



London, 21 July 2008
Doc. Ref. EMEA/403001/2008

**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	MEB	NL

Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW		
<p>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.</p> <p>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 anxiolytic) 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.</p> <p>Opposition was raised against the requirement to demonstrate efficacy on all three PTSD symptom clusters (re-experience, avoidance, and arousal). However, it is considered that PTSD is a unified diagnostic entity and therefore therapeutic effects needs to be demonstrated on the whole rather than on only some components of this disorder.</p>		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no.¹ + paragraph no.	Comment and Rationale	Outcome
<i>General</i>		
	<p>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</p>	<p>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.</p>

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.
	<p>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:</p> <ol style="list-style-type: none"> 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. <p>There is evidence of a difference between civilian and combat PTSD and to the attributes of PTSD in women <i>versus</i> men, more specifically to the acute trauma such as molestation <i>versus</i> 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.</p>	<ol style="list-style-type: none"> 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.
Introduction		
	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
Patients characteristics and selection of patients		
	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	As the guideline indicates, the scale should be validated. The CAPS is indeed a well known validated scale but the guideline is not intended to be prescriptive in this regard and other validated scales would be acceptable as well provided adequate evidence for their validity is provided. Using the same scale throughout the whole development program has the

	<p>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]).</p> <p>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 may function to some degree as a treatment instrument if given too often.</p>	<p>advantage of enabling combined analyses across studies (e.g. to obtain sufficient power for subgroups analyses).</p>
	<p>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.</p>	<p>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</p>
	<p>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:</p> <p>First there is not enough information about underlying biological differences between acute, chronic and delayed onset PTSD.</p> <p>Secondly, the pool of “acute” and “delayed onset” PTSD is relatively smaller and would be hard if not impossible to recruit.</p> <p>A better strategy would be to include chronic PTSD (which could</p>	<p>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.</p> <p>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</p>

	<p>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.</p>	<p>should take place with the strata defined by type of onset.’</p>
	<p>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 – all 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: <i>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 symptoms of PTSD</i></p>	<p>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.</p>
	<p>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</p>	<p>See response to previous point</p>
	<p>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</p>	<p>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.</p>

	<p>period to 3 months.</p> <p>Proposed text: <i>Chronic alcohol abuse or current / recent history of substance abuse (within the last 6 3 months)</i></p>	
	<p>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 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.</p>	<p>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 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.</p>
	<p>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.</p> <p>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.</p> <p>There is no pharmacological evidence that mild <i>versus</i> severe PTSD respond differently as in depression.</p>	<p>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.</p>
	<p>Line 84: Descriptive parameters of value are the duration of the disorder, civilian <i>versus</i> combat, female <i>versus</i> male, the presence/absence of childhood trauma-neglect-abuse, comorbidities, especially alcohol and substance abuse and type of trauma.</p> <p>The presence/absence of physical injury is relevant for acute PTSD.</p> <p>Furthermore there is evidence that the core difference is between acute trauma – such as a car accident <i>versus</i> a prolonged or repeated trauma such as combat. That should be the major specifier.</p>	<p>Agreed.</p>
	<p>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</p>	<p>See response to a similar previous comments.</p>

	<p>studied separately.</p> <p>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.</p>	
	<p>Line 89-91: Symptoms of PTSD and of depression share common features and major depression could occur following the exposure to a traumatic event, hence it is not suitable to exclude these patients from studies.</p> <p>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”.</p>	See response to a similar previous comments.
	<p>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.</p> <p>It is better to include patients with comorbidities as long as these are not the primary diagnosis or not the focus of clinical attention.</p> <p>Proposed text: It is suggested to amend line 97 to “Other anxiety disorders if they are the primary diagnosis”.</p>	See response to a similar previous comments.
Exclusion criteria		
	<p>Line 98: “Severe OCD symptoms not evaluated with DSM”</p> <p>It should be described how severity will be evaluated; by investigator’s opinion or using a well-established scale for assessing symptoms of OCD?</p>	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		
	<p>Line120-122: ‘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)’</p> <p>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 significant.</p>	<p>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.</p>
	<p>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.</p>	<p>The investigators are free to choose a severity scale provided it is well validated as indicated in the respective paragraph.</p>
	<p>Line 115-119: We are not aware that there is any accepted definition of response or remission in PTSD contrary to depression for example.</p>	<p>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).</p>
Strategy and design of clinical trials		
	<p>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</p>	<p>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.</p>

	<p>efficacy with only 2 doses (paroxetine). We propose to make this section a recommendation rather than a mandatory design.</p> <p>Proposed text: <u>Adequately controlled, parallel, fixed-dose studies, using at least three dosages (e.g. a fixed dose study with at least two dosages)</u> 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.</p>	
<p>Therapeutic confirmatory studies – short term trials</p>		
	<p>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.</p> <p>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.’</p>	<p>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.</p>
	<p>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</p>	<p>Excluding placebo responders limits generalisation as in real practice patients entering treatment do not first receive placebo prior to receiving active treatment.</p>

	opinion it would be appropriate to minimize placebo effects in adults and children.	
	<p>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.</p> <p>Proposed text: ‘Concurrent medication interfering with the test agent or effect is not recommended, <u>unless this is part of the study design (add-on study).</u>’</p>	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 proposed 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.
	<p>Line 159: ‘If patients are currently treated with an active agent, a washout period is necessary.’</p> <p>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.</p> <p>Proposed text: ‘If patients are currently treated with an active agent, a washout period is necessary. <u>In order to minimize the placebo response, such a wash-out period could be combined with a variable placebo run-in period.</u></p>	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		
	Page 169-170: ‘Efficacy in long-term controlled studies is usually expressed as the proportion of patients worsening (relapsing) and/or	The text refers to designs that include ‘relapse prevention’ and randomised withdrawal. Included in such designs is the possibility for

	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.	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.
Clinical safety evaluation General recommendations		
	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, <u>sexual dysfunction</u> .	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 223-224: ‘The chronic nature of PTSD increases the risk of dependence.’ The chronic nature of PTSD also increases the potential	‘and abuse’ added to the text.

	for drug abuse in this patient group. Please add this observation, in order to explain the need to report the information (lines 209-211).	
Textual comments	<p>line 223: under Clinical safety evaluation rebound/withdrawal/dependence,</p> <p>“The chronic nature of PTSD increases the risk of dependence.”</p> <p>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.</p>	Sentence changed.