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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR GENERALISED ANXIETY DISORDER

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GUIDELINE ON THE CLINICAL INVESTIGATION FOR THE TREATMENT OF MEDICINAL PRODUCTS INDICATED FOR GENERALISED ANXIETY DISORDER

This Guideline is intended to provide guidance on the evaluation of new medicinal products in general anxiety disorder (GAD). It should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Dose-Response Information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4),

- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9),

- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10),

- Adjustment for Baseline covariate – CPMP/EWP/2863/99,

- Missing data – CPMP/EWP/177/99,

- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A),

- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7),

- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH11),

- Pharmacokinetic studies in man (EudraLex vol. 3C C3A).

Three separate guidelines are available for obsessive-compulsive disorder, panic disorder and social anxiety disorder. Those guidelines supersede the previous Note for guidance on clinical investigation of medicinal products in the treatment of general anxiety disorder, panic disorder and obsessive-compulsive disorder (EudraLex vol. 3C C28A).

This Guideline is intended to assist applicants during the development of medicinal products intended for the treatment of general anxiety disorder, independent of the class of product under investigation. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

I.   INTRODUCTION

Generalised anxiety disorder (GAD) was introduced into the psychiatric nomenclature in 1980 with the publication of DSM-III. The diagnostic changes applied to GAD between DSM-III and DSM-IV have made it difficult to develop a consistent understanding of its course. The Epidemiologic Catchment Area (ECA) study found that the duration of DSM-III GAD was longer than five years in 40% of patients. The reported lifetime prevalence rates for DSM IV GAD in the general population is approximately 5-6% with rates as high as 10% among women aged 40 years and above and in elderly (aged 55-85 years) of about 7%.

Cross-sectional rates among primary care attendees are about 8%, making GAD the most prevalent anxiety disorder in primary care.

There are indications but no hard figures that GAD may be a disorder almost not occurring in children. The twelve months prevalence of DSM IV GAD in adolescents is about 1%.

The current treatment options for GAD include benzodiazepines (formally restricted to short term only) and other approved treatments for the short-term treatment of GAD (paroxetine and venlafaxine). Benzodiazepines are formally restricted to short-term use because of their

potential for excessive sedation, dependence, abuse and cross-tolerance with alcohol. As GAD is a more chronic disorder, treatment needs to be prolonged beyond short-term usage.

Diagnosis

The defining features of Generalised Anxiety Disorder (GAD) are excessive anxiety and worry, and the diagnosis can only be made when there is significant social, occupational, and functional impairment that has persisted for at least 6 months (according to DSM IV functional impairment is not necessary for the diagnosis if clinically significant distress is evident)

Differential diagnosis

All other anxiety disorders may be considered as differential diagnosis of GAD.

Severity

Patients with GAD may have many somatic complaints. This may account for the high use of medical resources among patients with GAD. In addition patients with GAD have higher risk of negative outcome (e.g. increased burden on the health care system, increased morbidity and mortality rates).

GAD is associated with diminished overall emotional health and identified evidence of decreased employment and corresponding increased reliance on public assistance, impaired social life (e.g. limited friendships or few recreational activities), and low ratings of life satisfaction.

In conclusion GAD is associated with significant psychosocial impairment and significant negative effect on quality of life.

Co-morbidity

GAD is frequently associated with a wide spectrum of other mental disorders, with a lifetime co-morbidity among 90.4% of the people who had a history of GAD (About 17% of the GAD patients report a lifetime major depression. Also other anxiety disorders are very common in patients with GAD).

II.   PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

II.1   Inclusion Criteria

The disorder should be classified according to an internationally acknowledged classification system, preferable the latest version of the DSM criteria. The latest version of ICD may also be used. The same classification system should be used for the whole development program of the medicinal product. The use of a severity rating scale alone is insufficient and is not equivalent to a diagnosis. Diagnosis should be made by an experienced psychiatrist and confirmed by a structured interview.

Further descriptive parameters, like severity, as well as a detailed history, e.g. of the duration of GAD and previous treatment outcome, should be recorded.

In addition cut-off scores, based on an appropriate severity scale (see section III.1) may be used as inclusion criteria.

It is highly desirable that the study population is homogeneous with respect to the indication for the dose finding and pivotal studies. However because of the high co-morbidity of other psychiatric disorders in patients with GAD this might be difficult (see also exclusion criteria).

As GAD patients are almost always out-patients the majority of the database should be in out-patients.

II.2 Exclusion criteria

(The exclusion criteria mentioned below are necessary to deal with the problem of co-morbidity)

Patients with a current or recent history of major depression (within 6 months of study entry).

Patients with predominant and/or severe depressive symptoms (e.g. not meeting the DSM IV MDD criteria). Patients should have low severity scores e.g. (<2) on item 1 of the HDRS.

Patients with severe symptoms of other anxiety disorders. Patients with severe OCD symptoms (not meeting the DSM IV criteria). Patients with a history or presence of any psychotic illness.

Patients with a bipolar disorder.

Patients with a primary or severe Axis II disorder.

Patients with chronic alcohol abuse, or current / recent history of substance abuse (within the last 6 months).

III. METHOD TO ASSESS EFFICACY

Results should be discussed in terms of both clinical relevance and statistical significance. When a statistically significant effect is found and it has been shown that the effect is robust and insensitive to the analysis used, this effect has to be addressed in clinical terms, depending on the purpose of the trial. It should be noticed that the relevance of the effect is a basis for the benefit/risk assessment. The sample size of the studies should take this into account.

III.1 Primary Efficacy Endpoints in confirmatory trials

Efficacy will be assessed by rating scales. The choice of rating scales should be justified from the test quality criteria (reliability, validity) and the sensitivity for change should be known. For the assessment of improvement specifically developed rating scales are necessary.

The Hamilton anxiety rating scale (HAM-A) is a widely used, though not optimal scale. Using a structured interview may be useful. The total scale can be used as primary endpoint, whereas the HAM-A psychic anxiety factor may be useful as a secondary endpoint.

Other scales could be used provided that they are appropriate and validated.

Improvement of symptomatology should be documented as a difference between baseline and post-treatment score, but should also be expressed as the proportion of responders and/or remission. Responders are defined as patients with a clinical relevant reduction from baseline on the primary outcome scale.

Remission is defined as a condition where no or only few signs of illness remain.

The cut-off on a validated rating scale has to be defined in the protocol and should be justified (for response and for remission).

In advance and if necessary during the study, investigators should be trained to become and stay inter-reliable.

III.2 Secondary Efficacy Endpoints in confirmatory trials

Global assessment (e.g. a score of 1 or 2 on the Clinical Global Impression Scale of Global Improvement) may be used as secondary endpoint

Other scales with a well-established efficiency, as Sheehan disability scale, may also be used as secondary endpoints.

III.3 Other supportive efficacy criteria

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Changes from baseline for the HAM-A psychic and somatic anxiety factors

CGI Severity of Illness

QoL may be used when validated for the patient population

IV.   STRATEGY AND DESIGN OF CLINICAL TRIALS

IV.1   Early Studies in Man

Pharmacodynamics

A variety of tests can be performed, but there is no specific model in humans for GAD. Studies of cognition, reaction time or on sleep architecture may be informative concerning the side effect pattern of the product.

Pharmacokinetics/Interactions

The usual pharmacokinetic studies should be performed. Especially in dose response studies l plasma levels may be studied.

Moreover in general the CHMP Note for Guidance on the Investigation of Drug Interactions (CHMP/EWP/560/95) should be followed to investigate possible pharmacokinetic and pharmacodynamic interactions. Concerning the latter, interactions with alcohol and other CNS active medicinal products should be investigated.

Dose-Response Studies

Controlled, parallel, fixed dose studies, using at least 3 dosages are needed to establish as far as possible the lower end of the clinical effective dose range as well as the optimal dose. Generally it is useful to add a placebo arm as well as an active comparator.

IV.2   Therapeutic Confirmatory Studies

IV.2.1   Short-term trials

In principle, to assess the effect of medicinal products short-term (at least 8-weeks) parallel, double blind, randomised placebo controlled studies are necessary. In addition, comparison with a standard product in an adequate dose is generally needed, in a three-arm design. The dose and the comparator should be justified.

Choice of control

As stated in the above the test product should be compared with both placebo and an active control, using a three or more arm design. The choice of active comparators should be justified. They should be chosen from one of the compounds already authorised for this indication. Depending on the pharmacological properties of the test product, this comparator could be chosen among other compounds of proven efficacy in this indication.

Though a placebo might be seen as an ethical problem, the use is necessary to show the effect of the new product unequivocally, as the effect in the placebo-group may be high and rather variable between studies.

Wash-out period

Generally a placebo run-in period to exclude placebo responders is not useful and may impair generalisation of the results. When patients are already treated with an active agent, a wash-out period may be necessary. Any reason to exclude placebo responders should be discussed.

Methodological considerations

The sample size should be justified, using clinical (responders = clinical relevant improvement

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from baseline on the primary outcome measure) and biostatistical criteria.

Statistical analysis should include various analyses; intention-to-treat and per protocol among others. The ITT analysis is however the primary analysis. The handling of dropouts and missing data should be prospectively planned in the trial protocol. The risk of under- or overestimation of the effect should be addressed. See further the biostatistical guidelines.

Additional psychotherapy, support or counselling should be prospectively defined in the protocol and their effects on treatment outcome should be analysed Formal Psychotherapy, however, might be excluded as there may affect the magnitude of effect.

IV.2.2   Long-term trials

In addition to the short-term trials, long-term studies are needed demonstrating that the effect of the product is maintained over time. The optimal design for demonstrating maintenance of effect is by means of a randomised withdrawal study. The design of the randomised withdrawal study in responders (RWS) is characterised by a first phase where patients are treated (open label usually) and a second phase where predefined responders/remitters from the first phase are randomised to either placebo or to one or more active compound arms. The duration of the open phase should be at least 2 months and may be of up to 6 months. The duration of the randomised phase is usually 6-12 months. At the start of the randomised phase the medication may need to be tapered off to prevent withdrawal phenomena.

In RWS efficacy usually is expressed as number of patients worsening (relapsing) and/or time to this event. Both efficacy criteria are of interest and should be submitted. The analysis should carefully consider the possible biases arising from drop-outs (not because of relapse) and the statistical methods of dealing with them.

Worsening or relapse has to be defined in the protocol and should be a clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits.

IV.3   Studies in special population

Elderly

Although the prevalence rate in elderly seems to be higher and older people seem to worry more and for longer time, the presentation of GAD does not seem to be essentially different from the younger population. In ICH E7 it is indicated that the efficacy and safety for the elder population can be derived from the total database, unless there are specific reasons not to do.

The extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the elderly for the pharmacodynamics of the product. Therefore defining a safe dose (range) in these patients is a main concern. Usually this should be addressed before licensing. In principle two approaches are possible. One in an analysis of the whole database, whereas the other would be to conduct specific trials in a specific patients population. The optimal design would be a placebo-controlled dose response study.

The first approach may be accepted as pivotal information for agents of known pharmacological classes, provided that sufficient elderly patients are included to allow a prospective subgroup analysis.

For new products with a new mechanism of action specific trials may be needed. In both situations pharmacokinetic studies may support the choice of the dose and should be conducted.

Children and adolescents

It is widely recognised that anxiety symptoms in children exists and may be a great burden for the children and their parents (or caregivers). However, in children GAD seems to be a disorder that (almost) does not occur and in adolescents it seems to have a low prevalence rate of about 1%.

Research in this group of patients, however, has increased over the last years, but experience is still limited. Mostly it appears to be seen in the context of another disorder. Therefore studies in children are probably impossible to conduct and the data may not be generalisable. Although the prevalence rate in adolescent is low studies may be of interest.

Rating scales should be specific for and validated in this group. Difference in impact of adverse effects, seen in adults, in children and adolescents should be considered. In line with the paediatric guideline (ICH E11), trials may be conducted after a marketing authorisation and licensing for adults is obtained.

Moreover, in line with the relevant guideline, effects on cognition, learning, development, growth and endocrine functions should be addressed; cognition and learning should be studied pre-licensing using recognised tests, validated for the age and patient group. Also the direct effect on endocrine functions in adolescents should be studied before marketing authorisation and licensing. Long-term effects on learning, development, growth and sexual maturation and function should be studied post-marketing, but appropriate protocols should be available when the use in children is applied for.

Studies in this patient population should be supported by adequate pharmacokinetic studies.

V.   CLINICAL SAFETY EVALUATION

V.1   General recommendation

Identified adverse events should be carefully monitored and should be characterised in relation to the duration of treatment, dose and/or plasma levels, recovery time, age and other relevant variables.

All adverse events should be fully documented with a separate analysis of adverse drug reactions, dropouts and patients who died during the trial.

Side effects that are characteristic of the class of the product being investigated should be carefully monitored. As both serotonine and dopamine seem to play a role in the pathophysiological process of the disease, possible side effects related to these neurotransmitter systems should be investigated, preferably using specific scales (e.g. serotoninergic syndrome, extrapyramidal symptoms). Interactions with other neurotransmitter systems (e.g. noradrenergic, cholinergic and histaminergic receptors) should also be monitored.

Clinical observations should be supplemented if necessary by appropriate tests.

Specific monitoring is needed in children/adolescents and the elderly (see section IV.3).

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

V.2   Specific adverse events

Rebound/ withdrawal/dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur.

Rebound and/or withdrawal phenomena should be investigated. Short term and long-term study designs should contain at least one visit after treatment discontinuation in order to assess the occurrence of withdrawal and rebound symptoms.

For new candidate compounds, at least one short-term and one long-term trial should incorporate a short withdrawal period to look for withdrawal symptoms. This could be done in a randomised withdrawal study where treatment is abruptly stopped in responders and patients are followed for a suitable time to detect possible rebound and withdrawal symptoms.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur. The chronic nature of GAD increases the risk of dependence. Based on the results of the animal studies, in vivo studies in humans may be required.

Central Nervous System (CNS) adverse reactions

Depending on the class of the investigated medicinal product and the possible interactions with various receptors, effects on cognition, reaction time and /or driving, and the extent of sedation should be studied.

Similarly it may be necessary to monitor psychiatric side effects (e.g. depression, mania, mood).

Suicidal behaviour should be monitored carefully. Special attention should be paid to attempted and completed suicides.

Haematological adverse reactions

Special attention should be paid to agranulocytosis, aplastic anaemia and reduction in platelet count.

Cardiovascular adverse reactions

Special attention should be paid to arrhythmias and conduction disorders, in particular QT interval prolongation, if the medicinal product belongs to a class associated with cardiovascular effects or in studies in which the active comparators with such profiles are used (e.g. clomipramine).

Endocrinological adverse reactions

Special attention should be paid to sexual disturbance, libido and weight gain.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (e.g. SIADH, prolactine secretion).

V.3   Extent of population exposure to assess clinical safety including long-term safety

The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure (ICH E1A).

Relevant data from other indications could be used as supportive safety information in the present indication.