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

**CONCEPT PAPER ON THE NEED FOR A GUIDELINE ON THE TREATMENT OF
PREMENSTRUAL DYSPHORIC DISORDER (PMDD)**

AGREED BY EFFICACY WORKING PARTY	February 2009
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1. INTRODUCTION

Many women of reproductive age have one or more signs of physical discomfort or emotional symptoms in the premenstrual phase of their menstrual cycle. In the majority of women the signs and symptoms are mild, however, between 5 to 8 % suffer from moderate to severe symptoms, which lead to substantial distress or functional impairment and are referred to as premenstrual dysphoric disorder (PMDD).

In the last decades a very broad diagnostic concept of premenstrual syndrome (PMS) has been used in clinical research, which produced different diagnostic criteria and highly heterogeneous study populations. Due to this the concept of PMS and the boundaries of the different impaired domains have been controversial and have not been accepted by regulatory bodies. However, recent advances and new research data improved the knowledge on diagnosis, frequency, pathophysiologic mechanisms and treatment options in PMDD. This led to treatment recommendations by learned societies for PMDD and several medicinal products are under development for this indication.

2. PROBLEM STATEMENT

Five percent of menstruating women meet criteria for PMDD, and about 20 percent of menstruating women are suffering from 'subthreshold' PMDD. So PMDD is a common disorder, however uncertainties still exist regarding the right study population, study duration, efficacy and safety endpoints to establish efficacy and safety.

Diagnostic Criteria

In the ICD-10 the syndrome is mentioned as 'premenstrual tension syndrome' in the Gynecology Section, at least one symptom out of a broad range of physical and emotional symptoms should be present without specification of severity. These criteria are not helpful at all for definition of study populations in clinical trials.

Following a NIH consensus conference PMS was introduced to the DSM-III as 'Late Luteal Phase Dysphoric Disorder' and was renamed with the DSM-IV to 'Premenstrual Dysphoric Disorder' (PMDD) (Table 1).

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- In most menstrual cycles during the past year, at least five of the following symptoms should have been present for most of the last week of the luteal phase, remitted within a few days after onset of menses, and remained absent in the week after menses. At least one symptom must be 1, 2, 3 or 4:
 1. Depressed mood or dysphoria
 2. Anxiety or tension
 3. Affect lability
 4. Irritability
 5. Decreased interest in usual activities
 6. Concentration difficulties
 7. Marked lack of energy
 8. Marked change in appetite, overeating, or food cravings
 9. Hypersomnia or insomnia
 10. Feeling overwhelmed
 11. Other physical symptoms – *e.g.*, breast tenderness, bloating.
 - Symptoms markedly interfere with work, school, social activities, or relationship
 - Symptoms are not just an exacerbation of another disorder.
 - The first three criteria must be confirmed by prospective daily ratings for at least two consecutive menstrual cycles.
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Table 1: DSM-IV diagnostic criteria for PMDD

These diagnostic criteria define the most severe subpopulation of the broader concept of PMS and were accepted by regulatory bodies to grant marketing authorisations for this indication for several serotonergic antidepressants and hormonal products.

A criticism on these criteria has been that they are in the appendix of DSM-IV (further studies needed) and that many women with clinically significant PMS symptoms do not fulfil the full diagnostic criteria of the DSM-IV (e.g. prominent mood syndrome or minimum of five different symptoms). Therefore the American College of Obstetrics and Gynecology (ACOG) recommended criteria defining moderate to severe PMS (presence of at least one psychological or physical symptom that causes significant impairment and is confirmed by means of prospective ratings). However, for the time being, with diagnostic criteria of the DSM-IV for PMDD, the most homogeneous study populations can be recruited for clinical trials. These criteria are in the process of updating and further validation, particularly with regard to better quantification of the different domains affected.

Pathophysiology of PMDD

The exact pathophysiology has not been understood and clarified. However, many research data have shown abnormalities in the hypothalamus-pituitary-ovary axis and brain serotonergic system in this patient population.

Based on these results treatment options that abolish fluctuations in gonadal hormone levels (GnRH analogues, oestradiol) or increase central serotonergic transmission (SSRI, NSRI) have been introduced or are under development.

Assessment Tools

Many new assessment tools, which can be used as outcome measures for the different domains of PMDD are under validation.

With the most recent developments in the diagnosis and understanding of PMDD it is considered as an adequate target for the development of pharmacological treatment, however, careful considerations on the adequate trial design of clinical studies are required.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

In the proposed guidance document guidance should be specified to:

- target population (diagnostic criteria, threshold for severity, inclusion and exclusion criteria),
- study duration (short-term efficacy, maintenance of effect),
- choice of endpoints (affective symptoms, functional relevance),
- validity of diagnostic criteria, measurement tools (self-ratings, observer-ratings),
- long-term safety (including effects on endocrinium),
- special populations (adolescence),
- presence and acceptance of co-morbidity (with regard to mechanism of action, e.g. hormonal products or antidepressants).

4. RECOMMENDATION

There are now substantial research data available to support a diagnostic entity of a severe form of premenstrual disorder, which causes clinically relevant functional impairment and requires treatment. New research data will be reflected in new versions of operationalized diagnostic criteria, e.g. ICD-11 and DSM-V. Therefore CHMP recommends to draft a guideline on the treatment of premenstrual dysphoric disorder (PMDD).

5. PROPOSED TIMETABLE

It is planned to circulate a draft CHMP guidance document 6 months after adoption of the concept paper by CHMP.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this guideline will involve the EWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is aimed that the Guideline on the development of new products for the treatment of premenstrual dysphoric disorder (PMDD) will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guidance document would improve quality and comparability of development programs for this indication by pharmaceutical companies.

8. INTERESTED PARTIES

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe E.V.

European Society of Gynecology.

European College of Neuropsychopharmacology.

Other Committees or Working Parties: PDCO and SAWP.

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