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GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER (PTSD)

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GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER (PTSD)

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EXECUTIVE SUMMARY

The aim of this guideline is to provide guidance for the planning of clinical studies concerning the treatment of post-traumatic stress disorder (PTSD), the only psychiatric disorder with a causal agent (the traumatic event) being part of the diagnostic criteria. There are several SSRIs that are currently used in the treatment of PTSD.

The present document should be conceived as general guidance, and should be read in conjunction with other applicable EU and ICH guidelines (refer to Section 3).

1. INTRODUCTION (background)

Post-traumatic stress disorder (PTSD) is a severe and disabling disorder. An essential feature of PTSD is the inclusion of a traumatic event as a precipitating factor of this disorder.

PTSD was first described in war veterans, then referred to as "shell shock" or "combat fatigue". Since 1980, it is recognised as a distinct diagnostic entity and is included in the Diagnostic and Statistical Manual of Mental disorders (DSM). Currently there is a tendency in the scientific community to establish more stringent diagnostic criteria of PTSD in the future.

The traumatic event can include direct injury, witnessed events or events experienced by others that are learned about. Examples of the first category can include disasters, severe automobile accidents, violent personal assault, being kidnapped, tortured or diagnosed with a life threatening illness and other threats to one's physical integrity. Witnessed events can include observing the serious injury or unnatural death of another person due to violent assault, accident, war or disaster. Events experienced by others that are learned about are, for example, violent assault, accident or serious injury.

Symptoms of PTSD are grouped into three clusters:

1. Re-experience/intrusion: flashbacks, intrusive recollections, nightmares.
2. Avoidance/numbing: avoidance of stimuli, feelings and activities associated with the trauma.
3. Hyper arousal: anxiety, sleep disturbances, anger, irritability and exaggerated startle response.

A distinction should be made between PTSD and the self-limiting stress response that most people experience after exposure to a traumatic event. Symptoms that resolve within 4 weeks of the traumatic event, may meet criteria for an Acute Stress Disorder, but not for PTSD. Acute stress disorder was added to DSM-IV to capture early responses to severe trauma that were likely to evolve into the full picture of PTSD. However, only a small proportion of patients with PTSD start with acute stress disorder and due to the ambiguity of its symptoms acute stress disorder is not considered as a reliable diagnostic entity for clinical trials.

PTSD can occur at any age, including childhood. Symptoms can emerge within months or sometimes years after the trauma has occurred. DSM distinguishes between acute (duration of symptoms less than three months) and chronic PTSD (if symptoms last longer than 3 months). When symptoms begin more than 6 months after the stressor, the disorder is defined as delayed onset PTSD.

According to DSM IV-R the lifetime prevalence of PTSD in community-based studies is quite variable: it is estimated between 1 and 14%. Studies of at-risk populations (e.g. combat veterans, victims of natural disasters or criminal violence) indicate prevalence rates ranging from 3 to 58%, depending on the population and the type of traumatic event. Women are twice as likely to experience PTSD compared to men.

Despite the severe burden of the disorder and its high prevalence, pharmacological treatment is limited. Serotoninergic agents, tricyclic antidepressants, mood stabilisers, adrenergic inhibiting agents, antipsychotics, and benzodiazepines have all been proposed for controlling symptoms of PTSD. However, to date only sertraline, and paroxetine have been licensed for the treatment of PTSD.

Pharmacological treatment of this disorder seems potentially promising. Biological dysregulations found among PTSD patients are numerous and cover the opioid, glutaminergic, noradrenergic and serotoninergic neurotransmitter systems, resulting in neuro-endocrinological disturbances and physiological symptoms. Neuroimaging studies in PTSD show alterations in brain function in the

following regions: medial prefrontal cortex, hippocampus, thalamus, amygdala, anterior cingulated gyrus, temporal cortex and visual association cortex. All these findings open new perspectives for pharmacological treatment, but also raise the question of how to deal with the complexity of the disorder.

The clinical response to a given medicinal product could depend on its pharmacological properties, on time to treatment after exposure to the trauma, on type of trauma and on predominant symptoms. Further challenges to conducting clinical trials in PTSD is the high prevalence of co-morbid depression, substance abuse and anxiety disorders and the diagnostic criteria to be used.

2. SCOPE

This document provides guidance to Marketing Authorisation Applicants (MAAs) and Marketing Authorisation Holders (MAHs) on various methodological aspects related to studies aimed at investigating the efficacy and safety of products for the treatment of PTSD. Acute stress disorder is considered as a premature diagnostic entity and not in the scope of this guidance.

3. LEGAL BASIS

These notes are intended to provide guidance for the evaluation of drugs in the treatment of Post Traumatic Stress Disorder. They should be read in conjunction with the Directive 2001/83/EC, as amended, Regulation (EC) No 1901/2006 on paediatric medicines, and current and future EC and ICH guidelines, especially those on:

- The extent of population exposure to assess clinical safety for drugs intended for long-term treatment in non life threatening conditions (ICH E1).
- General considerations for clinical trials (ICH-E8).
- Guideline on Clinical Trials in Small Populations.
- Statistical principles for clinical trials (ICH-E9).
- Choice of Control Group in Clinical Trials (ICH E10).
- Note for Guidance on the Investigation of Drug Interactions.
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A).
- Clinical testing of prolonged action forms, with special reference to extended release forms.
- Dose response information to support product authorisation (ICH E4).
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7).

4. MAIN GUIDELINE TEXT

DESIGN OF EFFICACY STUDIES IN ADULTS

Patients Characteristics and Selection of Patients

Inclusion Criteria

Diagnosis: Patients should be diagnosed according to an acknowledged classification system, preferably the DSM-IV-TR or future versions of the DSM. The latest version of the International Statistical Classification of Diseases and Related Health Problems (ICD) may also be used. Diagnosis should be made by an experienced psychiatrist and confirmed by a structured interview. The use of a severity rating scale alone is insufficient and is not equivalent to a diagnosis.

The same classification system should be used for the whole development program of the medicinal product.

In addition to diagnosis of PTSD, the severity of the disorder should be assessed using an appropriately validated severity scale. A minimum severity for inclusion should be defined and justified. However, including only patients with severe disorders might lead to a restricted indication.

Further descriptive parameters, like duration of the disorder, whether onset was immediate or delayed and the type of precipitating event (e.g. combat, abuse, natural disaster, whether physical injury was involved, and whether the event had an acute or a chronic nature), should be ascertained and specified in the inclusion criteria. The population included in any specific trial should be homogeneous with respect to aspects known or suspected to be related to treatment response (e.g. VA veterans). The dossier should include trials that are heterogeneous with respect to the type of population included. Separate trials should be performed in patients with acute, chronic and delayed onset PTSD.

As PTSD patients are usually outpatients the majority of the database should be in outpatients.

Exclusion criteria

Patients with a current or recent history of major depression (within 6 months of study entry) should be excluded from the study, specifically if the test product has an antidepressant effect. This in order to establish that effect on PTSD symptoms is not secondary to effect on depression.

Patients with predominant and/or severe depressive symptoms (e.g. not meeting the DSM-IV Major Depressive Disorder (MDD) criteria) should be excluded as well. Patients should have low severity scores (e.g. < 2) on item 1 of the Hamilton Depression Rating Scale (HDRS).

In addition, it will be necessary to exclude patients with recent or concurrent psychiatric co-morbidities, such as:

- Severe symptoms of other anxiety disorders;
- Severe Obssessive-Compulsive Disorder (OCD) symptoms (not meeting the DSM IV criteria);
- A history or presence of any psychotic illness;
- Bipolar disorder;
- A primary or severe Axis II disorder;
- Chronic alcohol abuse or current / recent history of substance abuse (within the last 6 months).

For all these disorders, a valid method of diagnosis should be used (i.e. experienced clinician, structured assessment) and documented.

The uses of concurrent medication interfering with test agent and outcome should be excluded.

Patients receiving specific psychotherapy for PTSD (e.g. trauma focused cognitive behaviour therapy, eye movement desensitization and reprocessing) should be excluded as well.

METHOD TO ASSESS EFFICACY

Primary efficacy endpoint

The primary endpoint should be based on an established severity scale (e.g. the Clinical-Administered Post-Traumatic Stress Disorder (CAPS) which captures the core symptoms of PTSD (according to DSM) and has known and acceptable psychometric properties. Furthermore, the scale needs to be validated in the target population before being used in the efficacy studies. In addition, raters should be trained in the use of the scale and reliability (i.e. inter-rater) should be demonstrated in the study setting.

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 remitters. Response should be defined as 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. Criteria for response and remission should be outlined and justified in the protocol.

Results should be discussed in terms of both clinical relevance and statistical significance. Improvement should be demonstrated on all core symptom clusters of PTSD (i.e. re-experience, avoidance and arousal).

Secondary efficacy endpoints in confirmatory studies

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, addressing additional issues such as social functioning (e.g. Sheehan disability scale) may be used provided they have well-established psychometric properties in a population with PTSD.

STRATEGY AND DESIGN OF CLINICAL TRIALS

Exploratory Trials

Pharmacodynamics

A variety of tests can be performed to support the working mechanism of the test product. These may demonstrate effects on dysregulated neurotransmitter systems in brains areas that hypothesised to be involved in PTSD.

Pharmacokinetics/Interactions

The usual pharmacokinetic studies should be performed. Specifically, in dose-response studies 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 three dosages are needed to establish the effective dose range as well as the optimal dose, based on efficacy and tolerability. It is useful to add a placebo arm as well as an active comparator to these studies.

Therapeutic confirmatory studies

Short-term trials

Depending on the claim, separate trials should be performed in patients with acute, chronic and delayed onset PTSD.

Parallel, double blind, randomised placebo controlled studies are necessary to establish acute efficacy. The duration of these studies should be derived from pilot studies indicating the time necessary for achieving a stable effect. It is expected that this will be around 10-12 weeks.

Comparison with a standard product already registered for the treatment of PTSD as a third study arm is recommended in order to be able to put the size of the effect into context in relation to standard treatment. The dose and the comparator should be justified.

The initial study period should allow for gradual dose titration guided by efficacy and tolerance.

A placebo run-in period to exclude placebo responders is not recommended as it may impair generalisation of the results.

Concurrent medication interfering with the test agent or effect is not recommended. If patients are currently treated with an active agent, a washout period is necessary.

Methodological considerations

Reference is made to the ICH-E9 statistical principles for clinical trials.

When estimating the effect on PTSD, it is necessary to control for the effect of treatment on depressive symptoms in the statistical analysis. The effect should be robust when residual depression symptoms are controlled for.

Long-term trials

Since PTSD is a chronic condition, long-term efficacy and safety should be demonstrated. A possible design for demonstrating maintenance of effect over longer duration is a randomised withdrawal study (RWS). The duration of the long-term studies should be justified.

Efficacy in long-term controlled studies is usually expressed as the proportion of patients worsening (relapsing) and/or time to this event. Both efficacy criteria are of interest and should be presented. The analysis should carefully consider the possible biases arising from dropouts and the statistical methods of dealing with them. Consistency between the results of these methods is expected under the assumption of efficacy.

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

STUDIES IN SPECIAL POPULATIONS

Elderly

There is little known about the course of PTSD in elderly populations, but there are some indications that PTSD in the elderly is associated with increased neurocognitive impairment and more somatic complaints.

Therefore defining a safe dose range in these patients needs to be addressed. For agents of known pharmacological classes, this could be done by pooling together elderly patients from different studies, provided that sufficient elderly patients are included in the adults trials to allow a prospective subgroup analysis. For new products with a new mechanism of action, specific elderly trials may be necessary. The optimal design would be a placebo-controlled dose response study. In both situations, pharmacokinetic studies should be conducted to support the choice of the dose.

Children and adolescents

The existence of PTSD in children and adolescents is widely recognised. However, child-specific characteristics of trauma and PTSD limit the use of pharmacological treatment for PTSD in this age group compared with adults. Results of several open trial studies suggest that propranolol may reduce acute PTSD symptoms (11) and prevent PTSD when given directly after trauma (12). Clozapine, in relatively modest doses, appears to have clinical benefits for adolescents with PTSD (13). Adrenergic agents, such as clonidin, used either alone or in combination with an SSRI may be useful when the primary symptoms are hyperarousal and impulsivity in childhood PTSD (14). Additionally, mood stabilizers and anticonvulsants have shown efficacy for some trauma symptoms (14, 15). However, many of these drugs have serious side effects and their beneficial response may be slow. Thus, the use of drug therapy as a single or first-choice treatment for PTSD in children is not yet recommended (13). Further and separate studies in children and adolescents are necessary. Specific rating scales have been found and validated in this group, which should facilitate the evaluation of the drugs in clinical trials.

In line with the new EU paediatric regulation (EC) No 1901/2006, as amended, a paediatric investigation plan (PIP) should be submitted early in the development of new drugs for PTSD to make sure that the appropriate development in children is included. The design of efficacy studies in the paediatric population is essentially similar to that required in adults. Depending on the type of medicinal product, a deferral of the studies in children until efficacy and safety data are obtained in adults might be envisaged by the Paediatric Committee (PDCO).

In line with the relevant guideline (ICH E11) 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. In addition, 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.

CLINICAL SAFETY EVALUATION

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 e.g. extra pyramidal symptoms, sexual dysfunction.

Specific monitoring is needed in children/adolescents and the elderly. Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided.

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 PTSD and hence the need for chronic use increases the risk of dependence and abuse. 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 and 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, prolactin secretion).

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.

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