European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. EMEA/403001/2008 Corr*

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

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	**Lundbeck**	
2	**Organon**	
3	**EFPIA**	
4	**Merck**	
5	**MEB**	NL

*The correction includes comments 3 and 4.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
Criticism was raised regarding the demand to demonstrate efficacy in acute, chronic, and delayed onset PTSD and in different levels of severity. The difficulty in recruiting patients to the different studies was mentioned as well as the lack of evidence to indicate that efficacy differs across different severity levels. No changes in the guideline were taken on board in response to these comments, as it is considered that given the experience with depression it is not unlikely that response would be dependent on severity. Furthermore, the non-responsiveness to treatment of Vietnam veterans might be due to chronicity and hence demonstration of efficacy across levels of chronicity seems important. There was a repeated opposition to the exclusion of patients with comorbid depression and anxiety from the study population. The argument is that the majority of patients with PTSD have these comorbid disorders and excluding them would result in a non representative study population. However, it is considered that, especially for compounds with known antidepressive (or anxiolitic) activity, it is essential to include patients with 'pure' PTSD in order to ascertain PTSD-specific efficacy and that this would not be possible if patients with comorbid depression or anxiety were to be included. Opposition was raised against the requirement to demonstrate efficacy on all three PTSD symptom clusters (re-experience, avoidance, and arousal). However, t is considered that PTSD is a unified diagnostic entity and therefore therapeutic effects needs to be demonstrated on the whole rather then on only some components of this disorder.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
General		
	A requirement to distinguish between acute, chronic and delayed onset PTSD when doing studies will make it virtually impossible to recruit (and analyse) the necessary number of patients in a reasonable time. The same holds true for the requirement to exclude patients with concomitant conditions such as depression or anxiety (which would exclude many patients with PTSD). Furthermore, the requirement of a fixed dose study with 3 doses, placebo and active comparator for PTSD	While the difficulties in recruiting and carrying out high quality PTSD studies are recognised, it considered that adequate demonstration of efficacy and optimal doses are essential for demonstrating efficacy and safety of treatment.

[1] Where applicable

	sets a very high bar when considering the high placebo rate.	
	From an ethical point of view, we are concerned about the necessity to study long-term safety and relapse in this patient group, as it would not be ethical to deliberately take patients off medication. Proper escape criteria should be defined or alternative designs such as a relapse prevention study should be added.	Long-term safety can be studied in a relapse prevention design and in open label long-term studies.
	It is our opinion that a requirement to show statistically significant improvement on all 3 symptom clusters may lead to rejection of products that are effective and useful for treating part of the symptoms (as the biology of the three types may well be different) and suggest to allow 'a change in the right direction' for some of the symptoms.	As PTSD is considered to be one diagnostic entity and the purpose of treatment is to treat this disorder, an effect on all three symptom cluster will need to be demonstrated.
	In our opinion the unique characteristics of PTSD are not emphasized in the proposed guideline, especially in the part devoted to study design in adults. PTSD is described as any other anxiety disorder, although: 1. It is the only psychiatric disorder with a known aetiology. Without exposure to trauma, one cannot diagnose PTSD. 2. It is much more prevalent than is known, and probably other disorders are diagnosed as primary when PTSD is actually the hidden primary diagnosis. The landmark article by Lecrubier in JCP in 2004 mentioned in the guideline, attests to this additional unique feature. There is evidence of a difference between civilian and combat PTSD and to the attributes of PTSD in women *versus* men, more specifically to the acute trauma such as molestation *versus* the repeated trauma such as combat. However, the guideline addresses only the "traditional" epidemiologic specifiers – children and elderly and does not address this third unique feature of PTSD.	1. The fact that exposure to a traumatic experience is part of the diagnosis of PTSD is reflected in the diagnostic criteria (DSM and ICD). 2. As there is no hard evidence to support the opinion that PTSD is often the primary diagnosis when appearing with comorbid disorders, this is not mentioned in the guideline. 3. The point regarding different types of trauma has been incorporated into the current version of the guideline (see page 4).
	Only two medications (from the same class) are approved for PTSD, and several other studies have been conducted, but not yet approved. PTSD is a disorder occurring worldwide, with an incredible societal burden that does not yet have a pharmacological treatment of significant value. Therefore there is an unmet need for medical treatment. In our opinion the conduction of studies should be encouraged. Taking a more flexible and encompassing approach, e.g. by not excluding all patients with comorbidities, can best facilitate this.	The point about exclusion of patients with comorbid disorders has been addressed previously. As stated earlier, inclusion of such patients will interfere with the possibility to discern a unique effect on PTSD rather than on these other comorbid disorders and therefore the requirement to include patients without comorbid disorders.
	It is not very clear from the guideline how the labelling text will be	Effect will need to be examined in all segments of PTSD

	depending on the segment of PTSD studies.	
	The guideline does not address the strategy of prevention of the disorder.	Although preventive approaches are currently emerging, it is considered that it would be premature to include this issue in the current guideline.
	The exclusion of co-morbidities (depression, substance abuse, anxiety) and patients receiving psychotherapy may affect the representativeness of the study population and hence the generalization of the results. As a consequence these exclusion criteria may need to be reconsidered.	See earlier responses
	The need for long term trials and randomized controlled designs is acknowledge. It is however advised to come up with a recommendation of the duration of such trials.	It is stated (line 168 in the draft guideline): 'The duration of the long-term studies should be justified'. This is considered sufficient as the guideline is not intended to be prescriptive in this respect.
Introduc-tion		
	Line 21-25: Acute Stress Disorder was added to DSM-IV in reaction to the minimum symptom duration criterion specified in DSM-III; with DSM-III criteria, PTSD patients would receive the diagnosis of Adjustment Disorder in the first 30 days of symptoms*. Symptoms of distress are common after trauma; the population of patients with Acute Stress Disorder is heterogeneous and composed of both patients who will spontaneously recover within 30 days and those that will progress to the PTSD diagnosis. The majority of patients with PTSD can be initially classified as having Acute Stress Disorder by DSM-IV-TR criteria until the 30-day minimum symptom duration criterion for PTSD is met. The symptoms of Acute Stress Disorder are clearly defined by DSM-IV-TR criteria. *Marshall RD, Spitzer R, Liebowitz MR. Review and Critique of the New DSM-IV Diagnosis of Acute Stress Disorder. Am J Psychiatry 1999;156:1677-85. *Replace:* 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.	The comment is partially accepted. The following text replaces the existing text: Acute stress disorder was added to DSM-IV to capture early responses to severe trauma that ~~were likely to~~ might 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.

	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. *With:* The population of patients with Acute Stress Disorder is heterogeneous and composed of both patients who will spontaneously recover within 30 days and those that will progress to the PTSD diagnosis.	
	Line 30: Recommend that text read DSM IV-TR not DSM IV-R	Agreed
	Line 36: Antipsychotics should also be included among the drugs studied for controlling symptoms of PTSD to avoid setting up limitations for developing new drug candidates to treat PTSD. The guideline should not focus only on what is approved but also look to the future in regards to research and development of novel treatments. The pharmacological rationale for treating PTSD with antipsychotics does exist and is well-described in the literature.	Agreed
	Line 38: FDA and EMEA have sertraline and paroxetine on their list of approved medication for PTSD, but not fluoxetine.	Agreed
	Line 47-50: Other important considerations include history of single vs. multiple different trauma, single vs multiple exposures to the same trauma, and other medical co-morbidities. These are additional factors which impact the "toxicity" of the trauma and can impact treatment response, they are important to assess in a historical context at baseline.	These characteristics are addressed later on in the document. For the introduction it is considered sufficient to generally indicate 'type of trauma'.
	Line 77: In addition to structured interviews, we would also recommend consideration of well validated semi-structured interviews (several have been developed and are less burdensome to the patient and interviewer).	Semi-structured interviews are less desirable as less gets documented.
	Line 81-86: We strongly recommend conducting a structured/semi-structured trauma interview at screening. Additional descriptors would include interpersonal vs. non-interpersonal trauma; if interpersonal, relationship to perpetrator; violent vs non-violent trauma; history of more than one trauma; age at incident trauma (one bringing pt to	Partly accepted (childhood trauma added).

	treatment); and age at first trauma. This information can all be ascertained in a good trauma history (a number of validated tools have been developed). As noted above, a variety of trauma-related factors can impact the potential "toxicity" of the trauma and a trauma interview helps to identify these factors. This information can be used to identify risk factors for non-response, chronicity, etc.	
Patients characteristics and selection of patients		
	Line 79: In the previous paragraph the guideline indicates that diagnosis could be via DSM or ICD. The statement “same classification system should be used for the whole development program” should be clarified so that it is understood that the version may change over time but the same system should be used. Rewrite as “The same classification system (DSM or ICD) should be used for the entire development program.”	Agreed
	Line 82: ‘…the severity of the disorder should be assessed using an appropriately validated severity scale’: Please add examples of scales that are considered by the agency as being appropriately validated. The gold standard Scale is the Clinician Administered PTSD Scale (CAPS). It has been the scale used for clinical trials since the early/mid 90’s, and is well validated. Other well validated questionnaires include the Mississippi PTSD scale (civilian and veteran versions), the PCL, and the Davidson Trauma Scales, to be used as possible adjunct scales (CAPS hits core symptoms, but may miss some “adjunct” symptoms in the more severely ill [Betemps E, Baker DJ. Mental Health Services Research 2004;6:117-25]). Please also indicate if it is necessary to use the same rating scale across the development program. We assume that for comparability across studies the same rating scale should be used across the program. But flexibility would be appreciated, such that in an individual study, CAPS can be used intermittently with a questionnaire, also to avoid that CAPS	As the guideline indicates, the scale should be validated. The guideline is not intended to be prescriptive in this regard and various validated scales could be acceptable provided adequate evidence for their validity is provided. Using the same scale throughout the whole development program has the advantage of enabling combined analyses across studies (e.g. to obtain sufficient power for subgroups analyses).

	may function to some degree as a treatment instrument if given too often.	
	Line 83: 'However, including only patients with severe disorders might lead to a restricted indication.': Please note that 'Severe PTSD' is not properly defined. Most clinical trials use a SCID diagnosis of PTSD as inclusion criterion, with a CAPS score of 55 or above. People are fairly symptomatic and uncomfortable at this level. The CAPS cutoff score (best sensitivity/specificity) that has been used by the CAPS developers is 65 or above. That score, however, would exclude some patients who really need it from proper treatment. A wide range of scores is seen among returning veterans – some with partial symptoms (40s and low 50s), moderate symptoms 50 to 65) and more severe from 65 up through about 115. Generally one finds higher ranges in combat versus civilian PTSD. For these reasons, the severity threshold (and the scale) that would be considered to lead to a restricted indication should be well defined.	Severity should be defined and well defended based on the severity scale used. It is the responsibility of the investigator/sponsor to provide evidence regarding the psychometric properties of scale used, including evidence supporting the range of scores associated with moderate and severe PTSD
	Line 81-83: We are not aware of data or any scale that separates PTSD into mild, moderate or severe according to defined cut off on a scale. Neither are we aware that it has any epidemiological or clinical or any other implication in the way that exists for depression on the MADRS or Hamilton scale. Furthermore, the symptoms of PTSD fluctuate in the same individual with time and it is unclear if the level of severity at a specific time point reflects severity over the course of time. There is no pharmacological evidence that mild *versus* severe PTSD respond differently as in depression. Data on cut off points on scale for differentiating mild, moderate or severe PTSD and its clinical/pharmacological relevance should be provided.	(See also response to previous comment) The burden of the proof is on demonstrating that efficacy holds across levels of severity.
	Line 84: Descriptive parameters of value are the duration of the disorder, civilian *versus* combat, female *versus* male, the presence/absence of childhood trauma-neglect-abuse, comorbidities, especially alcohol and substance abuse and type of trauma. The presence/absence of physical injury is relevant for acute PTSD.	Agreed

	Furthermore there is evidence that the core difference is between acute trauma – such as a car accident *versus* a prolonged or repeated trauma such as combat. That should be the major specifier. The descriptive parameters could be amended to include further examples as follows: Further descriptive parameters, like duration of the disorder, whether onset was immediate or delayed and the type of precipitating event, should be ascertained and specified in the inclusion criteria. *Other considerations may include presence/absence of childhood trauma-neglect-abuse, civilian versus combat, presence/absence of physical injury.*	
	Line 86: 'Separate trials should be performed in patients with acute, chronic and delayed onset PTSD.' We strongly urge to reconsider this requirement for the following reasons: First there is not enough information about underlying biological differences between acute, chronic and delayed onset PTSD. Secondly, the pool of "acute" and "delayed onset" PTSD is relatively smaller and would be hard if not impossible to recruit. A better strategy would be to include chronic PTSD (which could include delayed onset) and then to look in a post-hoc way if there are any differences. The acute phase is quite short and it would be difficult to recruit these subjects before they become chronic – also since many individuals improve spontaneously during this period, which would play havoc with "placebo" rates.	If a heterogeneous group of patients (with respect to onset) is included then a randomisation within strata defined by type of onset, should take place in order to enable an adequate comparison of the effect between strata. Changes made: 'Separate trials should be performed in patients with acute, chronic and delayed onset PTSD. Alternatively, if the different types of patients are included in the same trials then randomization should take place with the strata defined by type of onset.'
	Line 86 and 147-148: We envisage that common trials would be recommended for both acute and chronic PTSD: as long as there is no clear scientific consensus on the differential response to treatment modalities between acute and chronic PTSD but only a difference in severity and time course, separate trials are not appropriate. Delayed onset is a residual category: it should be identified but it does	See response to previous comment.

	not merit specific trials. *Replace:* Line 86: Separate trials should be performed in patients with acute, chronic and delayed onset PTSD. *With:* Line 86: For agents of known pharmacological classes common trials could be performed in patients with acute, chronic and delayed onset PTSD, provided that sufficient patients from each category are included to allow a prospective subgroup analysis. For products with a new mechanism of action, separate studies may be required. AND *Replace:* Line 147-148: Depending on the claim, separate trials should be performed in patients with acute, chronic and delayed onset PTSD. *With:* Line 147-148: Depending on the claim, **common** trials **could** be performed in patients with acute, chronic and delayed onset PTSD.	
	Line 88-94: Depressive symptoms are often present in PTSD patients, as are other anxiety symptoms. As far as known at this point, the relationship between depressive symptoms and PTSD is not understood. Relatively few individuals have PTSD symptoms alone – most have at least one past or current MDD diagnosis or recurrent MDD – al starting after the PTSD symptoms and trauma. The average Ham-D score of these patients is somewhere around 17-20. A more appropriate inclusion/exclusion criterion would be: 'MDD permitted, but only after development of PTSD symptoms', or alternatively – PTSD is primary, MDD secondary. Proposed text: *Patients with predominant and/or severe depressive symptoms (e.g. not meeting the DSM-IV MDD 93 criteria)* ~~*should be excluded as well. Patients should have low severity scores (e.g. < 2) on item 1 of 94 the HDRS*~~ *may be included provided they have developed*	The inclusion of patients with comorbid depression is not acceptable and this is particularly poignant in trials examining efficacy of compounds with known antidepressant effects. A specific effect on PTSD cannot be demonstrated in trials where patients with comorbid depression are included.

	symptoms of PTSD	
	Line 89-91: In two large epidemiologic studies, 85-88% of the men and 78-80% of the women with PTSD had comorbid psychiatric diagnoses*. Thus, the exclusion of patients with current or recent history of depression would significantly narrow the study population and impair generalization of study results. Lines 162-164 recommend controlling for the effect of treatment of depressive symptoms in the statistical analysis. *Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995 Dec; 52(12):1048-60. *Creamer M, Burgess, McFarlane AC. Post-traumatic stress disorder: findings from the Australian National Survey of Mental Health and Well-being. Psychol Med. 2001 Oct; 31(7):1237-47. *Replace:* 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. *With*: Population should have primary diagnosis of PTSD and subjects with a Major Depressive Episode that preceded PTSD should be excluded.	See response to previous comment.
	Line 97: Exclusion of 'Severe symptoms of other anxiety disorders' Other anxiety disorders are VERY common in PTSD. These disorders can often be traced back directly to the trauma events – example – the Vietnam veteran sniper who had to take about 10 showers a day to "wash" the blood (intrusive imagery) off of him. It is acknowledged that there may be a different biology that needs to be addressed in these individuals that requires additional medication, but treatment of PTSD would be indicated. **Proposed text:** ~~*Severe symptoms of other anxiety disorders*~~	See response to previous point

	Line 97: PTSD patients are renowned for having comorbidities. It is estimated that up to 75% have at least one. Therefore studying only "pure" PTSD is unrepresentative, and might provide a considerable bias and will not be useful in clinical application. It is better to include patients with comorbidities as long as these are not the primary diagnosis or not the focus of clinical attention. It is suggested to amend line 97 to "Other anxiety disorders if they are the primary diagnosis".	See response to previous point
	Line 98: The exclusion criteria indicate people with severe OCD symptoms should be excluded. Suggest deletion of *"Patients with severe OCD symptoms (not meeting the DSM IV criteria)"*, as this would be covered in the first part of exclusion criteria i.e. *"..severe symptoms of other anxiety disorders"*.	See response to previous point
	Line 82 and 110-114: The CAPS is a structured clinical, diagnostic interview. It is relevant for excluding patients with symptoms but not the full disorder. Beyond that it is not a severity scale as such. The PCL or the PSS scale could be included as examples of appropriate severity scales.	As the guideline indicates, the scale should be validated. The guideline is not intended to be prescriptive in this regard and various validated scales could be acceptable provided adequate evidence for their validity is provided.
	Line 102: The exclusion of alcohol/drug abuse for 6 months would also complicate clinical research very much as this co-morbidity is quite common. Most subjects would be lost to clinical trial – they simply can't wait that long for treatment. In clinical practice, three months is used and has shown to be adequate. We propose to limit the exclusion period to 3 months. **Proposed text:** *Chronic alcohol abuse or current / recent history of substance abuse (within the last ~~6~~ **3** months)*	DSM requirement for defining patients in remission from substance abuse is 12 month. Six month is therefore considered already lenient for patients' inclusion and a further reduction is not acceptable.
	Line 106/7: 'Patients receiving specific psychotherapy for PTSD (e.g. trauma focused cognitive behaviour therapy, eye movement desensitization and reprocessing) should be excluded as well.' This exclusion criterion would make it impossible to develop products as add-on therapy, specifically focusing on augmentation of cognitive	Inclusion of patients in whom pharmacological treatment is provided as augmentation to other therapies (e.g. psychotherapy) will have implication for the indication. For trials designed to examine the effect of augmentation, inclusion of such patients would be acceptable. However, inclusion of a mixture of patients, some of whom do receive additional

	behaviour therapy or of existing but inadequate pharmacotherapy. We agree that the number of patients on 'supportive therapy' in clinical trials should be limited. However, in our opinion the guideline should be phrased in such a way that it also leaves the option to study augmentation or synergy of verbal treatments with medication.	therapies while others do not, might confound the results in such a way that no conclusive conclusions might be inferred from the results. Furthermore, it would make more sense to first examine efficacy of monotherapy prior to examining augmentation.
	Line 81-83: We are not aware of data or any scale that separates PTSD into mild, moderate or severe according to defined cut off on a scale. Neither are we aware that it has any epidemiological or clinical or any other implication in the way that exists for depression on the MADRS or Hamilton scale. Furthermore, the symptoms of PTSD fluctuate in the same individual with time and it is unclear if the level of severity at a specific time point reflects severity over the course of time. There is no pharmacological evidence that mild *versus* severe PTSD respond differently as in depression.	The CAPS-2 for example separates PTSD severity into mild (scores 20-39) moderate (40–59); severe (60-79) and extreme (80+) (see e.g. Weather, Kean & Davidson (2001). It is expected that a dossier will contain patients from the whole range and not only patients with severe disorders.
	Line 84: Descriptive parameters of value are the duration of the disorder, civilian *versus* combat, female *versus* male, the presence/absence of childhood trauma-neglect-abuse, comorbidities, especially alcohol and substance abuse and type of trauma. The presence/absence of physical injury is relevant for acute PTSD. Furthermore there is evidence that the core difference is between acute trauma – such as a car accident *versus* a prolonged or repeated trauma such as combat. That should be the major specifier.	Agreed.
	Line 86 and 147-148: The existence of delayed onset PTSD is controversial and at best represents a small, relatively rare, sub-population that resembles chronic PTSD, and hence should not be studied separately. It may also be difficult in practice to perform separate trials in patients with acute, chronic and delayed onset PTSD. The distinction between acute and chronic PTSD lies in the duration of the episode, which refers to the natural course of the disease and cannot be predicted at baseline when symptoms are present.	See response to a similar previous comments.
	Line 89-91: Symptoms of PTSD and of depression share common	See response to a similar previous comments.

	features and major depression could occur following the exposure to a traumatic event, hence it is not suitable to exclude these patients from studies. Proposed text: It is suggested to amend "current or recent history of major depression within six months of study entry" to "current or recent history of major depression unrelated to the onset of PTSD".	
	Line 97: PTSD patients are renowned for having comorbidities. It is estimated that up to 75% have at least one. Therefore studying only "pure" PTSD is unrepresentative, and might provide a considerable bias and will not be useful in clinical application. It is better to include patients with comorbidities as long as these are not the primary diagnosis or not the focus of clinical attention. Proposed text: It is suggested to amend line 97 to "Other anxiety disorders if they are the primary diagnosis".	See response to a similar previous comments.
Exclusion criteria		
	Line 98: "Severe OCD symptoms not evaluated with DSM" It should be described how severity will be evaluated; by investigator's opinion or using a well-established scale for assessing symptoms of OCD?	As the text indicates (see line 103-104 of the original draft guideline: "For all these disorders, a valid method of diagnosis should be used (i.e. experienced clinician, structured assessment) and documented."
Method to assess efficacy – Primary efficacy endpoint		
	Line 112-113: There should be no need for further validation of the established scales in PTSD (e.g. CAPS). For further clarification regarding the scale to be used in efficacy studies, we would like to reword the sentence "Furthermore, the scale needs to be validated in the target population before being used in the efficacy studies."	As validity and reliability of a scale can vary across populations and settings, there is a need to validate the scale in the target population and the setting of the clinical trial.

	Replace: Furthermore, the scale needs to be validated in the target population before being used in the efficacy studies. *With:* If another scale is chosen (i.e. other than the CAPS), this scale needs to be validated in the target population before being used in the efficacy studies.	
	Line 113-114: The guideline indicates inter-rater reliability should be demonstrated in the study setting. Generally for short term studies, investigator training prior to study conduct is sufficient. In line with the wording in the other anxiety guidelines, we would suggest that this wording is replaced by: "In advance and if necessary during the study investigators should be trained to become and stay interreliable".	Inter-rater reliability needs to be demonstrated prior to the study.
	Line 115-119: We are not aware that there is any accepted definition of response or remission in PTSD contrary to depression for example. Suggest that the text includes an example of what would be deemed a clinically relevant reduction from baseline on for example the CAPS-2.	It is the responsibility of the company to define response and remission and to justify these definitions.
	Line 120-122: '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)' Please note that the biology underlying the various clusters may be different. For example: prazosin – seems to improve the nightmares and to some degree arousal – does it need to improve avoidant symptoms also to be an effective and useful medication. Requiring statistically significant improvement on all 3 symptom clusters would raise the hurdle considerably and may lead to rejection of products that are effective and useful for treating part of the symptoms. Please clarify that improvement in some of the symptoms can also be demonstrated by a 'change in the right direction' but not necessarily statistically	See response to previous similar point. As PTSD is considered to be one diagnostic entity and the purpose of treatment is to treat this disorder, an effect on all three symptom cluster will need to be demonstrated.

	significant.	
	Line 110-114: The CAPS is a structured clinical, diagnostic interview. It is relevant for excluding patients with symptoms but not the full disorder. Beyond that is it not a severity scale as such. It is suggested to consider the use of the PCL or the PSS scale.	The investigators are free to choose a severity scale provided it is well validated as indicated in the respective paragraph.
	Line 115-119: We are not aware that there is any accepted definition of response or remission in PTSD contrary to depression for example.	The investigators are responsible for defining response based on an acceptable rationale. For the CAPS a reduction of 15 points was proposed as being clinically significant (Weather, Kean & Davidson, 2001).
Strategy and design of clinical trials		
	Dose-response studies **Line 144:** Inclusion of 3 doses, a placebo-arm and active comparator means a 5-arm study. With the addition of multiple arms, the N would be so large as to be prohibitive, especially as the placebo rate is substantial. We also do not understand the need for 3 doses and for fixed dose studies. There is at least one example of a drug showing efficacy with only 2 doses (paroxetine). We propose to make this section a recommendation rather than a mandatory design. Proposed text: Adequately controlled~~, parallel, fixed dose~~ studies~~, using at least three dosages~~ (e.g. a fixed dose study with at least two 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.	An adequate examination of the minimal effective dose and the maximum tolerated dose is essential for effective and safe use and therefore for registration. The proposed changes can therefore not be accepted.
Therapeutic confirmatory studies – short term trials		
	Line 151: Consider time necessary for stable treatment effect of 8-12	Not accepted.

	weeks (more consistent with literature), rather than 10-12 weeks as proposed.	
	Line 152: '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.' We support that the optimal duration of the acute efficacy studies should be derived from pilot short-term studies. However, we feel that a 10-12 week treatment period in combination with the high placebo response and a difficult recruitment due to the stringent (rather unrealistic) exclusion criteria is very long. We propose to leave out the expectation that duration will be 10-12 weeks. It is not a necessary addition as the duration will automatically follow from the pilot studies. Proposed text: '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.~~'	The current text does not demand 10-12 weeks, rather provides an indication derived from previous knowledge. However, shorter duration may be accepted if well justified, i.e. by evidence from pilot studies. There seems no need to erase the suggestion of 10-12 weeks as this is not a demand but rather a suggestion.
	Line 156/7: 'A placebo run-in period to exclude placebo responders is not recommended as it may impair generalisation of the results.' We do not understand how a placebo run-in of placebo-responders interferes with generalisation of the results. Please clarify as in our opinion it would be appropriate to minimize placebo effects in adults and children.	Excluding placebo responders limits generalisation as in real practice patients entering treatment do not first receive placebo prior to receiving active treatment.
	Line 158: 'Concurrent medication interfering with the test agent or effect is not recommended.' Please also refer to our earlier comment (page 5, line 106). In more severely ill and chronic patients, it may be necessary to investigate augmentation of the effect of existing treatment (this is current practice). The guidance should not exclude such designs. Please delete or rephrase. Proposed text: 'Concurrent medication interfering with the test agent or effect is not recommended, unless this is part of the study design (add-	See response to previous point. Augmentation could in principle be accepted. However, it would make more sense for efficacy to be first demonstrated as monotherapy. Adding the poropsed text is considered as unnecessarily complicating the as it refers to a specific situation where a product is most likely already approved as monotherapy and currently being studied as augmentation.

	on study).'	
	Line 159: 'If patients are currently treated with an active agent, a washout period is necessary.' We suggest allowing such a wash-out period to be combined with a variable placebo run-in. Although in the present guidance, the use of a placebo run-in is discouraged, the placebo-response in PTSD is substantial and measures need to be taken to minimize these effects. It would give added value to the guidance if this need was acknowledged and potential solutions indicated. Proposed text: 'If patients are currently treated with an active agent, a washout period is necessary. In order to minimize the placebo response, such a wash-out period could be combined with a variable placebo run-in period.	See previous response regarding placebo run-in.
	Line 155: In clinical trials of a regulatory purpose dose titration is typically performed at fixed points and is either done because the protocol requires it or because the response is partial and the protocol allows for up titration. However it is not "guided" by efficacy/tolerance. If a patient cannot tolerate up-titration the protocol typically would require a withdrawal.	Ideally dose titration should be gradual and guided by efficacy and tolerance.
Long-term trials		
	Line 165: The guideline makes no recommendations of which scale should be used in long-term efficacy studies (PTSD specific vs. CGI). Also the guideline suggests "one or more visits"; suggest this is clarified as one visit is not likely to be sufficient for a Phase III study. Suggest that the guideline provides an example of a scale recommended for use in a long-term efficacy study and provides clearer guidance with respect to "one or more visits" as our experience is that one visit was not deemed acceptable.	As with scales for short-term trials, it is the responsibility of the company to make a well weighted choice of the scale to be used. Likewise, the definition of relapse based on 1 or 2 visits/assessments is the responsibility of the company. It is noted that a PTSD specific scale should be used and not the CGI.
	Line 165: It is important to re-evaluate trauma exposure over the course of time, as recurrent trauma exposure impacts treatment outcome. This point is rarely assessed in trials and is a major shortcoming which is not	Although this might be theoretically a valid point, this issue and level of detail does not seem to belong in a guideline.

	appreciated.	
	Page 169-170: 'Efficacy in long-term controlled studies is usually expressed as the proportion of patients worsening (relapsing) and/or time to this event.' Please note that a withdrawal design is not always ethical unless appropriate escape criteria are also included. The use of such criteria should be indicated in the guidance (e.g. allow patients to restart on active treatment if they reach certain worsening criteria. Alternative designs such as a 'relapse prevention' design (as described for depression) may be similarly acceptable.	The text refers to designs that include 'relapse prevention' and randomised withdrawal. Included in such designs is the possibility for treatment in patients who have relapsed according to predefined objective criteria.
Studies in special populations – Elderly	**Line 178-180:** Although there is no consensus whether elderly with PTSD have more somatic complaints or more somatic illness, there are indications that PTSD leads to an increase in actual illness. Please note that a review of medication treatment approaches to the elderly will be published shortly in J of Geriatric Psych (Mohamed S and Rosenheck R)	Noted.
	Line 191: Children and Adolescents – a rating scale is not suggested for use in this population even though it is indicated it should be specific for this group Suggest that the guideline provides an example of a validated scale recommended for use in children and adolescents	As was noted earlier, it is not the intention of this guideline to be prescriptive in this regards. The general guidance indicates that the assessment scales should be well validated in the target population.
	Line 191: Children and Adolescents – reference is made to the paediatric guideline (ICH E11) indicating that "trials may be conducted after a marketing authorisation and licensing for adults has been obtained". Suggest that this may need to be brought in line with the Paediatric Regulation to state that Deferral can be sought. Consider inclusion of the statement "A Deferral may be granted under the Paediatric Regulation."	It is considered the current text is sufficiently clear in this regard.
Clinical safety evaluation General recommendations		

	Line 203-204: It is important to highlight the need for vigilance in AE monitoring particularly when drug dose is changed (increase or decrease) Change the following text (proposed change in italics): Identified AEs 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 *such as any changes in drug treatment regime.*	Accepted.
	Line 209: Clarification on what specific monitoring is required for children/adolescents elderly or deletion of this statement.	It is the responsibility of the company to decided which monitoring is required.
	Line 209-211: Rephrasing of the statements on overdose required: Any information available concerning clinical features and therapeutic measures in accidental overdose or ~~deliberate self-poisoning~~ asymptomatic intentional overdose, regardless of clinical sequelae, should be provided.	The following changes are accepted: Any information available concerning clinical features and therapeutic measures in accidental or intentional overdose ~~or deliberate self-poisoning~~ should be provided.
	Line 207-208: Sexual dysfunction is a class side effect of SSRI's. Please add as an example. Proposed text: Side effects that are characteristic of the class of the product being investigated should be carefully monitored e.g. extra pyramidal symptoms, sexual dysfunction.	Accepted
	A 4th paragraph to be added under General recommendation, page 7: A recommendation for study enrolment could be the need for study investigators to have details of a friend or family member of the subject who will inform investigators of any clinical worsening or change in status Proposed text: Study investigators could be asked to retain details of a friend or family member of the subject who will inform investigators of any clinical worsening or change in status.	Accepted.

Specific Adverse events-Rebound/withdrawal/dependence	Line 215-217: '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.' See also our comment on page 6 (line 169). It is not ethical to withdraw an effective drug in order to study relapse.	As was mentioned earlier, in a randomised withdrawal study, patients who experience relapse can be treated with active medication. Furthermore, there is no ethical issue with withdrawal of an active treatment of which the efficacy has not yet been demonstrated.
	Line 215 and 218: Rebound and/or withdrawal phenomena should be investigated. This could be expanded to indicate how to do this. Suggest the text includes guidance on what methodology is expected to be used to assess these phenomena. Is an open ended question similar to that used to capture any AE acceptable to assess the occurrence of withdrawal and rebound symptoms e.g. "How have you felt since the last clinic visit?"	It is up to the company to come up with a design that is acceptable to study withdrawal and rebound. This is also dependent on the substance that is being investigated and therefore the guideline cannot be specific on this issue.
	Line 223-224: 'The chronic nature of PTSD increases the risk of dependence.' The chronic nature of PTSD also increases the potential for drug abuse in this patient group. Please add this observation, in order to explain the need to report the information (lines 209-211).	'and abuse' added to the text.
Central Nervous System (CNS) adverse reactions	Line 231: More clarity required regarding recording and monitoring of events of emergent suicidality Suggest the guideline makes it specific whether this should be via a specific rating scale (Columbia classification) or collection of specific adverse events during studies.	The company is responsible to design adequate monitoring and assessment of suicidal behaviours. The guideline is not intended to be specific in this.
Endocrinological adverse events	Libido, sexual disturbance and weight gain can be core symptoms of the disease not just of the treatment. Revise this section to state: "depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary and special attention should be paid to sexual disturbance, libido and weight gain".	Even if these symptoms are related to PTSD, the placebo control would help in ascertaining whether the investigated compound has an additional role in these symptoms.
Textual comments	line 223: under Clinical safety evaluation rebound/withdrawal/dependence,	Sentence changed.

	“The chronic nature of PTSD increases the risk of dependence.” The sentence is unclear. Dependence is a property of the compound not of PTSD. Probably the following is meant. If a compound evokes dependence, the risk is larger if intended for chronic use as in PTSD.	