London, 17 February 2011
Doc. Ref. EMA/607700/2010

Overview of comments received on the draft guideline on medicinal products for the treatment of insomnia (EMA/CHMP/16274/2009)

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

Stakeholder no.	Name of organisation or individual
1	Prof Malcom Lader, Emeritus Prof of clinical Psychopharmacology, King`s College London
2	Actelion
3	ECNP = European College of Neuropsychopharmacology
4	EFPIA = European Federation of Pharmaceutical Industries and Associations
5	AESGP = Association of the European Self-Medication Industry

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Professor Lader believes this guideline to be a thoughtful and very helpful document. He has been involved for many years in the study of hypnotic medications, in particular their residual effects the next day and their dependence and abuse potential. He regards the use of hypnotic medications to be a last resort in the treatment of most forms of insomnia particularly that vague entity, "primary insomnia". Most medications used in this context are benzodiazepines which are non-specific depressants inducing sleep by reducing vigilance and arousal. They have no focussed effect on abnormal sleep mechanisms. Antihistamines used ex-label or OTC are equally non-specific. Melatonin-based compounds are more specific but have low efficacy. Accordingly, the use of most hypnotics should be discouraged or at least minimised. Two possible ways of doing this are: 1) To encourage insomniacs with symptoms that fluctuate night by night to take hypnotics on an as-needed (PRN) basis rather than on a regular every-night basis. 2) To encourage insomniacs with early wakening to use "middle-of-the-night" remedies, assuming they are eventually licensed. He therefore suggests that the guidelines are extended to cover these 2 areas. The first is, he thinks, non-contentious; the second will need	**Ref.1:** Minimisation of hypnotic medications is undoubtedly

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	specific recommendations.	an important goal. However, as at the present time, there still exist several uncertainties, e.g. with respect to adequately validated endpoints in already established indications, these limitations first of all should be resolved before discussing further topics, e.g. further indications.
2	None	
3	This guideline suggests the use of cognitive tasks to evaluate the a) beneficial effects of the drug on daytime performance and b) to rule out any negative effects on cognitive function of drug administration. It is essential that the cognitive tasks are selected to be sufficiently sensitive and valid, both to the effects of prolonged loss of sleep (for a) or for detecting negative effects of drug treatment on cognition (for b). The exact tasks would need to be validated in separate studies (with the same parameters) to prove that they were sensitive to the aspects of cognitive function in question in relation to insomnia and the population being studies (e.g. elderly versus young patients, etc). ECNP welcomes the inclusion of secondary insomnia within the guidance, as this is a common and troublesome problem in psychiatric patients and in many physical illnesses. It should not be underestimated how much morbidity is associated with secondary insomnia. ECNP believes the interaction between factors associated with insomnia and factors present in mental disorders require careful consideration and distinction. It would be helpful if the introductory sections included a list of abbreviations that appear later in the text.	**Ref.2:** A special list of abbreviations will be added.
4	**General observations:** The guideline update is welcomed, is reasonably written and represents drug development so far in primary insomnia. In particular the following: - the general updating of the guideline to today's standards and to reflect new mechanisms of action in development for insomnia. - the amended name of the guideline (treatment of insomnia) which is preferred to 'hypnotics'.	

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	- the greater clarity provided on study designs to support both short term and long term efficacy. - the opportunity to use a randomised withdrawal design as an option for demonstrating long-term efficacy. - an approach to child/adolescent insomnia that does not require study of primary insomnia. - the special attention paid to individuals at least 75 years old who are a growing patient population. <u>A key issue is lack of worldwide harmonization on insomnia drug development.</u> Regulatory requirements different than or above what is required by other regulatory agencies will result in either an application not filed to the EMA, or delayed marketing applications, or an inability of applicants to obtain an approval for a marketing application from the EMA at the same time as from other regulatory agencies. As a direct result, availability of new insomnia medicines to patients would be delayed or limited. As insomnia is an important disease, benefit to risk should be considered in regulatory requirements. Therefore, flexibility in requirements should be allowed to the extent that it is possible. Some of the proposed changes below are intended to add flexibility so that one development program can address the requirements of the different agencies and foster global development. Furthermore, the requirement to obtain long-term efficacy data in paediatrics seems unreasonable especially if efficacy is already demonstrated in adults. The revised guideline raises several major questions that are not clearly addressed such as when to add active comparators in the development, and whether both subjective and objective sleep efficacy data are needed. Also "how to assess maintenance effect" and the "possibility of excluding placebo responders", which have been an ongoing discussion in the field for several years, and are not clarified. Flexibility in ways to incorporate these aspects into a development program can be stated in the guideline.	**Ref.3:** A better harmonization of development programs and regulatory requirements would be an important goal. However, the presented guideline offers special advice how to develop products for the intended population, the European population. The guideline has been specified in several sections.

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	Some additional more specific comments are included below. **Primary vs. Secondary Insomnia:** The guiding principle appears to be that efficacy proven in a population of patients with "primary insomnia" according to accepted diagnostic criteria (mainly DSM-IV) allows extrapolation to co-morbid ("secondary") insomnia. This should be stated more clearly together with confirmation that the labelling will thus not be restricted to primary insomnia only. Otherwise more explicit guidance would be necessary on how to handle the potential impact of concomitant treatment of the co-morbid condition on primary efficacy outcomes and the impact of pseudo-specific claims on labelling. **Short-term vs. long-term treatment:** It is recommended that requirements for assessing both short-term and long-term efficacy are harmonised and that both can be achieved in a long-term trial(s). As an example, the FDA will accept 3-month studies to support long-term treatment and for global programs it would be beneficial to have some consistency and common study duration. **Daytime Function:** Although insomnia has considerable impact on daytime function, the lack of validated assessment tools for global daytime function related to insomnia does not yet allow specific recommendations to be made for use of any particular assessment scale in regulatory trials. We propose that assessment of daytime functioning is recommended as an exploratory endpoint, but not as a mandatory co-primary endpoint.	**Ref.4: Not accepted.** Justification: The guideline does not state, that efficacy proven in a population of patients with "primary insomnia" can be extrapolated to co-morbid insomnia. It just describes, that development of a medicinal product should start in primary insomnia. **Ref 5: Not accepted** Justification: Treatment of insomnia should be as short as possible, therefore initially short-term efficacy has to be demonstrated. Nevertheless, efficacy and safety should also be assessed in a long-term study, unless safety reasons exist. Therefore, a study duration of about 6 month is considered necessary to provide an adequate safety profile. **Ref. 6: Not accepted** Justification: Based on the DSM-IV-TR criteria, in cases that only one/some efficacy criterion of sleep is studied, there still remains the need to demonstrate that a benefit in this single aspect is of clinical relevance, represented by an adequate day time functioning without significant distress or functional impairment. Therefore, improvement in quality of day time functioning is considered to be the most relevant outcome parameter.

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		However, it is acknowledged, that defining such a validated endpoint needs further studies.
	Polysomnography: Separate studies in inpatients or outpatients should not be needed as long as the evaluations and analyses are separate. Generally, in PSG trials of longer duration (more than 2 weeks), the scheduled laboratory assessment nights represent only a minor fraction of the total trial duration. In such instances, patient reports can be collected in non-sleep laboratory nights conducted in the subject's natural setting to provide independent evidence of subjective efficacy. This will simplify the development program allowing applicants to meet regulatory requirements of both EMA and other regulatory agencies using the same trials. Furthermore, two consecutive adaptation nights in studies requiring PSG evaluation adds extra burden for patients as well as potentially unnecessary cost to the sponsor. Given that one night adaptation may be adequate, some flexibility should be provided in the recommendation.	**Ref. 7: Not accepted.** Justification: The main focus is on clinical outcome measures in the natural setting. Therefore, if PSG assessments in the natural setting are performed on selected nights, the study cannot be accepted as performed in the natural setting with regard to influences/effects that are caused by PSG. However, ambulatory PSG evaluation is acceptable as supportive data. Two adoption nights are still considered necessary given the potential source of bias.
	Paediatrics: Benefit to risk should be considered in conduct of paediatric insomnia trials. The requirement for trials to be conducted only in severe, persistent insomnia refractory to usual behavioural and licensed pharmacological strategies, where possible causative or maintaining medical disorder have been excluded, seems overly restrictive and is not clear. It should therefore be clarified if children with neuropsychiatric disorders (e.g., ADHD or autism) can be considered as an appropriate target population in order to achieve a paediatric insomnia indication.	**Ref.8: Not accepted** Justification: a) The wording 'refractory to … licensed pharmacological strategies' has been deleted as no such strategies are licensed at the time of writing the guideline and to allow for the development of future first-line drugs for insomnia. The target patient population has been defined taking into account that the definition of insomnia in children is much more challenging than in adults. The sleep behaviours are usually described by the parents and not by the children themselves. Whether particular sleep behaviours are a problem depends on a complex combination of parental perceptions, expectations, cultural standards and biological norms. Prescribing medication prior to behavioural intervention can seems an appealing option for a busy clinician and exhausted family who feel they have already

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		done the 'bedtime stuff'. However the evidence shows the immediate and sustained value of behavioural approaches, even in difficult groups of children. (Gringras, Arch Dis Child 2008, 93, 976-981)
	Given that 6 month efficacy studies in adults are required, it does not seem appropriate for children/adolescents to be included in a long-term (6 month) study. If long term efficacy was shown in adults and short term efficacy in children, there should be consideration of not requiring long term efficacy data in children.	b) As there is still a lack of acknowledgment regarding insomnia in the paediatric population, efficacy as well as safety data from adults cannot easily be extrapolated to children, further long-term studies in this population are therefore considered necessary.
	Furthermore, there are no insomnia products approved in the EU for the paediatric population. As there is no active comparator registered, it would be inappropriate to expect conduct of a 3-arm study including placebo and an active comparator. See comments regarding lines 358-9 of the guideline for specific recommendations.	c) The wording has been amended to read: Three-arm studies including placebo and an active comparator should be performed once there is an EMA approved insomnia drug for the relevant age groups under study.
	Elderly Patients over age 75: It is assumed that elderly patients are aged 65 years and over and that the comment about those aged over 75 years is to note this growing population. Thus separate elderly studies if conducted would by default have an age cut off of 65 years and above. We understand the need to obtain data in patients over 75 years of age. Separate Phase I studies in this population may be feasible however, separate Phase II or III studies are not likely to be feasible and so flexibility should be allowed to derive conclusions from phase III adult studies which also include elderly patients.	**Ref.9: Accepted:** In general separate phase III studies in the elderly are not needed. However, the sponsor should ensure that sufficiently powered subgroup analyses are feasible, to get adequate evidence of efficacy and safety for this population.
5	None	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
73	**1**	Comments: the common factor Proposed change (if any): all with subsequent	**Accepted.**
92	**1**	Comments: Why is the prevalence so much greater in the elderly? Proposed change (if any):	**Accepted.** This information refers to DSM-IV-TR. The greater risk observed in the elderly could be attributed to changes in sleep processes, circadian factors and a higher incidence of medical diseases.
149	**1**	Comments: I do not think you can combine these two populations. I think efficacy should be established in one or other or both and the indications(s) listed accordingly. (see lines 159 onwards) Proposed change (if any):	**Accepted.** The guideline has been updated, accordingly.
152	**1**	Comments: Do the symptoms have to be present every night ? Proposed change (if any): Symptoms should be present more nights than not.	**Accepted.**
203	**1**	Comments: I entirely agree about the importance of daytime functioning. Proposed change (if any): Subjective assessments can	**Partly Accepted.** Justification: Based on the DSM-IV-TR criteria, patients who do not appear to have objective manifestations of sleep disturbances but whose sleep is sufficiently inadequate or non-

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		be helpful.	restorative meet the criteria for insomnia. In contrast, someone with night-time sleep disturbances, who gets only a few hours of sleep each night, but feels without associated distress, does not meet the criteria for insomnia. Therefore, non-restorative sleep, represented by quality of day time functioning is considered to be an important symptom. The final goal of medical approval in insomnia is to achieve sufficient and widely benefit in quality of day time functioning. This results in sticking to quality of day time functioning to be the most relevant outcome parameter.
216	**1**	Comments: elderly studies must be adequately powered separately Proposed change (if any): In the elderly, separate studies from younger patients are preferable but adequately-powered subgroup studies are acceptable.	**Accepted.**
225	**1**	Comments: the problem is the poor relationship between objective and subjective measures of sleep disturbance. Proposed change (if any):	**Accepted**. A comment was included.
232	**1**	Comments: actigraphy is a poor substitute for EEG studies. Proposed change (if any): Ambulatory polysomnography may lessen the artificiality of sleep laboratory studies. Actigraphy can contribute some additional data to polysomnography but is unacceptable	**Accepted.**

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		on its own.	
250	**1**	Comments: the problem of some patients, especially the elderly who rise once or more during the night is overlooked. It is important to know how impaired they are during the night. That is why so many old people fall over at night and break their hips. Proposed change (if any): In the elderly, these tests should be carried out 2-6 hours after administration.	**Accepted.** A comment has been included in section 7.2.
253-254	**1**	Comments: many of these tests have been developed empirically and do not accord with modern psychological practice. Proposed change (if any): These tests should be reliable and have a proper validity, for example, measuring episodic and procedural memory.	**Accepted.**
262	**1**	Comments: visual analysis is clumsy and outdated but we are stuck with it, as if computers had never been invented. Proposed change (if any):	**Accepted.**
266	**1**	Comments: the problem is the plethora of QoL scales all with a different context, e.g., cancer therapy	**Accepted.**

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		Proposed change (if any): Quality of Life assessments are relevant here, but should be interpreted cautiously.	
292	**1**	Comments: the pharmacodynamic sensitivity in the elderly should be kept under consideration Proposed change (if any):	**Accepted.**
294	**1**	Comments: these terms such as discontinuation, rebound, withdrawal, tolerance, dependence, psychic and physical, relapse and recurrence, need careful definition. Abuse , non-medical use, should be clearly distinguished. Proposed change (if any): add to definitions line 453 onwards.	**Accepted.** Further information has been implemented.
304	**1**	Comments: these checks should be random Proposed change (if any): including drugs of dependence	**Accepted.**
321	**1**	Comments: the problem with a randomised withdrawal study is that it excludes poor responders who may nevertheless have developed tolerance and dependence. Proposed change (if any): Those not coming into the maintenance phase should have their medication withdrawn under placebo control to detect any possible	**Accepted.**

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		dependence.	
322	**1**	Comments: I have never understood what time to relapse contributes, except perhaps showing when the investigators receive payment! Proposed change (if any):	
282	**1**	Comments: offset may be relatively delayed – the hysteresis effect. Proposed change (if any): insert offset	**Accepted.**
327-328	**1**	Comments: this is not properly structured. Proposed change (if any): Long-term and discontinuation problems should be addressed including withdrawal and dependence. A placebo-controlled run-out phase is appropriate. Vigilance should be maintained for any signs of abuse.	**Accepted.**
382	**1**	Comments: use in demented patients is widespread but rarely studied. Proposed change (if any): Demented patients should be separately assessed.	**Accepted.**
393	**1**	Comments: the effect size may be smaller in the elderly rendering power calculations somewhat difficult.	**Accepted.**

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		Proposed change (if any): It should not be assumed that the efficacy is the same in the elderly as in the young.	
414	**1**	Comments: phrasing imprecise Proposed change (if any):	**Accepted.**
414	**1**	Comments: disinhibitory and paradoxical effects need documenting in detail Proposed change (if any): Disinhibitory and paradoxical effects need documenting in detail.	**Accepted.**
421	**1**	Comments: again carefully structure wording. Abuse should be mentioned separately. Proposed change (if any): as above	**Partly accepted.** Justification: The wording regarding abuse has generally been revised.
424	**1**	Comments: abrupt discontinuation with the patient being aware of the disruption causes exaggerated withdrawal reactions. Proposed change (if any): Placebo control is helpful wherever feasible.	**Accepted.**
431	**1**	Comments: interaction with alcohol needs emphasis	**Accepted.**

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		Proposed change (if any): Interaction with alcohol is a particular problem and can be associated with disinhibition, paradoxical reactions, and drug-facilitated assaults.	
42 , 48, 108, 109 and section 4 (diagnostics criteria) line 129	**2**	Comments: In the draft guidelines reference is made to acute insomnia and to short term insomnia e.g. lines 42, 48, 108, 109. Whereas primarily and throughout the document chronic insomnia is addressed (e.g section 4: diagnostics criteria starting line 129) 'as requiring symptoms to be present for at least one month (previously 6 months)'- line 152 and 153, it would be appreciated if the following could be clarified: • the definition of acute insomnia and its difference from short term insomnia? • Is short term insomnia referred to for products that cannot be taken long term because of safety issues like tolerance, abuse and dependency potential? • Can one get approval only for acute insomnia e.g. in the hospital setting?, if yes what are the requirements. Proposed change (if any):	**Partly accepted.** Justification: In the draft guideline, reference is made to acute insomnia and chronic forms of insomnia, as well as to short-term treatment (instead of short-term insomnia) and long-term treatment. The term short-term insomnia has not been used so far. However, the main focus is on chronic insomnia. For acute forms of insomnia, a product could be licensed in short-term treatment, according to the presented study design.
58-60, and 197-204	**2**	Comments: Although it is acknowledged in the introduction to this guideline (line 95 and 96) that in younger patients insomnia with sleep-onset problems is more prevalent whereas in older patients sleep-maintenance is more disturbed, the guideline is not clear on what are the requirements to approve an indication for treatment of only sleep onset disorders or only sleep maintenance disorders	**Not accepted.** Justification: Based on the DSM-IV-TR criteria, in cases that only one/some efficacy criterion of sleep is studied, there still remains the need to demonstrate that a benefit in this single aspect is of clinical relevance, represented by an adequate day time functioning without significant distress or functional impairment. Therefore, improvement in quality of day time functioning is considered to be the most relevant outcome

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		In the paragraph starting with 197, there is implication that efficacy needs to be established in both parameters of difficulty falling asleep and difficulty maintaining sleep. In the case of improvement of only one of these aspects the requirement is to additionally have a mandatory co-primary endpoint of improvement in quality of day time functioning. We believe it is inappropriate and potentially unethical to require a co-primary for a parameter of improvement in quality of day time functioning (at the expense of alpha) for the following reasons: • The extent of impairment of day functioning, measured objectively, is not established in the field of insomnia. There are no objective measures of daytime function that demonstrate consistent impairment across studies in untreated patients with insomnia compared to healthy controls. Additionally, there are no objective measures of daytime performance or function that demonstrate consistent improvement across studies with insomnia treatment compared to placebo. • Similarly, while patients complain of impaired daytime function subjectively, adequate and well-validated assessment tools that measure subjective function or performance and that demonstrate consistent improvement across studies with effective insomnia treatment have not been developed. If one introduces a subjective assessment tool for quality of day time performance (questionnaire xxx) in the sleep diary, then this should be viewed as exploratory endpoint. Proposed change (if any):	parameter if only partial aspects of insomnia are improved. However, it is acknowledged, that validation of outcome measures for daytime functioning needs further study, this should be fostered by all stakeholders.

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205-208 and 229	**2**	Comments: We agree that efficacy should be established based on studies in the natural setting and that data in specialized setting or neurophysiological evaluations (PSG) should be supportive. However, it should be clarified that if adding to the baseline of a natural setting study, on selected nights, PSG measurement in outpatient clinics or in the home, on the entire study sample or a sub-population, then the study will still be accepted as performed in the natural setting. Proposed change (if any):	**Partly Accepted.** Justification: Given the need to establish efficacy in patients in their natural setting, it cannot be excluded that PSG measurements, also performed in this setting, would cause any bias. Therefore changes as proposed cannot be accepted.
217-218	**2**	Comments: Whereas we agree that studies in inpatients or outpatients should be conducted separately, please clarify whether it is accepted that PSG assessments conducted in an outpatient clinical setting are viewed as outpatient studies – whereas the use of hospitalized patients in an inpatient setting defines the 'inpatient' study'. Proposed change (if any):	**Not Accepted**. Please refer to the comment above. When PSG assessments are conducted in an outpatient clinical setting, then the study cannot be accepted as performed in the natural setting.
241-256	**2**	Comments: **Concerning psychometric tests** Taking into consideration the multiplicity of psychometric assessments considered in section 5.2.2. and the suggested requirement of a co-primary endpoint in improvement in quality of day time functioning, (paragraph starting line 197), please clarify which tests are expected to be required or acceptable.	**Partly accepted**. Justification: It is acknowledged, that at the present time, no adequately validated assessment tools with regard to improvement in quality of day time functioning exist; further studies are therefore deemed necessary. However, with regard to the above discussed aspects, it is still considered to be a

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		Proposed change (if any):	relevant co-primary endpoint.
255	**2**	Comments: Please clarify what is meant by 'parallel forms'. Proposed change (if any):	**Accepted.** An explanation was included.
310 - 312	**2**	Comments: It is mentioned that 'For pivotal studies in insomnia, the treatment duration should be at least 2 to 4 weeks of active treatment. It is also mentioned that if new MoA then product should be studies for longer duration. Please clarify that longer studies would be required for agents demonstrating a latency to full clinical effect, but not for agents for which full response is observed immediately following treatment initiation. Can you please also specify whether 'short tem insomnia can be an indication? And under what circumstances. Proposed change (if any):	**Partly accepted**. Justification: Line 310-312 refer to short-term trials. For short-term trials, a treatment duration longer than 2 to 4 weeks would be required for agents demonstrating a latency to full clinical effect. This requirement does not pertain to agents for which full response is observed immediatly following treatment initiation. Short term insomnia was not used as definition (see comment above).
313- 321	**2**	Comments: **On section *6.2.2 Long term Trials*** 1. Please clarify that a 6 month efficacy study (whether placebo controlled or randomized withdrawal design) is required only for the indication 'chronic treatment of insomnia' or is this required for every new chemical entity. Is a short term treatment of insomnia indication acceptable for any NCE and if yes under what conditions?	Point 1: **Not accepted.** Justification: Of note, short-term treatment is the preferably intended approval modality. However, generally, a long-term study is necessary (especially with regard to adverse events) unless there is a safety reason not to conduct these trials; in this situation, the indication would be “short-term treatment”.

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			The guideline was revised accordingly.
		2. Concerning randomized withdrawal design and 'sufficient duration', we suggest that a more useful protocol design generally incorporates a longer open-label first-phase treatment optimization and sustained evaluation period followed by a shorter randomized-withdrawal (active versus placebo) period. The open-label phase establishes the duration of long-term treatment and the randomized-withdrawal period duration is dictated by the amount of time required to fully lose treatment effect and beyond any potential rebound or withdrawal period. With current treatments a two to four-week period is fully sufficient.	**Point 2: Not accepted.** Justification: To adequately assess a potential loss of treatment effect, the setting of time standards as described in the draft guideline are still maintained.
		3. Please clarify whether 'extension study' in the sentence the 'alternative of a double-blind placebo-controlled extension study should last for 6 months' as well extention study' means that after a certain period of double-blind placebo-controlled (e.g 4wks -3 month.), study can continue as open label study for the rest of 6 months period. Proposed change (if any): Long-term efficacy has to be demonstrated in addition to the short-term trials. This might be done by a double-blind placebo-controlled extension study or by a randomised withdrawal design. In the withdrawal design, This is done in two time periods, in the first open and uncontrolled period the stabilized responders ***continue with the test treatment for 6 months or longer; thereafter, they are*** ~~continue with the test~~	Point 3: **Partly accepted.** Justification: Sentence was revised. The extension study should last for 6 month, be double-blind and placebo controlled. With regard to efficacy and safety aspects, the recommendation in the guideline has not been changed.

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		~~treatment for 2 to 4 weeks, thereafter they are re~~randomized ***to placebo or continued test treatment*** and followed ***for*** ~~by~~ at least ***2 to 4 weeks, or longer if needed,*** depending on the mechanism of action of the studied medicinal product.	
346-348	**2**	Comments: We agree that the separate pediatric trials should be conducted in severe, persistent insomnia refractory to behavioural therapy but not refractory to 'licensed pharmacological strategies'. It is possible that future drug treatments may have advantages in the pediatric population compared to conventional medications. It would not be advisable to consider restricting access to treatment with such an agent to only those that have failed standard drug treatments. Proposed change (if any): These should be conducted in severe, persistent insomnia refractory to usual behavioural ***strategies*** ~~and licensed pharmacological strategies~~, where possible causative or maintaining medical disorders have been excluded.	**Accepted.** The wording "refractory to … licensed pharmacological strategies" has been deleted.
61	**3**	Comments: The effects of discontinuing hypnotic medication should also be considered and highlighted Proposed change (if any):	**Not accepted.** Justification: This is already mentioned in section 4.1.
85-86	**3**	Comments: thought should be given to being more specific about in which biological fluid the levels of catecholamines are increased: more detail is needed	**Accepted.**

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		Proposed change (if any):	
109-10	**3**	Comments: The wording 'some issues relating to secondary insomnia…' seems very vague. Proposed change (if any): The particular issues of concern should be specified.	**Accepted.**
132	**3**	Comments: **:** 'DSM-IV-TR' has appeared earlier in the document and should have been abbreviated earlier e.g. line 68 Proposed change (if any): abbreviate at line 68 but not again later	**Accepted.**
135-136	**3**	Comments: Description of differential psychiatric disorders is crucial and difficult. Protocols should consider how this process is undertaken, with explicit details on the differential diagnosis of insomnia, GAD, and major depression. Proposed change (if any):	**Not accepted.** Justification: The sentence has been revised as efficacy first of all clearly should be established in primary insomnia.
139	**3**	Comments: 'WHO' abbreviation should be defined in full upon first use Proposed change (if any):	**Accepted.**
146	**3**	Comments: Diagnosis should ensure that disturbing	**Accepted.**

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		environmental factors are considered or excluded and the patient in question engages in adequate sleep habits/hygiene. Proposed change (if any): Insert a statement reflecting the above comment.	A statement was included.
166-167	**3**	Comments: To properly understand the aetiology and maintenance of secondary insomnia it is important to assess for the presence of mental disorders. Symptoms of depression and anxiety are of particular importance. Proposed change (if any):	**Accepted.**
167 and following	**3**	Comments: there is a large body of evidence indicating that sleep disorders (in particular insomnia) can precede the development of an index depressive episodes and the recurrence of depressive disorders. Proposed change (if any):	**Accepted.** The wording was revised.
182-185	**3**	Comments: The meaning of this sentence (beginning 'Pseudospecific claims' is not clear. Proposed change (if any): Clarification is needed.	**Accepted.** A further explanation was included.
192-196	**3**	Comments: How are the listed efficacy criteria to be assessed and when? Clarification of this should be stipulated within any given protocol.	**Partly accepted.** Justification: In general all these aspects should be studied. Depending on the patient population studied or a specific mechanism of action of a given product improvements in sleep

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		Proposed change (if any):	onset or maintenance might be in focus; however, as outlined earlier, it must be shown that improvement of one aspect of insomnia is of clinical relevance and not at the cost of other aspects of insomnia.
236	**3**	Comments: The possibility of investigating an 'add-on' treatment in cases where previous medications cannot be discontinued should be made explicit. Proposed change (if any): From: The screening and run-in periods are used to wash-out previously administered medicinal products which are incompatible with the trial, and for the qualitative and quantitative baseline assessments of patients To: The screening and run-in periods may be used to wash-out previously administered medicinal products which are incompatible with the trial procedures, and for the qualitative and quantitative baseline assessments of patients, except in investigations of potential add-on treatment evaluations.	**Accepted.**
238	**3**	Comments: It is debatable whether such patients (with major short-term fluctuations) should be excluded Proposed change (if any): Consider replacement with "studied separately"	**Accepted.**
248	**3**	Comments: Data secured from diary procedures are subject to demand characteristics and potential inaccuracies. To increase the quality of data, electronic diary procedures that utilize time-stamping should be	**Accepted.**

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		considered. Proposed change (if any):	
278-296	**3**	Comments: The text here represents a long list of recommendations. It would be sensible to use bullet points, to clarify this. Proposed change (if any):	**Accepted.**
298 and 308	**3**	Comments: The use of placebo is increasingly rejected by Research Ethics Committees in many countries. Proposed change (if any): **From**: Confirmatory trials should be double-blind, randomised three arm parallel group trials with placebo and an active comparator. **To**: Confirmatory trials should be double-blind, randomised three arm parallel group trials with placebo (greater level of evidence) and an active comparator or double-blind, randomised parallel group trials with active comparator (lesser level of evidence).	**Not accepted.** Justification: Further recommendation of placebo arms constitutes in the need to adequately demonstrate internal validity.
329	**3**	Comments: considered instead of consided but probably better in the active form Proposed change (if any): Analysis should carefully consider the possible biases arising from drop-outs	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
331	**3**	Comments: Given the high comorbidity with psychiatric disorders, concomitant CBT and other psychological treatments should be documented. These therapies often target processes that can have an effect on sleep. Proposed change (if any):	**Accepted.**
331-336	**3**	Comments: For secondary insomnia hypnotics are often added to existing medication and therefore interaction studies will be needed for extension of the license to secondary forms of insomnia. Proposed change (if any): Note to the above – pharmacokinetic and pharmacodynamic interactions with certain drug classes may also be beneficial.	**Partly accepted.** Justification: Section 6.1 reflects this sufficiently already.
417-420	**3**	Comments: 'Hard' outcomes such as falls in the elderly should also be routinely monitored. Proposed change (if any):	**Accepted.**
References	**3**	Comments: please ensure that strict alphabetical order is followed. Proposed change (if any):	**Accepted.**
42-43 and 107	**4**	Comments: The document refers to the treatment of acute and chronic forms of insomnia and it is specified that its main focus is on primary insomnia which according to its definition with a duration of at least 1	**Accepted.**

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		month, is a chronic disorder Proposed change (if any): Replace "treatment of acute and chronic forms of insomnia" by "acute and long-term treatment of insomnia"	
54-55	**4**	Comments: In the executive summary it is stated that results must be robust and clinically meaningful. The topic of "robustness" and "clinical meaningfulness" is however not taken up and some more details are not provided in the main body of the guideline. Proposed change (if any): The agency is encouraged to reflect on their view of clinically meaningful differences in relevant endpoints in insomnia trials.	**Partly accepted.** Justification: "robustness" and "clinical meaningfulness" efficacy outcomes are predominantly reflected via responder and remitter analyses. A corresponding explanation was implemented in the guideline.
66-67	**4**	Comments: The description of primary insomnia as having the possibility of being "situational" does not fit the definition of primary insomnia (see DSM IV). Situational insomnia might more easily be treated as a transient insomnia due to X, Y, or Z and more guidance on this type of insomnia and data requirements compared to primary insomnia would be helpful. Proposed change (if any): delete "may be transient/situational or persistent and"	**Accepted.**
70	**4**	Comments: Disorder of sleep maintenance mentions only frequent awakenings. The assessment of sleep maintenance should include total sleep time (TST) or wake after sleep onset (WASO).	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): frequent or long awakening	
74-75	**4**	Comments: There is a subpopulation of insomnia patients who experience more pronounced symptoms of restlessness, increased alertness, the inability to relax and to rest, and are thus in a constant state of hyperarousal that persists into the night and prevents sleep continuity. Proposed change (if any): We suggest adding the term "hyperarousal" following "daytime fatigue".	**Accepted.**
78	**4**	Comments: The document states *"… patients with a normal sleep pattern."* Proposed change (if any): … subjects with normal sleep pattern.	**Accepted.**
78	**4**	Comments: The guideline introduction notes that historically insomnia was regarded as a symptom rather than a disease but that recent findings are questioning this approach. Therefore, there is a need to clarify if the revised draft guidance is focused on assessing insomnia as a disease or a symptom or indeed both, and whether a medicinal product could be approved for the treatment of insomnia as a symptom rather than an as a disorder and furthermore, what clinical studies would be required to support such claims. Proposed change (if any):	**Accepted.** The draft guideline assesses, that insomnia is both a symptom and a disorder.

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82-83	**4**	**Comments:** "*….questioning this approach*." The referent for "*this*" is not clear. **Proposed change (if any):** It would be clearer to state something like the following: "*However, recent findings from basic and clinical research call into question the approach that views insomnia as merely a "secondary" condition rather than a disease in itself."*	**Accepted.**
After line 128	**4**	**Comments: Important.** Legal Basis. Suggest adding a reference to EMEA guidelines on extrapolation of results from clinical studies conducted outside of the EU to the EU population to clarify requirements. **Proposed change (if any):** Consider adding: - Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population. EMEA/CHMP/EWP/692702/2008	**Accepted.**
132-143 351-353 in paediatric section	**4**	**Comments: Editorial.** D. Diagnostic Criteria. Reference is made to the specific criteria i.e. ICD-10, ICSD-II, DSM-IV. However, these criteria continue to evolve and will change over time, likely more often than the insomnia guideline. **Proposed change (if any):** Suggest indicating instead that the latest DSM, ICD, or ICSD criteria should be used throughout the text as applicable.	**Not accepted.** Justification: It is acknowledged, that diagnostic criteria change over time, perhaps more often than guidelines. However, to keep the recommendations of the guideline traceable in reference to definitions that were valid at the time the guideline had been revised, we would like to point to the currently available diagnostic systems. However, a further comment with regard to DSMV has been implemented also.
145	**4**	**Comments:** Multichannel polysomnography is confusing. Polysomnography is by definition multichannel assessment ("poly").	**Accepted.**

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		Proposed change (if any): Please consider only using "PSG" (Polysomnography) throughout the document.	
145-146	**4**	**Comments:** Insomnia is a complaint and the diagnosis cannot be supported by PSG as proposed. PSG is a pharmacodynamic measure and can be used for POC or better understanding of the activity of a compound, but not as a diagnostic tool for the clinician. **Proposed change (if any):** Delete "Diagnosis can be supported by neurophysiological data from, for example, multichannel polysomnography""	**Partly accepted**. Justification: As we consider the use of PSG to be a helpful instrument, this was included. Nevertheless, as stated in section 5.1, primary "efficacy will be based on clinical relevant improvements of subjective sleep parameters".
146	**4**	**Comments:** The document states: "*Recently, both research diagnostic criteria for insomnia and quantitative insomnia diagnostic criteria have been reported to increase the homogeneity of study populations.*" This sentence is not clear. Please clarify.	**Accepted.** This part was amended.
147-151	**4**	**Comments:** It could be methodologically impervious to enrol patients with co-morbid insomnia and thus receiving treatment for their primary disease. It should be clarified whether patients suffering from secondary insomnia (due to a non psychotic co-morbid condition) can be included in studies provided the potential confounding effect of the primary concomitant treatment is kept under control (implies optimised, stable treatment of the primary condition). **Proposed change (if any):** This guidance seems to be contradictory and needs further clarification on the populations recommended to be studied in primary versus secondary insomnia. Also guidance is needed on how to deal with secondary insomnia confounding factors linked to treatment of the	**Partly accepted:** Justification: Primary, efficacy should be established solely in primary insomnia. The guideline has been revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		co-morbid disorder	
152-153	**4**	**Comments:** The document states: *"The definition of chronic insomnia requires symptoms to be present for at least one month (previously 6 months)."* The difference between chronic insomnia and "primary" insomnia as defined in DSM-IV-TR (line 133) should be clarified since a definition for 'chronic insomnia' is not available. **Proposed change (if any):** '(*previously 6 months*)' could be replaced by '(*the previous guideline stated 6 months*)'. (Also refer to comments on lines 132-142: suggest to refer to current criteria as these continue to evolve instead of specific criteria e.g. DSM-IV-TR as DSM-V will be out soon)	**Partly accepted.** Justification: The definition of chronic insomnia and primary insomnia was corrected accordingly. The proposed change regarding the previously 6 months was included.
155-157	**4**	**Comments**: The document states: *"If a placebo wash-out period is successfully accomplished, the need for further treatment with a hypnotic medicinal product has to be made plausible."* It is not clear from the text whether this is about the exclusion of placebo responders or whether patients with unstable baseline are included after the run-in period. The guideline should take into account the temporal variation in the natural history of the disease. Please clarify.	**Not accepted.** Justification: The need of plausibility for further treatment with a hypnotic medicinal product is based on the necessity of a predominantly homogeneous patient population without an almost temporal variation.
155	**4**	**Comments:** Please be consistent when describing the run-in period. "Wash-out" is used in line 155 and "run-in" is used in line 235. Please clarify if any difference.	**Accepted.**
175-185	**4**	**Comments:** The correct statement "the usual treatment for secondary insomnia associated is the treatment of the underlying condition" may not sufficiently acknowledge the frequent and important need for short term symptomatic treatment of insomnia in clinical practice,	**Not accepted.** Justification: Efficacy should be clearly demonstrated in primary insomnia. It is definitely considered more difficult to draw conclusions from secondary to primary insomnia, e.g.

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		for instance in case of bothersome insomnia associated with severe depression until onset of action of the antidepressant. Research on this important topic does not seem to be facilitated by the current wording in this chapter. In this context it may not be supportive, if claims of secondary insomnia are not being considered approvable unless differences in pathophysiology or mechanism of action have been established, which may be impossible to achieve in many cases. A indication for secondary insomnia should be considered approvable if appropriately studied in a well defined clinical trial population, and efficacy in treatment of primary insomnia has been established. **Proposed change (if any):** The usual treatment approach for secondary insomnia […] of the primary condition, however symptom oriented adjunctive treatment of insomnia may be required in some patients. [Delete: "Pseudospecific"] Claims of secondary insomnia in many disorders may not be considered approvable as long as not studied in clinical trial with a well defined patient population [instead of: differences in pathophysiology or in mechanism of action of medicinal products have been established between primary and secondary insomnia]	with regard to the parallel use of antidepressants in patients with major depression, as these medications e.g. could slow down effects in polysomnography and to distinguish between insomnia symptoms and symptoms of the second indication.
174-185	**4**	**Comments:** Diagnosis of secondary insomnia: 1) Please clarify whether the statement "New proposed research diagnostic criteria therefore require a strict correlation of onset and course of insomnia with the associated primary condition" (lines 174-175) is referring to the Research Diagnostic Criteria (Edinger, 2004, Sleep). If so, suggest to capitalize "Research Diagnostic Criteria (RDC) and provide the appropriate reference in line 174. 2) Does the guideline require the confirmation that onset of insomnia is secondary to the primary diagnosis? If so, what diagnostics are accepted?	**Partly accepted.** Justification: The description in line 174 is not made in reference to RDC. The guideline does not require the confirmation that onset of insomnia is secondary to the primary diagnosis as insomnia could also be a symptom of the diagnosis.

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		3) The statement on pseudospecific claims is somewhat confusing (lines 182-185). Can an example be provided for a type of labelling statement related to a secondary insomnia and associated study requirements? 4) The document states: "*Psychological, neurophysiological and endocrinological measures have shown many similarities between primary and secondary insomnia, particularly if they are considered as a state of hyperarousal, however, differences have been described as well.*" Please provide references to the differences described. Such data is important for potential development in secondary insomnia indication.	Regarding pseudospecific claims, an example was included. Ad 4 **Not accepted:** Justification: Sentence has been deleted.
180-185	**4**	**Comments:** This paragraph makes the entire section regarding secondary insomnia unclear, particularly when the final claim/indication is considered. As with many severe symptoms such as pain, hypertension etc, insomnia can be the result of multiple organic or psychiatric diseases or life events. After a prolonged duration of the disease, it can be difficult to determine whether the insomnia is primary or secondary. If the definitions of the relevant classifications are met, and there either is no underlying disease (primary insomnia) or the underlying disease does not lead to relevant variations in the sleep patterns, clinically a treatment will often be necessary. In the treatment of insomnia, this differentiation between primary and secondary insomnia is not considered helpful and does not reflect clinical practice. Therefore, the basis for not including patients with either primary or secondary insomnia in the same studies with the view to seeking approval for both insomnia types is not clear. Furthermore, an accurate tool for distinguishing between primary and secondary insomnia is not available. If studies are conducted in secondary insomnia and show benefit with an acceptable safety profile, it needs to be clearer	**Not accepted.** Justification: At first, efficacy should be clearly demonstrated in primary insomnia. As discussed above, it is considered definitely more difficult to draw conclusions from secondary to primary insomnia. Examples of the types of secondary insomnia were included.

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		whether these can be described in the label, eg in section 5.1 of SPC. **Proposed change (if any):** Further clarity on the issues highlighted above as well as inclusion of examples of the types of 'secondary insomnia' being referred to.	
188-209	**4**	**Comments:** The document states: *"However, in principal, establishing efficacy will be based on clinical relevant improvements of subjective sleep parameters of the patients in their natural setting."* Two complementary types are required but one (subjective sleep) will be crucial for the assessment. It's unclear if the objective data are as important (both required) or if it will be accepted to show effect in only subjective parameters. Please clarify the minimum objective data requirements.	**Accepted.** A comment was included.
192-196	**4**	**Comments:** Some indication of which of the efficacy criteria should be primary or secondary endpoints and what flexibility is allowed would be useful.	**Not accepted.** Justification: The subsequent paragraph provides a sufficient explanation.
193,195	**4**	**Comments:** The guidance proposes "sleep continuity" and "sleep duration" as the clinical efficacy criteria that should be evaluated. It would be useful to define sleep maintenance as a parameter with reference to sleep continuity and sleep duration. The addition of 'sleep quality' is welcomed as an endpoint in the treatment of insomnia. Patients with "pure non-restorative sleep" have poor sleep quality without a clear explanation for it such as inadequate sleep quantity or poor sleep	**Not accepted.** Justification: With regard to their self-containing importance for sleep maintenance, sleep continuity and sleep duration are kept as efficacy criteria.

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		continuity. Therefore, it should be sufficient to impact sleep quality only for an insomnia treatment, with perhaps some indication of impact on daytime functioning. A person can have insomnia disorder without short sleep, without difficulty initiating sleep, and/or without fragmented sleep, but cannot be diagnosed as having insomnia without subjectively poor sleep quality. **Proposed change (if any):** We suggest including sleep maintenance under the clinical efficacy criteria with sleep continuity and sleep duration as examples of separate measures of sleep maintenance. Sleep quality can remain included as such however the proposed DSM-5 criteria for primary insomnia lists "non restorative sleep" rather than sleep quality and it would be useful to include this terminology as well in the guidance.	
203, 249, 255	**4**	**Comments:** Daytime function and choice of tools. Though we understand the basis of the recommendation to demonstrate an effect on daytime function, we are not aware of a single validated comprehensive measure of daytime function that would assess the multiple aspects of daytime functioning (e.g. alertness, mood, performance, etc.) and would be sensitive to change; to achieve that, more research is needed in this area. Thus, flexibility will be needed for the specific tool and whether it is objective or subjective. We suggest using similar text as for the section on health related quality of life – see proposed change below. Until a global daytime function measure is validated and there is a marketed drug with positive data from such a measure, it is unclear how daytime function can be required as a primary endpoint. Further, it should be noted that daytime function is affected by many factors besides sleep, therefore, power to show treatment differences are anticipated to be low.	**Not accepted.** Justification: Based on the DSM-IV-TR criteria, patients who do not appear to have objective manifestations of sleep disturbances but whose sleep is sufficiently inadequate or non-restorative meet the criteria for insomnia. In contrast, someone with night-time sleep disturbances, who gets only a few hours of sleep each night, but feels without associated distress, does not meet the criteria for insomnia. Therefore, non-restorative sleep, represented by quality of day time functioning is considered to be an important symptom. The final goal of medical approval in insomnia is to achieve sufficient and widely benefit in quality of day time functioning. This results in sticking to quality of day time functioning to be the most relevant outcome parameter.

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		Furthermore, insomnia trials are generally laden with multiple parameters, multiple endpoints and often more than one dose resulting in multiple comparisons and consequently, an increasing sample size. Adding this additional parameter as co-primary endpoint will greatly increase the complexity of clinical trials for this indication**.** We propose to indicate that assessment of daytime functioning is recommended as an exploratory but not a mandatory co-primary endpoint. For clarity, we also propose that the guidance indicate daytime function domains that the Agency considers important. **Proposed change (if any):** Add text "Although insomnia has considerable impact on daytime function, the lack of validated assessment tools for global daytime function related to insomnia does not yet allow specific recommendations to be made for use of any particular assessment scale in regulatory trials."	
209	**4**	**Comments:** Does "specialized setting" refer to "polysomnography"? Please clarify.	**Accepted.** A comment was included.
216-217	**4**	**Comments:** The distinction between elderly and non-elderly adults seems to be artificial. It would seem more appropriate to focus on patient health and conduct studies addressing age-related impairment, i.e. renal and hepatic impairment, rather than focusing on separate studies based on chronological age. Please also refer to other elderly comments.	**Partly accepted.** Justification: In the light of expected different efficacy outcomes as well as a different spectrum of adverse events, separate analyses in the elderly are considered necessary. These can be conducted as separate studies or adequately-powered subgroups. However, it is agreed that separate studies are not categorically necessary. The paragraph was updated.
217-233	**4**	**Comments:** 5.1.1 Clinical Evaluation. Separate studies in inpatients or outpatients are not needed as long as the	**Not Accepted.** Justification: Establishing efficacy will be based on clinically relevant improvements of subjective sleep parameters of the

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		evaluations and analyses are separate. Generally, in PSG trials of longer duration (more than 2 weeks), the scheduled laboratory assessment nights represent only a minor fraction of the total trial duration. In such instances, patient reports can be collected in non-sleep laboratory nights conducted at the subject's natural setting to provide independent evidence of subjective efficacy. This will simplify the development program allowing applicants to meet regulatory requirements of both EMA and other regulatory agencies using the same trials. **Proposed change (if any):** change to "Subjective and objective endpoints can be obtained in the same trials but should be collected independently (i.e. in the appropriate setting) and evaluated separately".	patients in their natural setting. Separate studies in inpatients and outpatients are therefore needed. Please refer to the comment above.
225	**4**	**Comments:** While macrostructure of sleep is relevant for its recuperative value, microstructure is also important. Therefore, the reduction of arousal as a property of an insomnia treatment could be more relevant than numerical improvements of sleep stage percentages and time and duration of awakenings. **Proposed change (if any):** We suggest including the term "arousals" after "sleep time".	**Accepted.**
227-228	**4**	**Comments:** Further clarification is needed to help understand why results from actigraphy studies are considered "useful but not as conclusive as results from polysomnography." Actigraphy can be a very useful pharmacodynamic tool for assessments related to wakefulness, attention-movement behaviour, and likely sleep in difficult to instrument groups, such as autistic children.	**Not accepted.** Justification: The section already includes a justification with regard to difficulties under actigraphy in patients with primarily sleep-onset difficulties (please refer to published literature: Vallieres A, Morin CM. Actigraphy in the assessment of insomnia. Sleep 2003;26: 902-6).

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		Proposed change (if any): Use of actigraphy should be justified.	
229-233	**4**	**Comments:** More guidance on the opportunity for potential claims on sleep architecture being included in the label would be helpful, eg possible study design(s) to achieve such a claim in case further differentiation is required. It is unclear how changes in sleep architecture can translate (by themselves) to differentiation i.e. in the absence of a clinically meaningful difference in sleep onset, maintenance, or sleep quality/restorative sleep.	**Not accepted:** Justification: As at the present time, it is not well established how measurements of sleep architecture (e.g. slow-wave sleep) and subjective measurements (e.g.sleep quality) relate to each other, potential claims on sleep architecture are not considered helpful.
242-243 249-256	**4**	**Comments:** There are no objective measures of daytime behaviour and performance in insomnia patients. **Proposed change (if any):** Clarification is needed why this is stated as an efficacy criterion and if this implies that the use of very small selected patient samples can lead to specific labelling language concerning daytime performance. It would be preferable to limit the recommendation for assessment of daytime function to patient reported outcomes as they are defined as such in the diagnostic criteria.	**Not accepted.** Justification: It is acknowledged, that there is a lack of adequately validated objective measures of daytime functioning in insomnia patients. However, day time functioning is still requested to be a mandatory co-primary endpoint in cases only some aspects of insomnia are improved and the applicant intends to get approval for these criteria. However, there seems to be no other facility to really assess the clinical benefit of this single aspect for the patient`s outcome without assessing the most relevant issue, day time functioning the next day.
245	**4**	**Comments:** The document uses: *"Sleep questionnaires/visual analogue scales"* as heading. **Proposed change (if any):** Improved restorative sleep and quality of sleep	**Accepted.**
249-255	**4**	**Comments:** More guidance on acceptable scales or criteria for assessing next day functioning would be helpful.	**Partly accepted.** Justification: This is agreed with; however, due to the lack of adequately validated measures at the present time, further studies on this topic are considered necessary.
250-252, 281, 284 – 285.	**4**	**Comments:** Choice of Tools. Psychometric methods. b) improved daytime performance. Regarding the recommendation	**Partly accepted.** Justification: Lack of residual effects was included in section:

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		to perform psychological performance tests "not only in the morning but also in the afternoon and the evening of a day after medicinal product intake in order to demonstrate any effects on intellectual functioning the next day", please clarify the specific concern, if not residual effect. The applicant can then determine what testing is needed. Similarly: "special attention should be paid to ….circadian variation" and "circadian variations in pharmacodynamics should be considered". Please clarify the type of data being requested. For example, is dosing at different times of day to be assessed although most patients will take an insomnia medication before retiring in the evening? Finally, please clarify if demonstration of improvement in daytime performance using objective measures is required to claim efficacy (Line 249). To our knowledge, while subjective reports of impairment have been clearly documented, impairment in cognitive function and performance using objective measures and consequently showing improvement in patients with primary insomnia has not been consistently demonstrated. The available objective tools for measuring daytime performance are used to detect impairment rather than improvement due to treatment effect (*Reference*: J. A. Shekleton, N.L. Rogers, S.M.W. Rajaratnam Searching for the daytime impairments of primary insomnia Sleep Medicine Reviews 14 (2010) 47–60). We propose that objective/psychometric methods of daytime performance and cognitive function concentrate on detecting residual impairment rather than demonstrate improvement to indicate therapeutic effect. A significant barrier to showing objective improvements in daytime performance is the inability to	improved daytime performance. The type of data being requested depends on the intended indication. In general, dosing at different times of day is not considered necessary. **Not accepted.** Justification: Improvement in quality of day time functioning instead of impairment is considered to be a relevant endpoint. It is acknowledged, that at the present time, no adequately validated assessment tools with regard to improvement in quality of day time functioning exist; further studies are therefore deemed necessary.

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		demonstrate clinically meaningful performance decrement in multiple measures in studies with insomnia patients. **Proposed change (if any):** Line 249: b) Daytime performance "Depending on the type of study objective, psychological performance tests should be performed … in order to demonstrate **lack of residual** effects on intellectual functioning the next day. Suitable tests may assess …"	
255	**4**	**Comments:** Clarify the term "parallel forms" **Proposed change (if any):** Change to alternative tools or versions to assess behaviour or performance if this is what is meant.	**Accepted.** An explanation was implemented.
255	**4**	**Comments:** Daytime sleepiness can be measured repetitively, easily and objectively by pupillography**.** **Proposed change (if any):** We suggest considering the use of pupillography as an optional measure of daytime sleepiness.	**Not accepted.** Justification: pupillography as an instrument to assess daytime sleepiness is not an adequately validated measurement tool.
259-261	**4**	**Comments:** Sleep laboratory or ambulatory multichannel polysomnography. Consecutive nights (at least two as identified in the draft guidance) are not needed in a sleep laboratory to enable to patient to adapt to the sleep laboratory setting. It has been demonstrated that screening and baseline nights in a sleep laboratory (not consecutive nights) allow sufficient adaptation. We are aware of no data that demonstrate a requirement for consecutive adaptation nights. Furthermore, two consecutive adaptation nights does add extra burden for patients as well as potentially unnecessary cost to the sponsor. Given that one night adaptation may be	**Not accepted.** Justification: According to several potential bias and based on insomnia studies of the past, at least two consecutive adaptation nights are still advised.

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		adequate, some flexibility should be provided in the recommendation. **Proposed change (if any):** Please remove "At least two consecutive adaptation nights are considered appropriate …" and replace with the following statement "Studies must allow for the patient to adapt to the sleep laboratory setting e.g., one adaptation night could be considered appropriate."	
262-264	**4**	**Comments:** It would be helpful if the guidance included examples to illustrate the point more clearly.	**Accepted.** An example regarding standard rules for visual classification of sleep EEG studies was included.
275-303	**4**	**Comments:** General Strategy and Confirmatory Trials: If a Phase II dose response study is conducted, then Phase III studies need only to confirm remaining questions in terms of dose response and not to repeat dose selection studies. **Proposed change (if any):** To the statement "the minimum effective dose and maximum recommended dose should be determined", add the qualifier "or confirmed as needed, based on Phase II dose range study results".	**Accepted.** The sentence has been revised.
294, 421-427	**4**	**Comments:** There is a need to provide greater clarity in describing how dependence should be assessed and a need to distinguish between "dependence on continued use of a drug to prevent return of insomnia symptoms" from "dependence on continued use of a drug to prevent development of withdrawal symptoms and/or rebound insomnia".	**Not accepted.** Justification: Further adequately validated assessment tools are still needed, to describe these issues more precisely.

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299	**4**	**Comments:** "Confirmatory trials should be double-blind, randomised three arm parallel group trials with placebo and an active comparator." **Proposed change (if any):** Replace by "Confirmatory trials should be double-blind, randomised, two or three arm parallel group trials with placebo and an active comparator in one of the confirmatory trials at least".	**Accepted.**
302	**4**	**Comments:** Please provide more clarity with respect to population versus analysis approach. Seems that these concepts are confused. For example observed cases can be used in a repeated measured model for an ITT or for a completers population. **Proposed change (if any):** The analysis populations for efficacy should include the intent-to-treat (ITT) or full-analysis set population (FAS) in which patients are analyzed according to the treatment (group) to which they were randomized. An appropriate imputation procedure can be used to estimate the missing data or, for longitudinal data, observed cases (OC) without imputation may be analyzed using the mixed effects model if the data are missing at random (MAR). A supportive analysis of the completers population may also be performed when the data are missing completely at random (MCAR).	**Partly accepted.** Justification: Concepts were confused. This section has been revised in detail.
306	**4**	**Comments:** Short-term trials: It is stated that short-term efficacy be established in a study of at least 2-4 weeks duration. It should be clarified whether it would be acceptable to demonstrate short term efficacy in the context of a long-term trial by assessing intermediary time points (eg a parallel groups	**Not accepted.** Justification: Conventionally short-term studies are needed, thereafter long-term trials should be performed.

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		study with assessments during the first week, the second week, and 12th week). In addition, guidance or comment on the design of 'transient or situational insomnia' studies would be useful. **Proposed change (if any):** In section 6.2.1, add that assessment of short-term efficacy can be performed using early time points in a long-term trial to meet both the short-term and long-term efficacy requirements.	´Transient or situational insomnia` has been deleted as recommended (see comments above).
311	**4**	**Comments:** The term "longer study durations" is not clear. Does this refer to the "long-term" trial duration of 6 months? Please clarify	**Accepted.** Depending on a new mechanism of action improvements or side effects might require longer study duration.
313-330	**4**	**Comments:** Long-term trials: It should be clarified that long term efficacy does not always need to be demonstrated, for example if a long term indication is not being sought by a sponsor or the new treatment does not have a profile suitable for long term use (note: amount of safety exposure in this case preferably to be discussed in Scientific Advice) . What is the rationale for 6 month studies since 3 months could be considered a suitable duration to assess long term efficacy? For example, we are aware that FDA will accept 3 months and for global programs it would be beneficial to have some consistency and a common duration. Perhaps 3-6 months could therefore be stated with a note that the sponsor may need to justify the 3 months duration. What is the duration of studies in order to achieve an	**Not accepted.** Justifiation: In principle, a long-term study is needed (especially with regard to adverse events) unless there is a safety concern not to conduct these trials. In this`situation, the indication would be `short-term treatment`. **Not accepted:** Justifcation: Taking into account the potential lifelong nature of this illness, 6 month studies to almost adequately demonstrate long-term efficacy and safety for a medical product are considered justified. However, the current scientific literature (Perlis M. et al. Intermittent and Long-Term Use of Sedative Hypnotics. Current Pharmaceutical Design, 2008, 14, 3456-3465) already presents six month studies for long-term use for several hypnotics, also conducted in the United States. For an indication in chronic insomnia, recommendations are

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		indication in chronic insomnia given the definition of chronic insomnia on line 152 (> 1 month)? A comment on whether subjective endpoints alone are acceptable in long term trials would be useful given the impracticalities of an objective endpoint such as PSG in a long term study and assuming the availability of short term PSG data and the fact that there are large inter- and intra-individual variations in different PSG nights.	the same as described above. **Accepted.** The sentence has been revised accordingly.
322-325	**4**	**Comments:** The definition of number of patients relapsing or worsening in Lines 322-325 seems to be more related to the randomized withdrawal design and not to the double-blind placebo-controlled extension study. Please clarify. Please justify the requirement for long-term efficacy studies to be at least 6 months in duration. The drop-out rate may be high in a study of this duration and limit the interpretability of the efficacy results.	**Accepted.** a) The definition of number of patients relapsing or worsening is related to the randomised withdrawal design; the sentence has been corrected. b) Please refer to the comment above.
322	**4**	**Comments:** In section 6.2.2, the guidance states that ”Efficacy is usually expressed as number of patients worsening (relapsing) and/or time to this event”. Clarification is needed as to whether the expected endpoint be patient relapse or worsening and if this end point is in addition to the traditional sleep parameters such as TST and WASO or in place of them for a chronic use indication. **Proposed change (if any):** We would appreciate more clarity addressing the above issues.	**Accepted:** Depending on the mechanism of action and the primarily chosen endpoint that has been improved in short-term trials, both, worsening as well as relapsing is considered to be an adequate primary endpoint in long-term trials. However, the traditional sleep parameters such as TST and WASO should also be evaluated as secondary endpoints.
322 327 328	**4**	**Comments:** The guidance states that” In addition to efficacy and safety, the long-term clinical trials should address tolerance, rebound insomnia, abuse and dependence”. The guidance should clarify that a recurrence of symptoms or a rebound insomnia is not to be interpreted as proving a dependency. A means to study patients´ ability to use an insomnia treatment in a	**Accepted:** The section has been revised. **Partly accepted.** Justification: In general, an on demand strategy in long-term

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		sensible manner is to allow an on demand strategy in long term studies. This strategy is widely recommended by somnologists treating patients with insomnia to avoid tolerance and dependence, but even more to avoid the development of psychological helplessness, not being able to sleep without an external support.	studies seems to be a meaningful approach. However, at the present time this strategy cannot be adequately justified by a complete data package.
322-325	**4**	**Comments:** Long-term trials. We propose to allow flexibility in the design of the long term trials for the proof of long-term efficacy. It is unclear why extensive details are provided for the randomised withdrawal design given that no such design has been reported in the published literature with an insomnia medicinal product therefore; there is no precedent for a successful outcome with this design. **Proposed change (if any):** Change sentence two (lines 314-315) to include a provision for a stand alone double-blind placebo controlled trial (not just an extension). Delete the specifics regarding the design elements of the randomized withdrawal design (lines 315-320). Also, as relapse criteria in insomnia are based on quantitative data defined to be clinically relevant rather than on a rating scale which needs to be validated, delete end of the sentence, ie "scored on a validated … visits".	**Not accepted.** Justification: The provided study designs are deemed necessary to adequately assess long term efficacy in insomnia. especially with regard to the potential lifelong nature of this illness.
332-333	**4**	**Comments**: The guidance states that "Any treatment likely to impair alertness, intellectual function and behaviour should be excluded in order to eliminate any interference or bias particularly in exploratory clinical trials". As this very broad definition applies to many substances, continuous medication should be allowed, when unchanged. Furthermore, as exploratory trials have limited regulatory status, it should be clarified why they are mentioned. **Proposed change (if any):**	**Accepted.** A modification, including this aspect, was implemented.

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		"Any treatment likely to impair alertness, intellectual function and behaviour should be excluded, or be given in unchanged dosage beginning at least 4 weeks before entering the study and throughout the study, in order to eliminate any interference or bias, particularly in exploratory clinical trials".	
338	**4**	**Comments:** The chapter on the paediatric population contains comparably few details on the design of Paediatric Investigational Plans. For instance "homogeneous patient populations" are mentioned, but no suggestion is made how to categorize paediatric age groups, taking into consideration age dependent differences in physiology of sleep, or differences in cognitive development. The requirements for validation of endpoints for paediatric clinical trials (patient reported outcomes and actigraphy or PSG) should be clarified further. Also should a program in paediatrics always be accompanied by demonstrated efficacy and safety in adults. It should be made clearer whether it is possible to dedicate an entire program to the study of children and adolescents assuming adequate safety is demonstrated. Alternatively, flexibility in approaches can be noted in the guidance. **Proposed change (if any):** Please add more detailed discussion of appropriate age groups, and subpopulations to be studied. Please also provide guidance on validity of actigraphy and polysomnography, and validation of relevant endpoints in paediatric trials, as well as on whether a paediatric only development program is possible or indicate that development programs in paediatrics need to be considered on a case-by-case basis in a Paediatric Investigation Plan.	**Partly accepted.** Justifiaction: In general, the information given in this chapter results from the limited experiences made in the past within the paediatric population. For more detailed advices, further experiences have to be awaited. The design of PIPs will depend on various factors such as the mechanism of action of the drug. Validated outcome measures should be used. Categorisation of paediatric age groups is defined in ICH-E11. As the paediatric population represents a vulnerable subgroup and insomnia is neither a condition predominantly or exclusively affecting the paediatric population nor a serious or life-threatening disease, the enrolment of children in a clinical trial programme without prior demonstration of an acceptable risk/benefit balance in adults would not be considered justified.
345-348	**4**	**Comments:** Paediatric Populations. Benefit to risk should be considered in conduct of paediatric insomnia trials. The	**Partly accepted.** Justification: The wording 'refractory to … licensed

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		requirement for trials to be conducted only in severe, persistent insomnia refractory to usual behavioural and licenses pharmacological strategies, where possible causative or maintaining medical disorder have been excluded seems overly restrictive and is not very clear. Children with neuropsychiatric disorders, including Autism, PDD, and ADHD were identified as a population in need of pharmacological management of insomnia, since they do not usually respond to non pharmacological intervention and as an appropriate target population to study insomnia (Pharmacologic Management of Insomnia in Children and Adolescents: Consensus Statement Jodi A. Mindell, Graham Emslie, Jeffrey Blumer, Myron Genel, Daniel Glaze, Anna Ivanenko, Kyle Johnson, Carol Rosen, Frank Steinberg, Thomas Roth and Bridget Banas. Pediatrics 2006;117;e1223-e1232). It is not clear whether the Agency considers secondary insomnia such as in children with ADHD or with other neuropsychiatric disorders an appropriate target population for paediatric studies. Finally, it is not clear what is meant by "refractory…to licensed pharmacological therapy", since there are no medicinal sleep products approved in the EU for the paediatric population. **Proposed change (if any):** Change statement to "The general recommendation is for trials to be conducted in patients with insomnia refractory to usual behavioural strategies where possible causative or maintaining medical disorder have been excluded." It should be clarified if children with neuropsychiatric disorders (e.g., ADHD or autism) can be considered as an appropriate target population in order to achieve a paediatric insomnia indication. Benefit –to –risk should be considered and patient population selection should be justified._Replace as well by "to usual therapeutic strategies" and delete the rest of the sentence.	pharmacological strategies' has been deleted as no such strategies are licensed at the time of writing the guideline and to allow for the development of future first-line drugs for insomnia. The target patient population has been defined taking into account that the definition of insomnia in children is much more challenging than in adults. The sleep behaviours are usually described by the parents and not by the children themselves. Whether particular sleep behaviours are a problem depends on a complex combination of parental perceptions, expectations, cultural standards and biological norms. Prescribing medication prior to behavioural intervention can seem an appealing option for a busy clinician and exhausted family who feel they have already done the 'bedtime stuff'. However the evidence shows the immediate and sustained value of behavioural approaches, even in difficult groups of children. (Gringras, Arch Dis Child 2008, 93, 976-981)

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355-357	**4**	**Comments:** The guidance states that separate paediatric populations should be studied (e.g., children with autism) for proof of concept and pivotal efficacy trials. Because this is a very different from the approach taken with adults, it should be clearly noted that primary insomnia is not a required diagnosis for a registration program in the paediatric population.	**Partly accepted:** Justification: Proof of concept studies can be conducted in secondary insomnia such as in children with ADHD or with other neuropsychiatric disorders. As efficacy and safety data obtained in children with secondary insomnia cannot be extrapolated across paediatric sleep disorders in general, this needs to be followed by a pivotal trial to demonstrate efficacy and safety in a wider group of paediatric insomnia patients.
356	**4**	**Comments:** The diagnostic definition autism/learning disorder is unclear for "learning disorder". **Proposed change (if any):** Replace by ADHD if this is the intention, or further clarify.	**Accepted:** Learning difficulties have been replaced with mental retardation.
358-359	**4**	**Comments:** Paediatric Populations. As stated previously, there are no medicinal sleep products approved in the EU for the paediatric population. As there is no active comparator registered, it appears inappropriate to expect a 3-arm study including placebo and an active comparator. Also, dose-response can be established in Phase II and then confirmed in pivotal efficacy trials. **Proposed change (if any):** Qualify the requirement for an active comparator arm for paediatric trials until such time that there is an EMEA approved insomnia drug for the relevant age groups under study i.e. an active comparator cannot be required if none is approved for an age group. If a Phase II dose response study is conducted, then Phase III studies need only to confirm remaining questions in terms of dose response and not to repeat dose selection studies.	**Accepted.**
359	**4**	**Comments:**	**Accepted.**

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		The study design including active reference seems to conflict with the recommendation to enrol patients with persistent insomnia refractory to usual licensed pharmacological strategies (line 347). Please clarify.	Recommendations in line 347 have been changed.
360	**4**	**Comments:** Currently, standardized therapies for insomnia in children population are not widely available. **Proposed change (if any):** add "if possible" prior with standardised behavioural interventions	**Accepted.**
365	**4**	**Comments:** Please clarify the remark **"**Next-day performance or school performance should be explored as co-primary endpoint." If it is to be explored it cannot be pre-specified as co-primary. In addition, please also refer to earlier comments on using daytime function as a co-primary endpoint for which we recommend that this should not be a mandatory requirement. **Proposed change (if any):** "In such cases next day performance or school performance should be explored."	**Partly accepted.** Justification: The sentence regarding next-day performance or school performance was adapted; reflecting these parameters to be a co-primary endpoint.
366	**4**	**Comments:** "The duration of efficacy trials should be as for the adult population" Given that 6 month efficacy studies in adults are required, it does not seem appropriate for children aged below 12 years, for example, to be included in a 6 month study. If long term efficacy was shown in adults and short term efficacy in children, there should be consideration of not requiring long term efficacy in children. **Proposed change (if any):** Replace by: add "short term" in the sentence prior	**Not accepted.** Justification: For CNS-active compounds the extrapolation of adult efficacy/safety data, either short- or long-term, to the paediatric population is not considered appropriate.

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		"efficacy".	
381-403	**4**	**Comments:** Elderly. It is assumed that elderly patients are aged 65 years and over and that the comment about those aged over 75 years is to note this growing population. Thus separate elderly studies if conducted would by default have an age cut off of 65 years and above. We understand the need to obtain data in patients over 75 years of age. Separate Phase I studies in this very elderly population may be feasible however, separate Phase II or III studies are not likely feasible. It does not seem appropriate for elderly patients aged over 75 years, for example, to be included in a 6 month study if long term efficacy data is already available in adults and can be extrapolated to the elderly. **Proposed change (if any):** Suggest to reword that it is recommended to obtain data and to assess safety and efficacy in elderly ages >75 years of age (to include a placebo-control comparison) and not mandate to conduct separate pivotal studies in the age group.	**Accepted.**
401	**4**	**Comments:** Elderly – separate elderly trials are not required even with new medicinal products with a new mechanism of action provided that a safe dose range is defined. We recommend providing flexibility. **Proposed change (if any):** Change to "for new medicinal products with a new mechanism of action, specific trials may be useful. However, elderly patients can be included in studies with non-elderly patients provided that a safe dose range has been predefined in this age group and statistical analyses will assess efficacy and safety in the elderly separately.	**Not accepted.** Justification: According to a potential different sensitivity in the elderly for the pharmacodynamics of the product to be studied, specific trials in the elderly for new medical products with a new mechanism of actions are justified.
414	**4**	**Comments:** Line 414 and 430 are not fully consistent with regards	**Accepted.**

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		to clinical studies to assess dependency. The document says "must be addressed in clinical trials" first and then states "studies may be necessary". Please clarify.	The sentence in line 430 has been deleted.
414-415	**4**	**Comments:** In section 8, the use of validated questionnaires to assess adverse events is mentioned. Pharmaceutical companies do not typically use questionnaires but rather ask open-ended questions. However, monitoring of specific adverse events of interest by clustering of event terms, following SMQs established in the MedDRA coding system, is performed. Would this approach be considered acceptable? If not, further information would be helpful to understand why the use of questionnaires is desirable. Are there specific data indicating that this type of data collection is superior to asking open-ended questions? **Proposed change (if any):** We would appreciate more clarity addressing the above issues.	**Not accepted.** Justification: Validated questionnaires are deemed necessary to adequatey and objectively assess parts of the adverse events.
417-420	**4**	**Proposed change (if any):** For more precision the chapter referring to hangover could include the assessment described in 249-256	**Partly accepted.** Justification: A cross-reference was included to section 5.2.2
421-430	**4**	**Comments:** The evaluation of abuse is not dealt with in this section. The text in the section describes investigation on rebound and dependency. Please consider providing guidance on abuse. Guidance on acceptable methods/measures (eg AE reporting and scales/questionnaires) to assess rebound and withdrawal phenomena as well as suitable study designs should also be included. Reference to the abuse/dependence guidance could be included.	**Not accepted.** Justification: Further adequately validated assessment tools are still needed to describe these issues more precisely.
423	**4**	**Comments:** As an abrupt stop of medication in very many	**Accepted.**

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		substances can leads to withdrawal effects, without proving a dependency (e.g. antidepressants, antiepileptics, etc), it should be recommended to taper patients out of their study medication for drugs that are shown to lead to withdrawal effects. Thus, artificial deteriorations can be avoided, and the clinical approach mimicked. In insomnia patients, treatment recommendations recommend a slow tapering of hypnotics in order to avoid a recurrence of symptoms as appropriate depending on the profile of the medication. **Proposed change (if any**): "Trials should be designed in such a way that these phenomena can be studied but are not forced. While in some trials treatment could be stopped abruptly, especially after long term studies, treatment should be tapered down slowly if there is evidence of withdrawal for the medication."	
428-430	**4**	**Comments:** In general, more information on required animal studies would be useful, especially considering the level of information provided in the original guideline. Reference to the abuse/dependence guidance could be included. Together with lines 294-296 the guidance suggests that preclinical studies to assess potential abuse liability should be conducted "*to establish a basis for further studies required in the clinical trials before relevant human studies are initiated."* The guidance should list recommended types of studies are being referred to (eg "tests" within a clinical study, a clinical trial or something else), and it should also be clear what "*relevant human studies*" means (eg a human abuse liability study), and whether all novel insomnia agents are required to have a human abuse liability study irrespective of preclinical data. Alternatively, the guideline should clarify the that types of studies	**Accepted.** A cross reference to the guideline on the non-clinical investigation of the dependence potential of medicinal products has been included.

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		recommended for assessment of benefit to risk will depend on the mechanism of action and accruing data on the medication.	
436-438	**4**	**Comments:** In section 8.1, it is recommended to evaluate haematological adverse reactions (leukopenia, agranulocytosis, aplastic anaemia, and reduction in platelet count). Understanding the need for such an evaluation for an insomnia treatment would be helpful. **Proposed change (if any):** We would appreciate more clarity addressing the above issue.	**Accepted.** Based on the accepted adverse event profile for a medicinal product in insomnia, haematological analyses as well as liver parameters, especially in long-term treatment, are considered necessary to define the given adverse event profile. Liver parameters have been added.
444	**4**	**Comments:** It is not clear from the document how we are supposed to monitor the sexual development in pediatric population. Please explain.	**Partly accepted.** Justification: The PDCO noted the request for guidance on how to monitor sexual development in the paediatric population. This will be addressed by PDCO out with this current guideline as it is an issue pertaining not only to the development of insomnia drugs.
478	**4**	**Comments:** The definition of "psychic dependence" also includes "pharmacological dependence". The described non-clinical settings apply more to investigation of "pharmacological abuse".	**Accepted.** This section was revised.
54-55	**5**	**Comments:** In the executive summary it is stated that results must be robust and clinically meaningful. The topic of "robustness" and "clinical meaningfulness" is however not taken up and some more details are not provided in the main body of the guideline. **Proposed change (if any):** The agency is encouraged to reflect on their view of clinically meaningful differences in relevant endpoints in insomnia trials.	**Partly accepted.** Justification: "robustness" and "clinical meaningfulness" efficacy outcomes are predominantly reflected via responder and remitter analyses. A corresponding explanation was implemented in the guideline.
170-185	**5**	**Comments:** The correct statement "the usual treatment for	**Not accepted.** Justification: "Pseudospecific claims" was explained.

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		secondary insomnia associated is the treatment of the underlying condition" may not sufficiently acknowledge the frequent and important need for short term symptomatic treatment of insomnia in clinical practice, for instance in case of bothersome insomnia associated with severe depression until onset of action of the antidepressant. Research on this important topic does not seem to be facilitated by the current wording of this chapter i.e. if claims of secondary insomnia are not being considered approvable unless differences in pathophysiology or mechanism of action have been established. This may be impossible to achieve in many cases. A claim of secondary insomnia should be considered approvable if appropriately studied in a well defined clinical trial population, and efficacy in treatment of primary insomnia has been established. **Proposed change (if any):** The usual treatment approach for secondary insomnia […] of the primary condition, however symptom oriented adjunctive treatment of insomnia may be required in some patients. [Delete: "Pseudospecific"] Claims of secondary insomnia in many disorders may not be considered approvable as long as not studied in clinical trial with a well defined patient population [instead of: differences in pathophysiology or in mechanism of action of medicinal products have been established between primary and secondary insomnia]	Efficacy should be clearly demonstrated in primary insomnia. It is definitely considered more difficult to draw conclusions from secondary to primary insomnia.
338-380	**5**	**Comments:** The chapter on the paediatric population does contain comparably few details on the design of Paediatric Investigational Plans. For instance "homogeneous patient populations" are mentioned, but no suggestion is made how to categorize paediatric age groups, taking into consideration age dependent differences in physiology of sleep, or differences in cognitive development. The agency should clarify their view on	**Partly accepted.** Justification: The information given in this chapter result from the limited experiences made in the past within the paediatric population. For more detailed advices, further experiences have to be awaited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the requirements for validation of endpoints for paediatric clinical trials (patient reported outcomes and actigraphy or polysomnography). **Proposed change (if any):** Please add more detailed discussion of appropriate age groups, and subpopulations to be studied. Please provide guidance on validity of actigraphy and polysomnography, and validation of relevant endpoints in paediatric trials.	