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# COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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# GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PANIC DISORDER

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| GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PANIC DISORDER |
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This Guideline is intended to provide guidance on the evaluation of new medicinal products in panic disorder (PD). 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, general anxiety 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 panic 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

Panic Disorder (PD) is a common, distressing and often disabling condition in which the affected individual suffers from recurrent and unexpected attacks of intense anxiety accompanied by sympathetic arousal, which cause significant distress. However, in general these attacks occur in absence of objective danger. With repeated attacks, they grow fearful of situations or circumstances from which escape might be difficult (e.g. small rooms, elevators, crowded train, subway, etc.) or where help might not be available (e.g. alone or distant from home). However, the key feature of PD is the panic attack.

Therefore the primary goals of treatment for PD are:

- diminution of the frequency and intensity of panic attacks

- decrease of anticipatory anxiety

- reduction of phobic avoidance.

Both psychopharmacological and psychological treatments are effective but not much is known about which approach is superior for which patient. Effective psychopharmacological treatment for PD was first reported in 1964 by Klein and colleagues using imipramine. There

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have since been randomised clinical trials using different tricyclic antidepressants and recently several selective serotonin reuptake inhibitors (SSRI), which are now emphasized as first line-treatment in patients with PD. Despite these improvements of the therapeutic armamentarium benzodiazepines are still used in the treatment of the acute panic attack and are concurrently prescribed to antidepressants in clinical practice, even though they are restricted to short-term use due to their potential for side effects (excessive sedation, dependence, abuse, cross tolerance with alcohol). As PD is a chronic disorder treatment needs to be prolonged beyond short-term use which is highly problematic with the usage of benzodiazepines.

## I.1 Diagnosis

Panic Disorder (PD) involves recurrent and unexpected attacks of intense anxiety accompanied by sympathetic arousal, which cause significant distress for the affected individual. Patients with panic symptoms should be given a thorough diagnostic evaluation both to establish whether a diagnosis of panic disorder is justified and to reveal the presence of other psychiatric or general medical conditions.

The DSM-IV-TR requires recurrent unexpected panic attacks plus at least 1 month of persistent concern about experiencing additional attacks, worry about the implications or consequences of attacks, or a significant change in behaviour related to attacks to establish the diagnosis of PD. Specific criteria for a panic attack are included in the DSM-IV-TR recognising the fact, that attacks of anxiety occur as well in other anxiety and non-anxiety psychiatric disorders. The DSM-IV-TR criteria require that at least 4 of 13 criteria must be present to diagnose a "full" panic attack, with fewer than 4 of the 13 symptoms a panic attack is referred to as "limited symptom attack". Agoraphobia is a fear of places or situations from which escape might be difficult or where help may be unavailable in the event of a panic attack or panic symptoms. This fear leads to avoidance of a variety of situations such as being alone or away from home, being on bridges or in elevators etc.

The ICD-10 criteria for PD are similar but do not specify a threshold beyond recurrent attacks. Therefore the diagnostic criteria as outlined by DSM-IV-TR are preferred.

## I.2 Differential Diagnosis

When symptoms of major depression and PD coexist, it is essential to determine which disorder is primary. It has been reported, many patients with panic disorder develop major depression and up to twenty percent of patients with primary major depression suffer from panic attacks.

There are a variety of medical conditions that may cause panic attacks and others that may produce panic-like symptoms. In either case it is important to rule out such conditions. Moreover a variety of medicines, drugs and alcohol, during intoxication or withdrawal, may cause anxiety including panic attacks.

## I.3 Severity and Burden of Disease

Patients with PD have many somatic complaints (e.g. chest pain, shortness of breath, etc.) and are convinced that they are physically ill (e.g. myocardial infarction) and resist the thought that their disorder may be psychiatric. This accounts for the high use of medical resources among patients with PD. In addition patients with PD have higher risk of negative outcome (e.g. increased burden on the health care system, increased morbidity and mortality rates).

PD is associated with diminished overall emotional health, decreased employment and impaired social life (e.g. limited friendships or few recreational activities), and low ratings of life satisfaction. Therefore PD is often associated with severe psychosocial impairment and substantial negative effect on quality of life.

### I.4     Epidemiology and Co-morbidity

Findings from epidemiological studies show lifetime prevalence rates of up to 3 to 5 % for PD, of 5 to 10 % for unexpected panic attacks and of up to 20 % for any significant panic during lifetime. The typical age at onset is between later phase of adolescence and the mid-30s, however, panic disorder with or without agoraphobia has been described in children and adolescents as well. Females are affected twice as frequently as males. Other results from the Epidemiological Catchment Area Study have shown that PD is associated with high levels of subjective distress, frequent use of emergency services, impaired social functioning, substance abuse and a high rate of suicide attempts.

Co-morbidity is highly common among patients with PD. The co-morbidity rates are especially high for other anxiety disorders (GAD, social phobia) and depressive disorders. In PD coincidence rates are highest for phobic disorders and major depression.

## II.     PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

### II.1     Diagnosis and Inclusion Criteria

The disorder should be classified according to an internationally acknowledged classification system, preferable to the latest version of DSM, using the diagnostic criteria herein. The use of a severity rating scale alone is insufficient and is not equivalent to a clinical diagnosis. Diagnosis should be made by an psychiatrist or by a non–psychiatrist physician experienced in anxiety disorders and who is trained in the use of structured interviews to confirm the diagnosis and exclude relevant comorbid disorders.

Further descriptive parameters, like severity (e.g. frequency of panic attacks, degree of anticipatory anxiety, degree of phobic avoidance), as well as a detailed history, e.g. of the duration of PD, degree of functional impairment and previous treatment outcome, should be recorded.

In addition to the diagnostic criteria cut-off scores based on appropriate scales may be used to include patients with a certain degree of severity.

For the dose finding and pivotal studies it is recommended to include patients with PD without significant comorbities. Otherwise interpretation of study results may be inconclusive, e.g. treatment effects of an antidepressant on PD with comorbid major depression.

As the majority of PD patients are out-patients this should be reflected in the study population.

### II.2     Exclusion Criteria

Excluded should be patients with:

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

- predominant depressive symptoms (not meeting the DSM IV MDD criteria), patients should have low severity scores, e.g. <2 on item 1 of the Hamilton Depression Rating Scale

- predominant or severe symptoms of another anxiety disorder

- schizophrenia or other disorder with psychotic symptoms

- bipolar disorder

- a current or recent history of substance abuse disorders (within 6 months of study entry).

- a primary or severe Axis II disorder (personality disorders)

- formal behavioural, cognitive or cognitive-behavioural therapy (these therapies have been empirically validated and in general have been proved effective for PD treatment. They have been shown to be more effective than no treatment, psychosocial "placebo" intervention and even some psychopharmacological interventions. Therefore, patients with ongoing specific psychotherapy for PD should not be included in confirmatory trials.

- with ongoing relevant psychotropic co-medication for panic disorder (such medication should be washed out).

## III.   METHODS TO ASSESS EFFICACY

Results should be discussed in terms of both statistical significance and clinical relevance. When a statistically significant effect is found and it has been shown that the effect is robust with respect to the assumptions underlying the primary analysis, this effect should be addressed in terms of clinical relevance (responders, remitters), depending on the purpose of the trial. It should be noticed that the clinical 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

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 in PD specifically developed rating scales are necessary.

In PD not only the recording of the frequency and severity of panic attacks (full and limited attacks) should be assessed but also the severity of agoraphobic avoidance and anticipatory anxiety should be evaluated. Therefore, several scales have been developed for measurement of specific symptoms according to the diagnostic criteria of PD, which may be more appropriate for use in clinical trials, e.g. the Panic Disorder Severity Scale (PDSS) and the Panic and Agoraphobia Scale (PAS), than focussing only on frequency and severity of panic attacks. Other Scales may be used as well, if they are validated and reliable in PD.

However, in many trials carried out in patients with PD frequency of panic attacks has been used as primary endpoint. For that reason improvement in assessment scales, e.g. PDSS or PAS, should be supported by a relevant decrease in frequency and severity of panic attacks.

Improvement of symptomatology should be documented as a difference between baseline and post-treatment score, however, in order to allow an estimate of clinical relevance the proportion of responders or remitters should be presented. For this appropriate cut-off-points on validated rating scales should be defined and justified in the protocol.

In advance and if necessary during the study investigators should be properly trained for diagnostic criteria and for assessment of patients with the applied rating scales. Methods should be foreseen in the study protocol to assess inter-rater reliability.

### III.2   Secondary Efficacy Endpoints

Depending on the choice of the assessment used as primary efficacy endpoint, other assessments may be used as secondary efficacy endpoints.

Moreover global assessments (e.g. a score of 1 and 2 on the Clinical Global Impressions Scale of Global Improvement) or changes from baseline in the Sheehan Disability Scale may be used as secondary endpoint.

### III.3   Other Supportive Efficacy Criteria

- Clinical Global Impressions Scale - Severity of Illness

- QoL may be used when validated for the patient population

## IV. STRATEGY AND DESIGN FEATURES OF CLINICAL TRIALS

### IV.1 Early Studies in Man

#### IV.1.1 Pharmacodynamics

A variety of tests has been performed in patients with PD using several pharmacological active substances. Clinical studies using functional neurophysiological or neuroimaging techniques have been initiated to confirm the involvement of specific brain structures in the experience of anxiety or fear. However, there is no specific model in humans for PD.

Studies of cognition, reaction time or on sleep architecture may be informative concerning the side effect pattern of the product.

#### IV.1.2 Pharmacokinetics/Interactions

The usual pharmacokinetic studies should be performed (see note for guidance on pharmacokinetic studies in man). Especially in dose response studies plasma levels should be investigated.

Moreover in general the note for guidance on drug interactions should be followed to investigate possible pharmacokinetic and pharmacodynamic interactions. Concerning the latter, interactions with alcohol and other CNS active medicinal products should be analysed.

#### IV.1.3 Dose Response Studies

Randomized, 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 recommended to add a placebo arm as well as an active comparator.

Usually the duration of these trials is between 8 and 12 weeks.

### IV.2 Therapeutic Confirmatory Studies

#### IV.2.1 Short-term Trials

In principle, to assess the effect of medicinal products randomised, double blind, parallel-group studies are necessary. In general three-arm-studies including placebo and active comparator are requested. The dose of the new compound as well as the dose of the active comparator has to be justified. The duration of the studies is at least 8 weeks.

#### IV.2.1.1 Choice of Control Group

As stated above the test product should be compared with both placebo and an active comparator, using a three- or multi-arm design. These designs are highly recommended, as the trial will be internally validated (addressing the problem of assay sensitivity). The aim of the study may be superiority over placebo or active comparator, non-inferiority against active comparator, or at least demonstration of a similar balance between benefit and risk of the test product in comparison to an acknowledged standard agent.

Though a placebo might be seen as an ethical problem in studies, the use is necessary to show the effect of the new product unequivocally, as the effect in the placebo group may be high in patients with PD and rather variable between studies (range 25% to 75%). The choice of active comparators should be justified. They should be chosen from one of the compounds already approved in this indication. Depending on the pharmacological properties of the  test product, this active comparator could be chosen among other compounds of proven efficacy for this indication.

### IV.2.1.2 Run-in Period/Wash-out Period

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

### IV.2.1.3 Methodological Considerations

It is important to demonstrate that the effect of the medicinal product is specific for PD and is not due to secondary therapeutic effects on psychiatric comorbid conditions. Sample size should be calculated based on an effect size that is clinically relevant. It may be useful to take the clinical relevance (responders/remitters) into consideration. The statistical analysis should include various analysis, among others intention-to-treat (ITT) and per protocol. However, the ITT analysis is the primary analysis. The handling of dropouts and missing data should be prospectively planned in the study protocol. The risk of under- or overestimation of the effects should be addressed. See further the statistical guideline (ICH 9) as well as the Points to consider document concerning missing values. However, it may be considered that clinical assessment of significant effects is done by inspection of the clinical relevant improvement from baseline on the primary outcome measure defined by remitters/responders.

### IV.2.2   Long-term Trials

Because of the chronic course of PD, in addition to the short-term trials demonstration of long-term efficacy has to be established in at least one well-designed study. This might be done by a randomised withdrawal design. In these studies responders to the investigational treatment of sufficient duration are re-randomized to investigational drug or placebo. This is done in two time periods, in the first open and uncontrolled period the responders continue with the test treatment for 8 to 12 weeks, thereafter they are re-randomized and followed by at least 6 months.

In these studies 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. Nevertheless, in the study protocol it has to be justified whether one or both are used as primary endpoint.  The analysis should be 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.

However, for such studies, the protocol should include specific measures to prevent complications of the disease (e.g. serious worsening, suicidal ideation) like close monitoring and the possibility to use rescue medication or to switch deteriorating patients to appropriate treatment with reference compounds.

### IV.3      Studies in Special Populations

### IV.3.1   Elderly

In comparison to other anxiety syndromes PD has been reported to be rare in the geriatric population and seldom arise for the first time in older people. However, phobic avoidance is as common as in younger age groups with reported prevalence rates between 0.7% and 12.0%. In ICH E7 it is indicated that the efficacy and safety for the elderly 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 not only efficacy, but defining a safe dose (range) in these patients is a main concern. Usually this should be addressed before marketing authorisation and 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.

### IV.3.2   Children and Adolescents

PD seems to be a disorder that also occurs in children and adolescents, often starting as separation anxiety disorder. Research in this group of patients has increased recently, but experience is still limited.

Trials in the non-adult population may be relevant and should be conducted in children (6-12 years) and adolescents (> 12 years) separately. For both age categories studies are needed, as presentation of symptoms and natural course may be different. Rating scales should be specific for and validated in the age groups (e.g. multidimensional anxiety scale for children (MASC)). Development of the product solely in adolescents could also be considered, but the results would not be generalisable to young children. Differences in impact of adverse effects seen in children and adolescents in comparison to adults should be considered, particularly attention should be paid to suicidal ideations and behavioural abnormalities in children and adolescents. In line with the paediatric guideline (ICH E11), trials may be conducted after a licence 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 paediatric populations is applied for.

## 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 serotonin 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 sections IV.3.1 Elderly and IV.3.2 Children and adolescents).

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

## V.2 Specific Adverse Events

### V.2.1 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 PD increases the risk of dependence. Based on the results of the animal studies, in vivo studies in humans may be required.

### V.2.2 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.

### V.2.3 Haematological Adverse Reactions

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

### V.2.4 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).

### V.2.5 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.2 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.