2 Study designs

While certain methodological requirements pertain to all studies performed in patients with various anxiety disorders, there are additional specific features for different fields of application.

To assess the effect of the medicinal product, placebo controlled trials are necessary. In addition, comparison with a standard product, if any, is generally needed, preferably in a three-armed, parallel group design. The treatment should be preceded by a placebo wash-out. Patients should start the treatment on a stable symptom baseline, and any decision to exclude placebo-responders should be discussed.

Active treatment phases should be followed by placebo discontinuation and/or medicinal product free follow-up phases.

The sample size should be justified from biometrical-statistical criteria. Biometrical analysis should include standard as well as intent-to-treat analysis. In case of multicentre trials special attention has to be paid to dealing with possible sources of treatment unrelated
variation (for prerequisites and assumptions that have to be met, - see note for guidance on Biostatistical Methodology in Clinical Trials).

Cross-over designs are generally considered as inappropriate because of their risk of uncontrolled carry over effects.

Prior and concomitant medication has to be documented in detail. Relevant medication has to be washed out. If appropriate, rescue medication should be provided.

Concomitant psychotherapy should be considered very carefully. Specific psychotherapy should be avoided in confirmatory trials. Standardised psychotherapeutic support or counselling may be given as supplementary treatment, but must be strictly standardised and documented in detail, and its effect should be checked as a co-variable.

Compliance controls and screenings for other additional illicit psychotropic substances are recommended. This refers to the initial placebo run-in period and the shift to the active substance as well as to treatment and placebo discontinuation or follow-up phases.

While studies in anxiety disorders are generally connected with a high risk of uncontrolled intervening error variance due to manifold psychosocial influences and thus usually show high placebo response rates, this is even more obvious in outpatient studies. Every effort should be made to document possible intervening influences (life events).

Previously established dose response-relationships from pharmacodynamic studies should be reproduced in clinical models. The effective dose range should be determined. This has to be done separately for each indication.

For multicentre trials inter-rater reliability should be documented.

### 3.2.1 Study designs in Generalised Anxiety Disorder

In Generalised Anxiety Disorder a double-blind treatment phase of 4-6 weeks is generally considered adequate for proof of efficacy, but it may be longer depending on the onset of desired effect.

### 3.2.2 Study designs in Panic Disorder

For clinical product trials in Panic Disorders, the treatment duration should not be less than 8 weeks, depending on the frequency of attacks. In case of studies in panic attacks with and without agoraphobia, the results should be analysed separately. The effect on both, panic attacks (see 3.3.3) and agoraphobia should be taken into account.

### 3.2.3 Study design in Obsessive Compulsive Disorder

For Obsessive Compulsive Disorders a treatment duration of 8 to 12 weeks is considered appropriate, and careful account must be taken of any associated depressive symptoms as response co-variables.

### 3.2.4 Maintenance therapy and relapse rate

Due to the chronic character of most anxiety disorders, longer double-blind placebo-controlled studies are necessary to show that the effect found in the acute phase is maintained. Depending on the disorder, 6 months placebo controlled trials are necessary. This may be done with responders to the acute treatment using relapse as a criterion. In case long-term
use is ethically not justifiable because of known dependence risks, consequences for the labelling have to be discussed in the Clinical Expert Report.

3.3 Efficacy criteria

The choice of assessment methods depends on the symptomatology that is being investigated. At any rate the choice of instruments should be justified from test quality criteria (reliability, validity, availability of norm data for the population in question). Choice of endpoints and clinical relevance of expected effects (e.g. degree of symptom reduction experienced by responders) have to be discussed in the trial protocol with reference to other comparative data or publications available.

3.3.1 Observer rating scales

Observer rating scales include comprehensive scales as well as (secondary) global clinical rating scales (Clinical Global Impression).

3.3.2 Self assessment scales

Assessment of subjective feelings of reduced anxiety is done by anxiety questionnaires and self rating (mood) scales.

3.3.3 Behavioural measures

Specific behaviour measures (counting of events) are useful target variables especially in Panic Disorder (e.g. number and severity of panic attacks) and Obsessive Compulsive Disorder (e.g. construction of specific prime symptom scales according to the individual presentation of rituals or ruminations). Patient diaries are advisable.

4. Safety assessment

4.1 Monitoring of unwanted effects

4.1.1 ADR

Adverse events occurring during the course of the treatment should be carefully recorded, with particular regard to neurological and psychological changes (e.g. those involving gait, speech, co-ordination, nystagmus lethargy, amnesia, depression and/or suicidal tendencies). Identified ADRs should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Neuropsychological tests should be applied accordingly in healthy volunteer and at least some patient studies.

Adverse reaction scales should be standardised for use in studies with psychotropic medicinal products. Clinical observations should be supplemented by appropriate laboratory tests and cardiological recordings.

4.1.2 Sedative effects

Since sedative compounds are used in the treatment of anxiety disorders, these effects have to be measured. They may be defined as decreased vigilance and impaired concentration and may be measured by psychometric tests (mood scales, concentration and attention tests,
simple arithmetic procedures, vigilance tests, e.g. critical flicker fusion) or, to a certain extent, by means of EEG recordings.

If the compound used is claimed not to be sedative, this should be demonstrated both in clinical and specific trials with appropriate design including positive control.

Special attention should be paid to:

4.1.3 Effects on driving and operating machinery

This is important standard information for every package insert. Vigilance and performance tests, psychomotor test batteries, reaction tests as well as car-driving simulators and standard over-the-road driving tests are considered appropriate to determine whether an anxiolytic substance may impair vigilance and psychomotor functions. As motivational factors can affect the results in those tests, the duration should be long enough (minimum one hour).

Placebo as well as positive controls are necessary in these studies in order to avoid false negative results.

However, the limited relevance of experimental models for the extrapolation to real life situations should be critically discussed.

4.1.4 Overdosage

All available - pharmacological and clinical - information concerning symptoms and therapeutic measures in accidental overdosage or deliberate self-poisoning should be provided. Sponsors and clinical investigators should be prepared with an emergency protocol as well as suitable case record forms to obtain certain information (e.g. pharmacokinetic data) immediately in the wake of accidental or deliberate overdose.

4.2 Dependence potential

For ethical reasons there are only very limited opportunities to investigate the dependence potential of a new therapeutic agent in humans. But there are several other phenomena which may be considered as indicative of a medicinal product's abuse potential:

4.2.1 Mood and/or behavioural changes

Alterations in healthy volunteers' or patients' mood and behaviour after medicinal product intake should be carefully investigated. Special attention should be paid to signs of euphoria, altered consciousness, or hallucinogenesis.

4.2.2 Development of tolerance as an indicator for dependence potential

Tolerance can be defined as a decrease in specific pharmacodynamic effect and will usually lead to an increased dosage. It is detectable by careful surveillance of patients' medicinal product intake behaviour.

4.2.3 Discontinuation phenomena as an indicator for dependence potential

Discontinuation phenomena and rebound anxiety may be considered as other indicators for a medicinal product's dependence potential. Therefore every study should end up in a placebo
discontinuation phase and/or medicinal product free period, the length of which is determined by kinetic parameters and the length of the preceding treatment phase.

As discontinuation phenomena are less probable after short term treatment, some special medium term (more than 2 months) and Long-term (more than 6 months) studies should be performed in addition to short term studies (4 to 8 weeks), provided, the substance seems free from dependence potential. Careful attention should be paid to detailed assessment of symptoms by subjective and objective rating scales (symptom checklists, questionnaires) and objective measures of arousal. Baseline data (pre-treatment values) as well as scores during treatment should be available.

Rebound, relapse and recurrence are difficult to distinguish but may be differentiated by the time lapse and the severity with which the symptoms occur. Rebound and relapse are likely to occur soon after plasma concentrations become subtherapeutic, and rebound is likely to be associated with severe symptoms beyond baseline level. Recurrence can only reliably be defined as a return of symptoms after the patient has remained symptom-free while off treatment. These problems should be critically discussed with reference to baseline values.

4.3 Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see The note for guidance on The Extent of Population Exposure to assess Clinical Safety for Medicines intended for Long-term Treatment of Non-life-threatening Conditions).

5. SPECIAL STUDIES

5.1 Studies in special groups of patients

The need for separate studies in special groups of patients who may be at increased risk should be considered. As mentioned before, studies in elderly patients are mandatory (see also note for guidance Clinical Investigation of Medicinal Products in Geriatrics).

Clinical investigations of antianxiety medicinal products in children have to be performed in separate studies if the claim pertains to the treatment of this target population (see note for guidance Clinical Investigation of Medicinal Products in Children).

5.2 Interaction studies

5.2.1 Interaction with alcohol

With most currently available antianxiety medicinal products, concomitant intake of alcohol will lead to an additive or even potentiated depression of the CNS, and to more or less severely pronounced sedation. This will be relevant for driving and operating machinery and correspondingly will require warnings in the package insert. For safety reasons investigation is required into whether concomitant intake will lead to more sedation than intake of one of the components alone. Neurophysiological (EEG) and pharmacopsychological methods (performance tests, self rating scales) would be considered as appropriate.
5.2.2 Interaction with CNS active substances

Other psychotropic or CNS-active substances such as antidepressants or neuroleptics are likely to be given concomitantly. Therefore interaction effects should be investigated, not only in pharmacokinetics, but as the clinical relevance of altered serum levels is often unknown, also in clinical models and in patients.

5.2.3 Interaction with cardiac medicinal products

Since anxiety disorders also occur in elderly patients who suffer from multiple diseases, special interaction studies are necessary. As cardiac disorders and thus concomitant treatment with cardiac medicinal products are very common in elderly patients, interaction effects should be investigated.

5.2.4 Neuroendocrinological parameters

Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuroendocrinological parameters (e.g. growth hormone) may be necessary.