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**COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE  
(CHMP)**

**CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE  
DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF POST-  
TRAUMATIC STRESS DISORDER**

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<b>KEYWORDS</b>	<i>Post-traumatic stress disorder, anxiety disorder</i>
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## 1. INTRODUCTION

Post-traumatic stress disorder (PTSD) is a severe and disabling disorder, with the essential feature that it has to be precipitated by exposure to a traumatic event. It was first described in war veterans and also referred to as “shell shock” or “combat fatigue”. Since 1980, PTSD has been recognised as a distinct diagnostic entity and it was included in the third edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-III). 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.

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 as men.

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.

## 2. PROBLEM STATEMENT

There are several reasons why a guideline on how to conduct clinical trials focusing on the pharmacological treatment of PTSD is timely.

First, PTSD is one of the most common psychiatric disorders. Despite the severe burden of the disorder and its high prevalence, pharmacological treatment is limited. Serotonergic agents, tricyclic antidepressants, mood stabilisers, adrenergic inhibiting agents, and benzodiazepines have all been proposed for controlling symptoms of PTSD. However, to date only sertraline, fluoxetine, and paroxetine have been licensed for the treatment of PTSD.

Second, pharmacological treatment of this disorder seems potentially promising. Biological dysregulations found among PTSD patients are numerous and cover the opioid, glutaminergic, noradrenergic, and serotonergic neurotransmitter systems, resulting in neuroendocrinological disturbances and physiological symptoms. Neuroimaging studies in PTSD show alterations in brain function in the following regions: medial prefrontal cortex, hippocampus, thalamus, amygdala, anterior cingulate gyrus, temporal cortex and visual association cortex. All these findings open new perspectives for pharmacological treatment, but also raise the question how to deal with the complexity of the disorder. The clinical response to a given medicinal product could depend on its pharmacological properties, time to treatment after exposure to the trauma, type of trauma, and predominant symptoms.

A further challenge to conducting clinical trials in PTSD is how to deal with co-morbid depression, substance abuse and anxiety disorders and what diagnostic criteria should be used.

### **3. DISCUSSION (ON THE PROBLEM STATEMENT)**

Due to these recent scientific developments, the low efficacy of available treatments, the complexity of the disorder, its high prevalence, and its severe burden, there is a need for conducting new clinical trials in this patient population.

The main topics to be addressed will be related to the design of efficacy studies in adults and to safety evaluation:

#### **1. Design of efficacy studies in adults**

- Need for separate trials for chronic and acute PTSD and for PTSD with delayed onset
- Choice of diagnostic criteria: DSM IV-R versus WHO International Classification of Disease (ICD-10).
- Need for stratification according to the type of trauma and predominant symptoms in acute response to trauma
- How to deal with co-morbidity (anxiety disorders, substance abuse, depression)
- Need to distinguish the treatment effects on PTSD from the effects on depressive and anxiety symptoms
- Definition of primary endpoints:
  - o Scales to be used, validation of these scales, self-reported versus investigator-rated items
  - o Definition of responders, remitters
  - o Definition of clinical relevance of a responder
- Need for and choice of active comparator, e.g. SSRI
- Duration of the trial
- Need for trials demonstrating maintenance of efficacy
- Role of biomarkers, including neuroimaging (PET, fMRI)
- How to deal with psychological interventions

#### **2. Studies in special populations**

- Need for and design of specific trials in children and adolescents

#### **3. Safety assessment**

- Special attention should be paid to monitor the risk of dependency and withdrawal symptoms
- Need to monitor effect of treatment on suicide related behaviours

### **4. RECOMMENDATION**

Currently there is no guidance document available. Taking into consideration the recent scientific developments in this field and the high prevalence of this disorder, it is considered useful to draft a guideline for the treatment of PTSD. Special attention should be paid to the distinction between acute and chronic PTSD and to the problems of co-morbidity such as depression and anxiety disorders.

### **5. PROPOSED TIMETABLE**

It is anticipated that a first draft CHMP guidance document may be available 12 months after adoption of the concept paper.

### **6. RESOURCE REQUIREMENTS FOR PREPARATION**

The preparation of the guideline will involve the EWP.

## **7. IMPACT ASSESSMENT (ANTICIPATED)**

It is anticipated that the “Note for guidance on the development of medicinal products for the treatment of PTSD” will help to achieve more consensus in the evaluation of such products by regulatory authorities. Furthermore it is expected that such a document would improve quality and comparability of the studies submitted by industry.

## **8. INTERESTED PARTIES**

It is envisioned that ECNP should be consulted.

## **9. REFERENCES TO LITERATURE, GUIDELINES, ETC**

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