21 July 2011
EMA/71893/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'guideline on the treatment of premenstrual dysphoric disorder (PMDD)' (EMA/CHMP/607022/2009)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Bayer Schering Pharma
2	College ter Beoorderling van Geneesmiddelen, Medicines Evaluation Board, Den Haag, the Netherlands
3	H. Lundbeck, A/S
4	Merck Sharp Dohme (Europe) Inc.
5	Therapeutic Goods Administration (TEG), Canberra, Australia

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General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We very much welcome the draft EMA Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD). The guideline fully reflects the challenges and difficulties of diagnosing PMDD and assessing the effects of medicines targeting this condition.	N/A
2	In general, the guideline is well written and presents a balanced view of the issues. However, there is one important issue that require further discussion which is related to the periodic nature of PMDD and to the possibility that treatment may be either continuous or periodic. The guideline does not touch on this issue and it is recommended to address both possibilities and consider implications for study design of a continuous vs. a periodic treatment regimen (e.g. for duration of the studies). The 6 month study duration requirement is supported provided that additional measures are incorporated in the study that are designed to reduce dropout (e.g. shorter scales, IVRS)	Accepted. See revised sections 1.3, 4.3.3 and 4.5.3. **Proposed change:** Since PMDD is an intermittent, cyclic illness periodic and continuous treatment interventions should be considered which may have different impacts on treatment compliance (see 4.3.3) and on long-term safety (see 4.5.3) (6, 15, 21, 43). Shorter rating scales are not endorsed.
3	H. Lundbeck A/S welcomes this guideline and appreciates the opportunity of providing comments.	NA
4	None	NA
5	Section 1.2 mentions the various bodies that have provided diagnostic criteria for premenstrual conditions but does not provide advice on which of these diagnostic criteria should be used in clinical trials. It states that the DSM-IV criteria allow for recruitment of the most homogeneous population but does not recommend application of these	Accepted. See also MEB comment and proposed change in lines 91-95

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	criteria in recruitment for clinical trials. A firmer statement on which diagnostic criteria should be used in clinical trials would be very helpful. ACOG should be defined. Is this organisation the American Congress of Obstetricians and Gynaecologists?	 Yes. Abbreviation is explained in line 85.

Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
91-95	2,5	**Comment:** The guideline should more clearly explain the choice of diagnostic criteria (DSM-IV) and state that these criteria are research criteria that are liable to change and that these changes may influence the position presented in this guideline.	Accepted. **Proposed change:** In conclusion, for the time being, the most homogeneous study population can be recruited with the DSM-IV diagnostic criteria which should therefore be used for clinical trials in PMDD. As research criteria these DSM-IV criteria are in the process of updating and further validation, particularly with regard to better quantification of the different domains affected. These changes may influence the position presented in this guideline.
91-94	4	**Comment:** The adherence to the DSM-IV criteria for PMDD indeed provides a homogeneous study population, but it limits the target population significantly. Up to 20% of reproductive women are recognized as 'nearly threshold' cases, just not meeting all DSM-IV criteria. Also they require treatment and as such, this group should be investigated in clinical trials as well.	Not accepted. This Guideline explicitly refers to PMDD and not to PMS or borderline cases. It is not the issue of this guideline to recommend trials in other populations.
97-98	3	**Comment:**	

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		The statement that “the etiology is considered multi-factorial and many research data have shown abnormalities in the hypothalamus pituitary-ovary axis and brain serotonergic system in this patient population” may be questioned. As correctly stated in the following paragraph of the guideline, most studies of the pituitary-ovary axis have thus failed to reveal any abnormalities in women with PMDD when compared to controls, and there are also few if any studies showing clear-cut abnormalities with respect to brain serotonergic transmission in subjects with PMDD. Instead, the notion that sex steroids and serotonin are involved in the pathophysiology of this condition is based primarily on pharmacological studies. **Proposed change (if any):** The sentence(s) in question could preferably be phrased: “The etiology is considered multi-factorial. Many research data suggest an involvement of the hypothalamus-pituitary-ovary axis and of the brain serotonergic system in the patient population with this condition.”	Partly accepted. **Proposed change (see also MEB comment):** The exact pathophysiology of PMDD is not well understood and clarified. The etiology is considered multi-factorial. Research data have shown abnormalities in the hypothalamus-pituitary-ovary axis and brain serotonergic system in this patient population.
105-107	3	**Comment:** It is stated that “studies on PMDD rather favour abnormal hypothalamic-pituitary regulation across the menstrual cycle and abnormal luteal phase cortical	Partly accepted since abnormal hypothalamic-pituitary regulation is one of the discussed underlying mechanism in literature (see ref. 25, 39).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		excitability as underlying mechanism". Data suggesting abnormal hypothalamic-pituitary regulation are however few (see above), and the findings regarding cortical excitability should probably be regarded with some caution until replicated. **Proposed change:** Please consider omitting the sentence, or replace it with the following sentence: "Studies on PMDD rather favour the notion that women with PMDD display higher responsiveness with respect to the influence of sex steroids on the brain than symptom-free women."	**Proposed change:** Studies on PMDD rather favour the notion that women with PMDD display higher responsiveness with respect to the influence of sex steroids on the brain than symptom-free women suggesting abnormal hypothalamic-pituitary regulation across the menstrual cycle and abnormal luteal phase cortical excitability as underlying mechanism (16, 26).
123-124	4	**Comment:** The distinction between PMDD and other psychiatric disorders is very difficult and requires high expertise. In case a COC is investigated for PMDD, subjects are recruited in women's health and gynecological centers. They often do not have the expertise to handle the DSM-IV criteria. Please give guidance how this should be dealt with.	Accepted. **Proposed change:** The diagnosis of PMDD requires interdisciplinary expertise. PMDD should be separated from differential diagnostic categories including both psychiatric and nonpsychiatric disorders and physicians should be trained in handling the DSM-IV criteria (see DMS-IV criterion C, Table 1).

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123-124	2	**Comment:** In what sense mandatory? This sounds like already the body of the guideline in which the conduct of the trials is prescribed while this is actually in the introduction(background) phase. So I would phrase it differently, something like “PMDD should be sperated form differential diagnostic categories…”	Accepted. See proposal above
167-211	2	**Comment:** The structure is not always clear. For example section 4.1 starts with diagnostic criteria, continues with rating scales, and then goes back to diagnosis. The clarity of the document could be improved by improving the flow (see also comments in the body of the guideline).	Accepted. Section 4.1 was revised as recommended: start with diagnostic criteria, then the prospective issue, then instrument choice. Validation, training of assessors
173-175	4	**Comment:** The screen failure rate may be extremely high due to the difficult diagnose of PMDD, but mainly also due to the need of two consecutive cycles for confirmation, without any treatment for PMDD / or the use of COCs (in case this is the IP). Please address this issue in the guideline.	Not accepted. Since this is not the issue of the guideline.
183-184	3	**Comment:** In advance and if necessary during the study raters (e.g. physicians) should be properly trained for assessment of patients with the applied rating scales.” Although the training of raters is always commendable, this sentence may give the reader the impression that	Accepted. See revised section 4.1.

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		observer rating is essential for making the diagnosis. Unless it is assumed that the rater meets with the woman daily for two cycles, which obviously is not an option, this message however contrasts to the following sentence in the same paragraph, stating that "retrospective reporting is not acceptable as retrospective recall of symptoms is unreliable". (The assessments of raters is thus always to a large extent based on the retrospective recall of the patient.) Given the fact that retrospective recall of symptoms in indeed unreliable, and that daily assessments are the key to this diagnosis, PMDD is hence a condition where the diagnosis must be made almost entirely on the basis of the patients' daily self-rating of symptoms. Needless to say, a clinician interviewing and observing the patient, preferably in the midst of the luteal phase, may add important information, but is far less important than the daily rating performed by the patient herself. **Proposed change:** Please consider replacing the sentence with: "Although the core element of making a diagnosis of PMDD is the daily, prospective self-report of symptoms, this diary-based information should be supplemented by a structured interview conducted by the study raters (e.g. physicians), who should be properly trained for	

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		assessment of patients with the applied rating scales."	
184-186	4	**Comment:** Please be more clear what is meant with 'inter-rater reliability. Normally, this is between e.g. two physicians, but comparison between patient and physician (which is referred to here) is not a straight forward approach.	See amended section 4.1. lines 200-204. Of course, between physicians or centers is meant. This should be clear.
194-195 4.1. Subject characteristics and selection of subjects	4	**Comment:** What is the rationale for a minimum duration of 4 days for symptom presence?	According to DSM-IV criteria symptoms should be present for most of the time during the last week of the luteal phase… Which should be then at least 4 days. In clinical studies average luteal scores were calculated from the 5 most symptomatic days (Cohen et al (6), Yonkers et al (41)).
196-200	4	**Comment:** What is the meaning of this paragraph on symptom severity. It is not related to diagnosing PMDD.	Not accepted since diagnosis of PMDD depends also on symptom severity (pre- versus postmenstrual symptom severity within the cycle) and can only be made until premenstrual pathology is confirmed by two consecutive cycles of prospective symptom monitoring. Of note, symptom severity for efficacy assessment is usually the difference between the average luteal phase symptomatology of baseline qualification cycles versus treatment cycles (between cycles). However, section 4.1 was reworded and this should be clearer now.
204	3	**Comment:** It is stated: "Although the comorbidity…"	Accepted.

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		Proposed change: Change to: "…although the lifetime comorbidity…"	
207-208	3	**Comment:** It is stated that "symptoms of PMDD tend to persist beyond successful pharmacological treatment of MDD in women diagnosed with both…". This is probably correct if the depression is treated, e.g., with a non-serotonergic antidepressant or with electroconvulsive treatment, but evidence in the literature for this is in fact lacking, and this issue is not addressed in the cited reference (i.e. ref 40). Moreover, if the depression is treated with any of the most commonly used antidepressant, i.e. with a selective serotonin reuptake inhibitor (SSRI), it is in fact most likely that the PMDD symptoms will indeed remit as well, and even faster than will the symptoms of depression. **Proposed change:** Please consider omitting the latter part of the sentence, so it reads: A key feature of depressive disorders is that symptoms are almost always present every day of the cycle.	Accepted

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222-232 section 4.1.2 . Exclusion criteria	2	**Comment:** Exclusion criteria should explicitly state that patients with other axis I disorders, specifically MDD and anxiety disorders should be excluded, especially when examining compounds with known efficacy for these indications. It is not clear why patients receiving therapeutic counselling should be excluded. It would seem that this could be left to the discretion of the sponsor.	Accepted. This was a contraindication in the YAZ trials, but might be too unspecific. Agreed.
227-231	4	**Comment:** Many patients use hormonal contraceptive methods primarily for contraception, not for PMDD therapy. If the washout period for these contraceptives has to be 3 month prior to screening, recruitment will be significantly impaired. Please reconsider this period for hormonal contraceptive use.	Not accepted. The wash-out period is usually 3 months in clinical trials (4, 6, 41, Yaz studies).
235	3	**Comment:** It is stated that “the primary outcome should be prospective self-recording of overall premenstrual symptomatology”. In many previous DSM-based PMDD trials, one has however *not* regarded reduction in the “overall” premenstrual symptomatology as primary outcome measure, but rather the reduction in the key mood symptoms (such as irritability, affect lability and depressed mood). Given that it remains a controversy if	Not agreed. All impairment items should be measured: Psychological/physical and also functional impairment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		all symptoms listed in the DSM-IV criteria should indeed be regarded as parts of one and the same syndrome, and that the concept of PMDD is based on the assumption that the mood symptoms are the most important ones for the condition bearing this name, it may be argued that this strategy is a more reasonable one than to include also less important symptoms in the primary outcome parameter. Intermittent administration of SSRIs, which in most current guidelines are regarded as first line of treatment, is not as effective for somatic symptoms as for mood symptoms, and probably entirely devoid of effect on one of the listed somatic symptoms, i.e. headache; nevertheless, it is regarded as a highly useful treatment for PMDD. Calculating the effect size for the effect of this treatment on a large number of symptoms, many of which may in fact be absent at baseline, would clearly mask the very marked effect of this treatment on the key target symptoms, and would hence to some extent be misleading. Likewise, to require that all items listed in the DSM criteria (including the somatic symptoms) should be included in the primary effect parameter may render the evaluation of novel treatments more difficult, given that these, like the SSRIs, may exert more marked effects on the key mood symptoms than on those symptoms that, in the DSM criteria, are regarded as less important. Moreover, if all DSM symptoms are included in the	

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		primary parameter, the apparent effect size for a drug mainly reducing the mood symptoms may be highly influenced by the design of the study, in the sense that a considerably higher effect size is to be expected if one, when designing the trial, decides to regard the PMDD item 11 as *one* symptom, rather than if each somatic symptom is assessed separately. In a situation where all DSM-listed symptoms cannot be expected to respond equally well to all treatments, and where it is no consensus regarding how to translate the DSM criteria into a rating scale, the recommendation that the "over-all premenstrual symptomatology" should be the primary effect parameter may hence prove to be counter-productive. In this context, it should be mentioned that, for other psychiatric disorders, such as depression and psychosis, the list of DSM items, which often may be regarded as somewhat arbitrary, are usually *not* used for the assessment of treatment. We hence suggest that it would be more useful to require that DSM *key* symptoms are included in the primary effect parameter, and that the effect on other symptoms, such as the somatic ones, should be included among the secondary outcome parameters. (In the case a new treatment targeting mainly one or several of the somatic symptoms, but with none or less effect on the mood symptoms, the term PMDD, as currently defined, will probably not be the ideal label, but will have to be replaced with something else.)	

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		Proposed change: Please consider replacing the sentence with: “The primary outcome should be prospective self-recording either of the overall premenstrual symptomatology or of the key mood symptoms of the disorder”.	No change. See also lines 249-258
237	2	**Comment:** The average between the 2 prospectively assessed cycles? Or don´t you want to be so specific?	Agreed
239-241	2	**Comment:** The guideline could allow for alternative methods to capture clinical relevant outcome (besides 50% symptom reduction) provided these are well justified. For example, improvement in functioning, work productivity, presenteism at work measured via e.g. SF36.	Partly accepted. SF 36 is considered to be too unspecific and can be only accepted as additional secondary endpoint. See section 4.2.2. and alternative wording below.
239-241	1	**Comment:** The draft guideline recommends to use a responder analysis in order to gauge the clinical relevance of an improvement in symptomatology. While we agree with the Agency that the clinical relevance of a change in a rating scale needs to be quantified, we are of the opinion that artificially defining a 50%-reduction to be the threshold of clinical relevance might not be justified. This holds especially true for the DRSP scale	Partly accepted. 50% reduction in symptoms should be kept. It depends on the lower limit of the scale use, e.g. if a DRSP score ranging from 21 to 126 is used, a 50% reduction would be given by a reduction from 81 to 51 or from 101 to 61.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		which has a range from 21 to 126 points. E.g., a patient who rates four symptoms as 'extreme' and the other symptoms as 'not at all' would be a non-responder by definition because her baseline score of 41 can at maximum be reduced to a score of 21 if there is complete symptoms relief after treatment. **Proposed change (if any):** "A clinically relevant treatment response ~~has been~~ should be defined prospectively in PMDD treatment trials.~~, as a 50% reduction in symptom ratings post-treatment versus baseline.~~ The threshold of a clinically relevant response should be based on the patients' perspective and the properties of the instrument used."	**Proposed change** In order to allow an estimate of clinical relevance, improvement should also be expressed as the proportion of responders. A clinically relevant treatment response should be defined prospectively and has been suggested in PMDD treatment trials, as a 50% reduction in symptom ratings post-treatment versus baseline (2). The relative reduction in symptom ratings that defines a clinically relevant treatment response should be based on the difference to the lower limit of the scale used.
242-243	4	**Comment:** A clinical relevant treatment response may vary between ratings. Please clarify for which rating the 50% reduction applies.	See comment above
242-243	2	**Comment:** Rating scales again-combine with previous text	Agreed. Sentence was moved to first paragraph in section 4.2.1.
264	4	**Comment:** By mentioning only the DRSP scale in the secondary	The wording of this paragraph and wording is slightly altered to make it broader.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endpoints, it suggests that only this scale is acceptable for these trials. However, in the rest of the guidance it is mentioned as an example, not as the only acceptable method. Please make this broader.	
268-272	4	**Comment:** As mentioned previously in this guidance, retrospective reporting is not acceptable as retrospective recall of symptoms is unreliable. When you use clinician ratings based on patient interview, you ask the patient to retrospectively discuss their symptoms. This is not preferred and will lead to discrepancies between the ratings. Therefore, clinician ratings will not improve the validity and should be omitted.	Not accepted. Clinician ratings are an important supplement and should be used as secondary endpoint. See also Section 4.1 and comment below.
268-272	3	**Comment:** The following is stated: “For rating scales that rely on self-ratings the validity of the outcome scales should be confirmed by observer-ratings. Therefore, in research studies, clinician rating scales should be used in addition to the patient´s symptom reports. Clinician ratings are based on patient interview, including the patient´s symptom reports and global assessment of symptom severity, improvement and adverse events. Physicians must be trained for using the different rating scales (see 4.1).” As discussed above (in the comment regarding lines 183-184), this statement may be regarded as	Partly accepted. There is no need to ask for the patient’s symptom reports. The clinician ratings should be supplemented by the patient interviews.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		contradictory to the (accurate) statement elsewhere in the document that “retrospective recall of symptoms is unreliable”. The reader may hence question why an unreliable assessment (i.e. the patients’ retrospective recall during interview) should be used to confirm the validity of a more reliable assessment, i.e. the prospective daily rating. We certainly do not argue against the use of structured interviews as a supplement to the symptom diaries, but one should perhaps avoid any wording indicating that the former is more accurate and informative than the latter, especially if one (most reasonably) argues that the primary effect parameter should be based on the symptom diaries only. **Proposed change:** Alternative wording: “Although the assessment of efficacy should be based on prospective self-rating, this should be supplemented by observer-ratings based on structured interviews undertaken by the clinician. Clinician ratings should include the patient´s symptom reports and global assessment of symptom severity, improvement and adverse events. Physicians must be trained for using the different rating scales (see 4.1).”	**Proposed change:** Although the assessment of efficacy should be based on prospective self-rating, this should be supplemented by observer-ratings based on structured patient interviews undertaken by the clinician and global assessment of symptom severity, improvement and adverse events. Physicians must be trained for using the different rating scales (see 4.1).
256-277	1	**Comment:**	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The draft guideline recommends several “important secondary endpoints” in section 4.2.2. In the last paragraph of this section, the use of questionnaires as “additional secondary endpoints” is suggested. However, the draft guideline also recommends to adjust for multiplicity (line 277) which appears inappropriate. According to section 3 of the EMA’s PtC on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99), no adjustment for multiplicity is necessary for secondary endpoints (unless of course a label claim is intended). **Proposed change (if any):** “Used tools should be justified ~~and adjusted for multiplicity~~”.	**Proposed change:** All assessment tools used should be justified based on psychometric properties and the outcome corrected for multiplicity in case a label-claim is made (4, 22).
287-288	3	**Comment:** The following is stated: “Due to the subjective nature of the primary endpoint, two well-conducted therapeutic studies are required for a specific claim in this indication.” The subjective nature of the primary endpoint however justifies particular regulations regarding the required number of trials *only if it may be expected to cause the outcome of trials to differ more than would have been the case if the endpoint had been less subjective*. And this is not at all the case for PMDD, where more than 40	Not agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		controlled trials unanimously (with the exception of one small and poorly designed trial only) show SSRIs to be superior to placebo (regardless of which rating instruments that have been used for assessment of response). In spite of the subjective nature of the primary outcome, the effect of SSRIs in PMDD is hence very robust and predictable, and far more so that the effect of these drugs in, e.g. depression, where many trials fail to separate active drug from placebo. Obviously, it is usually a reasonable requirement that the efficacy of a new treatment should have been shown in at least two independent trials. Given the remarkable consistency in the outcome of previous PMDD SSRI trials, it is however not scientifically justified to make this an absolute requirement for PMDD. Such a policy might indeed have negative practical consequences for the future treatment of PMDD in Europe. Indeed, PMDD is (as stated in the EMA guidelines) a common and stressful condition, causing marked impairment (probably including an increased risk for suicide), for which an effective and safe treatment (i.e. the SSRIs) has been developed. That this treatment is not made available in EU Member States clearly can be regarded as an unmet medical need. The notion that SSRIs, as a class, are very effective for PMDD, gains massive and unanimous support from	

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		numerous previous trials, and is well in line with the current view on the physiological role of serotonin. From a scientific point of view, this stresses that sufficient information regarding both the efficacy and safety of an SSRI could be available from one trial and this could hence be a situation where it would be possible to grant market authorisation on the basis of one trial only. In such situations it must be documented that the trial *i)* is of good quality, *ii)* shows statistically and clinically convincing results, and *iii)* lend support to the interpretation based on the primary outcome measure by means of the results for the secondary outcome measures. It should finally be underlined that the requirement of two independent studies seems highly relevant in case a treatment based on a novel mechanism of action should be developed. On the other hand, one might argue that less stringent requirements with good reasons could be applied in the case of an extremely well documented class action, as is the case for the SSRIs. Indeed, the evidence for an efficacy of SSRIs in PMDD is probably more robust and consistent than for any of those indications currently approved for treatment with this group of drugs in Europe. **Proposed change:** Please consider reviewing the requirement on efficacy	**Proposed change:** Due the subjective nature of the primary endpoint, more than one well-conducted clinical trail should be performed.

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		data to take into account the above comments and consider a potential reduction in the required efficacy data package provided that data from the literature show the robustness of positive results as it is the case e.g. with SSRIs.	Slightly alternative wording since the primary endpoint is really subjective.
287-293	4	**Comment:** In case of a placebo-controlled study on the effect of a COC on PMDD, the menstrual bleeding pattern will reveal whether the subject is on placebo or on the IP. Therefore, these studies cannot be performed double-blind. Please address this in the guidance.	See Lines 299-302 where is a special paragraph on blinding
300-301	4	**Comment:** For placebo-controlled studies with COCs, there is no use to pay special attention to blinding, as these trials cannot be performed double-blinded due to the COC effect on the menstrual bleeding pattern.	Partly accepted. **Proposed change:** Special attention should be paid to blinding even though this might be difficult in studies investigating medicinal products which may influence the menstrual bleeding pattern (e.g. COCs). The applicant should indicate a priori how this will be handled.
314-315	3 see also general comment 2	**Comment:** It is stated that “placebo-controlled data are needed over at least 6 cycles (2 run-in cycles + 6 treatment cycles), especially since a large placebo effect is expected”. First, it deserves to be pointed out that a difficulty in separating active drug from placebo is (as discussed	Not agreed. Data are needed over at least 6 treatment cycles since PMDD is a chronic condition and long-term treatment will be used in clinical practice. Robust clinical evidence (at least 6 months placebo controlled data) is needed, especially since large placebo effect is expected.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		above) in fact *not* a major problem in PMDD studies, at least when the tested drug is as effective as are the SSRIs. It is true that the improvement in the placebo group in PMDD is often large, but this notwithstanding, >40 placebo-controlled trials, many with apparently low statistical power due to low sample size, unanimously have shown the tested SSRI to be superior to placebo. Second, the problems of conducting long-term trials in the PMDD field should be underlined. PMDD trials thus differ markedly from other psychiatric treatment studies in two important regards. One is that the treatment period must be preceded by two months of symptom rating in order to confirm the diagnosis (as mentioned in the EMA guidelines); also in a study with a treatment period of three cycles only, the patient is thus included in the study for five cycles/months. And the other one is that patients participating in PMDD drug trials have to perform a relatively elaborated self-rating of symptoms on a daily basis, which obviously could be regarded as a considerable burden, both psychologically and in terms of time-consumption. While experience shows that it is possible to obtain a reasonable self-rating compliance for 2+3 cycles, it is questionable if it would be possible to motivate women to participate in studies longer than that: a study lasting for e.g. 6 treatment cycles would require that women randomized to the placebo group are asked to rate their symptoms daily for 8-9 months without	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		obtaining any effective treatment. In fact, in spite of the very extensive research on the efficacy of SSRIs in PMDD, there is only one randomized parallel group study of an SSRI in PMDD that have lasted for longer time period than three cycles, i.e. a study by Steiner and co-workers (1995) on fluoxetine. Furthermore, the difficulties in motivating placebo-treated women with PMDD to remain in a controlled trial for a long period is illustrated by the fact that the drop-out rate in the placebo group in the Steiner study was >50%, which obviously makes it very difficult to interpret the outcome; this was in fact one of the reasons for EMEA not to grant a manufacturer of fluoxetine marketing authorisation for this compound in 2003. In addition, it could be argued that the attention, and hence the accuracy of the assessments, is probably markedly reduced by time, also for those remaining in a study, if this exceeds 5 months. For the SSRIs paroxetine and sertraline, no controlled studies exceeding three cycles have thus been undertaken; nevertheless, both compounds have been approved for PMDD in the US, and used successfully for more than a decade. Had data from long-term studies been required by the FDA, no SSRI would hence have been approved for intermittent use in PMDD in the US, and only fluoxetine for continuous treatment, the latter approval being based on a trial that EMEA in 2003 found reasons to criticize because of the very high	

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		drop-out rate. Whereas it is hence difficult, if at all possible, to conduct long term placebo-controlled trials in PMDD with reasonably low drop-out rate, it may, on the other hand, be questioned if such studies are indeed warranted, at least when the given treatment is intermittent administration of an SSRI. In other SSRI indications, such as depression and various anxiety disorders, the onset of action is slow and gradual, the symptom reduction obtained after 3 months often better than that obtained after 2 months, and that obtained after 6 months often better than that obtained after 3 months. In these disorders, studies lasting for, e.g., 8 weeks, which are not unusual, e.g., in the depression field, obviously will provide only limited information on the maximal efficacy of the given treatment (and the possible risk for tolerance development). In PMDD, on the other hand, each luteal phase may be regarded as a separate episode of the condition, and each period of intermittent drug administration as a complete treatment period. The literature hence clearly shows that the symptom reduction is as marked in the first treatment cycle as in the following ones: there is hence no gradual increase (or reduction) in efficacy over time that requires long term treatment to assess. **Proposed change:**	

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		Please consider omitting paragraph 4.3.3, or replace with wording that is less mandatory, and takes the infeasibility of conducting long-term trials in PMDD into account.	
320-321	5	**Comment:** There is an error in this sentence. It should refer to the prevalence of moderate to severe PMS in adolescent girls but this is not clear from the current sentence.	Not accepted. Should be clear from the sentence.
323-325	4	**Comment:** Please consider to 'recommend' that adolescents are to be included in the development program, instead of 'requested'. As the PMDD diagnose is rarely made for adolescents, it may lead to major recruitment problems in clinical trials. In addition, clinical trials in adolescents will be guided separately via a paediatric investigation plan.	Not accepted. PDCO had no comment on existing wording.
323-325	3	**Comment:** It is stated that “there is a need to demonstrate that specific therapeutic strategies have similar beneficial effects in adolescents and it is requested to include adolescents in the development program according to the prevalence in the general population”. As mentioned in the guidelines, epidemiological studies do suggest that premenstrual symptoms may appear already shortly after the onset of menses. On the other hand, studies as well as clinical experience strongly	Only partly accepted. There is a paragraph on special safety concern in adolescents.

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		indicate that the typical treatment-seeking PMDD patient is around the age of 35-40, and that adolescents seldom seek treatment for this condition, suggesting that it may be much less of a burden for patients at young age. While pharmacological treatment of young women with premenstrual complaints hence seems to be less of an unmet medical need than that of middle-aged women, there are reasons to argue that some treatments, that may be very helpful for adult women with PMDD, for safety reasons should not be used in pubertal women, such as treatments abolishing the production of ovarian hormones. Given the importance of sex steroids for the development during puberty, even testing such a treatment of PMDD in young women may in fact be regarded as unethical. If it is made mandatory that every new treatment for PMDD should be tested also in teenagers, the development of treatments that may prove safe and useful in adults may hence be effectively arrested. **Proposed change:** While any treatment for PMDD meant to be used also by teenagers must obviously be the subject of thorough investigation in this age group, the paragraph would benefit from a statement indicating that EMA acknowledges the fact that drug treatment of PMDD in pubertal girls may be less of an unmet medical need	**Proposed change:** Special ethical considerations and safety concerns in adolescents have to be taken into account.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		than drug treatment of PMDD in adults, and that there are treatments that may be very useful for adults that *should not be used*, or even tested, in young women.	
347	1	**Comment:** The draft guideline recommends that “Special attention should be paid to long-term effects on endocrinium”. We see a need to be more specific regarding endocrine parameters to be investigated. **Proposed change (if any):** Special attention should be paid to long-term effects on endocrinium, this should depend on the mode of action of the examined substance, e.g., evaluating effects on the hypothalamus-pituitary-ovary axis.	Accepted. **Proposed change:** Depending on the mode of action of the examined treatment special attention should be paid to long-term effects on endocrinium.