EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
EMA/CHMP/16274/2009 previously (EMEA/16274/2009) Rev. 1
Committee for medicinal products for human use (CHMP)

Guideline on medicinal products for the treatment of insomnia

Date of first Adoption	**September 1991**
Date of entry into force	March 1992
Revised draft Agreed by EWP	September 2009
Adoption by CHMP for release for consultation	22 October 2009
End of consultation (deadline for comments)	30 April 2010
Agreed by CNSWP	October 2010
Adoption by CHMP	17 February 2011
Date for coming into effect	September 2011

This guideline replaces NfG "Clinical Investigation of Hypnotic Medicinal Products (3CC27a from March 1992). Reference.[1]

Keywords	***Insomnia, primary insomnia, secondary insomnia, diagnostic criteria, co-morbidity, special populations, polysomnography, treatment options, short-term efficacy, long-term maintenance.***[2]

[1] NfG "Clinical Investigation of Hypnotic Medicinal Products (3CC27a from March 1992).

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Table of contents

Executive summary **3**

1. Introduction (background) **3**

2. Scope **4**

3. Legal basis **5**

4. Diagnostic criteria **5**

4.1. Diagnosis of Primary Insomnia 5

4.2. Diagnosis of secondary insomnia 6

5. Assessment of therapeutic efficacy **7**

5.1. Criteria of efficacy 7

5.1.1. Clinical Evaluation 8

5.1.2. Sleep Laboratory or amulatory studies with multichannel polysomnography or actigraphy 8

5.2. Study design and methods 8

5.2.1. Run-in period 8

5.2.2. Choice of tools 9

6. General strategy **10**

6.1. Early pharmacology and pharmacokinetic studies/pharmacodynamic studies 10

6.2. Confirmatory Trials 10

6.2.1. Short term Trials 11

6.2.2. Long term Trials 11

6.3. Concomitant treatments 12

7. Special populations **12**

7.1. Paediatric population 12

7.2. Elderly 13

8. Safety evaluation **14**

8.1. Specific adverse events to be monitored 15

Definitions **16**

References **17**

Executive summary

This Guideline should be considered as general guidance on the development for medicinal products for acute and long-term treatment of insomnia. Its main focus is on primary insomnia, however, it also covers some issues on secondary or co-morbid insomnia. This document should be read in conjunction with other relevant EMA and ICH guidelines.

Based on efficacy and safety data, several drugs have been approved for short-term treatment of insomnia (e.g. benzodiazepines, benzodiazepine-like products, melatonin).

Depending on the sleep disturbance (e.g. sleep onset latency or number of awakenings) studied, distinct assessment tools for clinical and neurophysiological assessments should be used, refined or newly developed. The typical design to demonstrate efficacy is a randomised, double-blind, placebo controlled, parallel group study comparing changes in the primary endpoint. It is strongly recommended to include an additional active comparator in at least one of the confirmatory trials. The results must be robust and clinically meaningful. Besides statistically significant results on the original scale, this requires the incorporation of responder/remitter analyses to adequately assess clinical relevance.

Recent progress in basic science and current medical practice has fostered new interest in more efficacious treatment options for the short-term treatment and particularly for long-term treatment of insomnia. For regulatory purposes, long-term treatment of insomnia requires a different approach, particularly with regard to long-term studies (patient population, study duration, choice of endpoints, risk of tolerance and dependence, etc.). If an indication for long-term treatment of chronic insomnia is sought, the absence of tolerance and dependence potential should be established in addition to long-term efficacy and safety.

Taking into consideration that insomnia has considerable impact on cognitive, affective and physical domains, an efficacious treatment should not be limited to improvement of all or some aspects of sleep parameters, but also produce clinically relevant improvement in daytime functioning and quality of life.

1. Introduction (background)

While there is a great inter- and intra-individual variation across the life span in the need for sleep, sleep problems pertain to the most frequent symptoms presented in medical practice. Sleep disorders include hypersomnias, parasomnias, sleep-wake-schedule disorders, and – most commonly – insomnias. Primary insomnia occurs despite having an adequate opportunity to sleep. Based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) of the American Psychiatric Association, it is characterised by one or more of the following main criteria that last for at least one month:

– difficulties in initiating sleep;
– disorders of maintaining sleep (frequent or long awakening);
– premature awakening;
– feeling of non-restorative sleep;
all with subsequent impaired daytime functioning.

The term insomnia can be further characterized by acute or chronic sleep disturbance, which creates daytime fatigue, hyperarousal, impaired social or occupational functioning, and reduced quality of life. Patients with insomnia are less productive workers, show an increased risk for errors with higher frequency of motor vehicle and workplace accidents, and utilize medical health care systems to a greater degree than subjects with normal sleep pattern. Originally, insomnia was regarded as a symptom, not an illness in itself. This was based on the fact that insomnia is not present in isolation in the vast majority of patients. However, in some patients no underlying cause can be identified (primary insomnia). Moreover, insomnia often coexists with psychiatric, medical, other sleep or substance use disorders (secondary or co-morbid insomnia). However, recent findings from basic and clinical research call into question the approach that views insomnia as merely a “secondary” condition rather than an illness in itself. The present document regards insomnia as both.

There are now several lines of evidence that insomnia may be a disorder of hyperarousal in the CNS that overrides the normal control of sleep. Research studies have shown increased levels of catecholamines (e.g. measured in the urine), increased basal metabolic rate, increased body temperature, increased heart rate, increased CNS metabolic rate, elevated electroencephalographic activity and overactivity of the hypothalamic-pituitary-adrenal axis. The exact pathophysiology of insomnia is still unknown.

The reported prevalence rates of insomnia are highly variable and not many well conducted epidemiological studies are available. Population surveys indicate a 1-year prevalence of insomnia complaints of about 30-45 % in adults. The prevalence of primary insomnia, based on DSM-IV-TR-criteria, has been estimated between 1 and 10 % of the general adult population and up to 25% in the elderly. In specialized centres for sleep disorders, approximately 80% of patients suffer from chronic insomnia; 15 to 25% of these individuals with chronic insomnia are diagnosed with primary insomnia. In younger patients, insomnia with problems in sleep onset is more prevalent whereas in older patients sleep maintenance is more affected.

Several well-established assessment tools are available for characterizing sleep disorders and insomnia symptoms, including questionnaires, sleep diaries, symptom rating scales, polysomnography (PSG) and actigraphy.

2. Scope

Whilst the previous guidance was mainly driven by experience with hypnotic agents, this guideline takes into consideration other approaches based on different mechanisms of action and recent results from basic research. The generally rapid increase of sleep problems in the adult population and particularly in the increasingly ageing population with its accompanying set of chronic illnesses is recognized. In the last decade significant progress has been made in basic and clinical research in sleep disorders. Therefore the aim of this updated document is to provide guidance for the conduct of clinical studies for acute and long-term treatment of insomnia incorporating new research data and experience from recent clinical trials and development programs. This document addresses not only primary insomnia, but also some issues relating to secondary insomnia (e.g. definition, how to handle the underlying conditions). Other sleeping disorders such as narcolepsy, obstructive sleep apnoea and shift work sleep disorders are not within the scope of this guideline.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83 as amended and relevant CHMP Guidelines, among them:

- Dose-Response Information to Support Drug Registration (CPMP/ICH/378/95 (ICH E4))
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96 (ICH E9))
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96 (ICH E10))
- Adjustment for Baseline covariate (CPMP/EWP/2863/99)
- Guideline on missing data in confirmatory clinical trials (CPMP/EWP/177/99 Rev. 1)
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)
- Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95 (ICH E1A))
- Studies in support of special populations: geriatrics (CPMP/ICH/379/99 (ICH E7))
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)
- Guideline On The Non-Clinical Investigation Of The Dependence Potential Of Medicinal Products, EMEA/CHMP/SWP/94227/2004
- Note For Guidance On Clinical Investigation Of Medicinal Products In The Paediatric Population (CPMP/ICH/2711/99)
- Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population (EMEA/CHMP/EWP/692702/2008)

4. Diagnostic criteria

During the development of this guideline DSM-IV is under revision, and will be replaced by DSM-V. This might have consequences for the definitions of the disorders as given in this guideline.

4.1. Diagnosis of Primary Insomnia

In most development programs the clinical diagnosis of primary insomnia has been based on the DSM-IV-TR: difficulty in initiating or maintaining sleep or non-restorative sleep that lasts for at least 1 month (criterion A), which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion B). The disturbance of sleep does not occur exclusively during the course of another sleep disorder (criterion C) or mental disorder (criterion D) and is not due to the direct physiological effects of a substance or a general medical condition (criterion E). The diagnostic criteria of the International Classification of Diseases (ICD-10) of the World Health Organization (WHO) and the International Classification of Sleep Disorders (ICSD-II) by the International Society of Sleep Disorders may also be used. When using ICD-10, the diagnostic criteria for Nonorganic Insomnia (code F 51.0) should be met. When using ICSD-II, the criteria for “psychophysiologic insomnia” should be used as they most closely resemble the DSM-IV-TR criteria for primary insomnia.

To ensure accurate diagnosis of primary insomnia, the diagnosis should be established by a semi-structured or structured clinical interview that allows exclusion of relevant co-morbidities. For diagnosis, neurophysiological data from, for example, polysomnography as a pharmacodynamic measure are considered helpful. Diagnosis should ensure that disturbing environmental factors are considered or excluded and the patient in question engages in adequate sleep habits/hygiene. Excessive alcohol or caffeine consumption should also be excluded. Recently, both research diagnostic criteria for insomnia (e.g. difficulties in initiating sleep, difficulties in maintaining sleep) and quantitative insomnia diagnostic criteria (e.g. sleep onset latency, sleep duration) have been reported to increase the homogeneity of study populations. In order to reduce the amount of variability of clinical signs and symptoms only patients with primary insomnia are considered appropriate for such studies. Insomnia associated with major affective or psychotic disorders seems less appropriate because of the amount of variability.

The definition of chronic insomnia requires symptoms to be present for at least one month (the previous guideline stated 6 months). Within this period of time, symptoms should be present more nights than not. In some recent development programs intermittent use of medicinal products for treatment of chronic insomnia has been studied and might be an option in patients with chronic insomnia.

The diagnosis must be established at screening and confirmed at study inclusion/randomisation. Prior and concomitant medication should be documented in detail. If a placebo wash-out period during the run-in period is successfully accomplished, the need for further treatment with a hypnotic medicinal product has to be adequately justified. In interpretation of such wash-out results regard must be paid to the half life of the substance which should be washed-out and to the possibility of withdrawal phenomena.

4.2. Diagnosis of secondary insomnia

In general, insomnia, occurring as a symptom or consequence of another primary psychiatric disorder or medical condition, is referred to as “secondary” insomnia. In the DSM-IV-TR the main categories of secondary insomnia are insomnia related to another mental disorder and insomnia related to another general medical condition. The ICSD-II includes stricter diagnostic categories for insomnia secondary to medical, psychiatric, substance abuse or primary sleep disorders such as restless legs syndrome. Therefore the use of ICSD-II criteria may be more appropriate to define the patient population for clinical efficacy and safety trials in secondary insomnia. To properly understand the aetiology and maintenance of secondary insomnia it is important to assess the presence of mental disorders. Symptoms of depression and anxiety are of particular importance.

There are several data on the epidemiology of secondary insomnia; however, most studies have generated data on insomnia in general rather than on specific diagnostic categories. Psychiatric disorders, such as major depression and anxiety disorders, are the most prevalent primary axis-I diagnoses associated with secondary insomnia. The usual treatment approach for secondary insomnia is treatment of the underlying condition with the expectation that insomnia will improve in parallel with improvement and remission of the primary condition. On the other hand, it is sometimes difficult to decide if insomnia is in fact only a symptom of e.g. major depression or if the depressive symptoms are a consequence of insomnia. New proposed research diagnostic criteria therefore require a strict correlation of onset and course of insomnia with the associated primary condition.

Because of these uncertainties, development of a medicinal product in adults should always start in primary insomnia to establish efficacy and safety and only later on should focus on secondary insomnia in addition to primary insomnia. In primary insomnia trials patients should be carefully screened to ensure that those with secondary insomnia are not included, as underlying secondary causes of insomnia are not always readily apparent if not specifically sought. Pseudo-specific claims of secondary insomnia in many disorders (e.g. insomnia related to substance abuse) may not be considered approvable as long as no differences in pathophysiology or in mechanism of action of medicinal products have been established between primary and secondary insomnia.

5. Assessment of therapeutic efficacy

5.1. Criteria of efficacy

Two complementary types of trials are required to demonstrate efficacy in the clinical development programme: (1) trials documenting effects on subjective (usually self-rating) endpoints in the ”natural” setting and (2) trials documenting effects on objective endpoints (polysomnography). The following clinical efficacy criteria should be evaluated as a minimum acceptable standard:

– sleep onset latency;

– sleep continuity;

– sleep duration;

– feeling of restorative sleep and quality of sleep;

– subsequent daytime functioning in the natural setting.

Ideally, all these aspects will be improved by treatment with a given medicinal product in the phase three programme. It is recognised that improvement in individual criteria may be important for particular subgroups of patients, but if only one aspect of insomnia (e.g. difficulty falling asleep or difficulty maintaining sleep) is improved, the clinical relevance of these effects may be difficult to establish. In such cases the demonstrated effects should be based on a clear understanding of the underlying mechanism of action, should be robust and consistent and be supported by improvement in quality of day time functioning (mandatory as a co-primary endpoint). In this context, the additional measurement of sleep architecture by multichannel polysomnography is considered helpful for phase three studies.

The measurement techniques for the evaluation of anti-insomnia effects indicative of therapeutic efficacy include psychometric methods and neurophysiological measurements (sleep laboratory studies). For proof of concept, objective data (e.g. polysomnography) are mandatory. However, in principle, establishing efficacy will be based on clinically relevant improvements of subjective sleep parameters of the patients in their natural setting. These results should be supported by data obtained in specialized settings (sleep laboratory studies) or by neurophysiological evaluations (PSG).

5.1.1. Clinical evaluation

Subjective feelings of delayed sleep onset, disturbed sleep maintenance or persistent non-restorative sleep leading to impaired daytime function are the core symptoms of insomnia. Therefore pivotal clinical studies focussing on these symptoms should be performed in the natural setting of affected patients. Differences in sleep patterns and severity in acute and chronic forms of insomnia should be taken into consideration. In reference to an indication claimed for both children and adults, separate studies in children and adolescents are always considered mandatory. In the elderly (patients aged 65 and older), separate studies from younger patients are the preferred approach but subgroup studies that are adequately-powered for separate analysis for the elderly are also acceptable. Studies in inpatients or outpatients should be conducted separately.

The efficacy criteria and assessment techniques for the evaluation of treatment effects may vary depending on the type of study (see 5.2.2).

5.1.2. Sleep laboratory or ambulatory studies with multichannel polysomnography or actigraphy

Sleep laboratory studies permit extensive assessments with electrophysiological as well as psychometric methods before, during and after the night when applicable.

They allow “objective” quantification of sleep onset latency, number and duration of awakenings, total sleep time, arousals etc., but clearly establish an artificial setting for the patients. Therefore and as there is only a poor relationship between objective and subjective measures of sleep disturbance, the results of these studies are considered only supportive to the clinical improvement of insomnia symptoms in phase III. Results from actigraphy studies are considered useful but not as conclusive as results from polysomnography, particularly with regard to sleep onset latency.

For proof of concept or dose finding studies, results from sleep laboratory studies, placed as pharmacodynamic measurements, are fully acceptable as primary evidence. Moreover, they will be helpful to address changes of sleep architecture in primary or secondary insomnia depending on mechanism of action of a given product or the patient population studied. Ambulatory polysomnography may lessen the artificiality of sleep laboratory studies. Actigraphy can contribute some additional data to polysomnography, but is unacceptable if used as a unique method.

5.2. Study design and methods

5.2.1. Run-in period

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. During this time patients should be required to limit caffeine and alcohol consumption. Patients with major short-term

fluctuations of their condition should be studied separately. Placebo can be given during this period to assess compliance with study treatment.

5.2.2. Choice of tools

- **Psychometric methods**

Psychometric methods should be used to measure behaviour and performance as indicators of therapeutic efficacy. The choice of assessment methods should be justified with respect to test reliability, validity and availability of normative data for the population in question.

a) Improved restorative sleep and quality of sleep

Assessment of subjective feelings of improved and restorative sleep (sleep quality rating) and consequent improved daytime functioning is done by sleep questionnaires and self rating scales (usually by patient diaries). To increase the quality of data, electronic diary procedures that utilize time-stamping should be considered.

b) Improved daytime performance

Depending on the type of study objective, psychological performance tests should be performed – not only in the morning but also in the afternoon and the evening of the day after medicinal product intake in order to demonstrate any effects on intellectual functioning the next day. Suitable tests may assess alertness, perceptual speed, concentration, continuous attention, cognitive speed and information processing. These tests should be reliable and have a proper validity, for example, measuring episodic and procedural memory. For tests that are prone to learning and memory effects on repeated administration (e.g. digit-symbol-substitution tasks), parallel forms (alternative versions of a test that cover the same) should be provided.

- **Sleep laboratory or ambulatory multichannel polysomnography**

In sleep laboratory studies or more recently by ambulatory studies existing sleep disorders are verified by multichannel polysomnographic recordings. At least two consecutive adaptation nights are considered appropriate to allow patients to adapt to the unfamiliar and artificial setting by this type of measurements (the same applies to healthy subjects).

Visual classification of sleep EEG studies should follow internationally acknowledged rules (standard rules defined e.g. by Rechtschaffen and Kales). If automatic classification systems are used, the validity of classification criteria should be critically discussed.

- **Health related quality of life**

Quality of Life assessments are relevant here, but should be interpreted cautiously. Although insomnia can have a considerable impact on quality of life (QoL), the lack of validated assessment tools for QoL related to insomnia does not yet allow specific recommendations to be made for use of any particular assessment scale in regulatory trials. In theory, questionnaires, semi- or structured interviews and assessments may be used in patients with insomnia. These should address all key domains of insomnia and be sensitive to clinically meaningful changes. Studies are required to validate any instruments used

for the assessment of QoL in patients with insomnia before claims about improvement in quality of life can be made in the product information.

6. General strategy

Development of a medicinal product for the treatment of insomnia should start in primary insomnia; subsequently secondary insomnia could be an additional claim.

6.1. Early pharmacology and pharmacokinetic studies/pharmacodynamic studies

Initial studies of a potential medicinal product for the treatment of insomnia will follow the normal pattern (pharmacokinetics, pharmacodynamics, single and repeat dose tolerability) with the following special features:

- Pharmacokinetic parameters should be separately investigated in subgroups such as elderly persons and children/adolescents as well as in young adults, since these groups may have different pathologies and pharmacokinetic conditions.
- Special attention should be paid to cumulation effects and circadian variation.
- Onset, offset, nature and duration of CNS effects should be documented by neurophysiological (polysomnographic) measures and psychometric tests (dose-effect-curves, time-effect-curves). Again, separate studies in the elderly and children/adolescents are considered necessary and again circadian variations in pharmacodynamics should be considered.
- Sleep laboratory studies in healthy volunteers without symptoms of insomnia may be useful in investigating pharmacodynamics and dose response-relationships. Specific adverse effects associated with medicinal products for the treatment of insomnia (e.g. amnestic effects, especially anterograde amnesia) should be investigated in appropriate experimental models in healthy adult volunteers (e.g. learning and memory tests after administration of medicinal product, memory assessment the morning after medicinal product intake: selective reminding tests, recognition memory).
- Pharmacodynamic interaction studies with drugs commonly used in any subpopulation should be conducted, including psychotropic drugs. The pharmacodynamic sensitivity in the elderly should be kept under consideration.
- The risk of tolerance and dependence must be addressed in clinical trials. Preclinical animal models should be used to study these risks and to establish a basis for further studies required in the clinical trials before relevant human studies are initiated.

6.2. Confirmatory Trials

Confirmatory trials should be double-blind, randomised, two or three arm parallel group trials with placebo and should usually include an active comparator in at least one of the confirmatory trials. Dose response-relationships should be verified and reproduced in clinical endpoints. The incorporation of responder/remitter analyses, at least for the primary endpoint, is considered essential to adequately assess clinical relevance.

Based on Phase II dose-finding study results, the minimum effective dose should be confirmed and the maximum recommended dose should be determined provided that more than one dose is tested in phase III trials. The sample size should be justified. The analysis populations for efficacy should include the full analysis set (FAS) and the per-protocol population. In the event that non-negligible amounts of missing data are presented, sensitivity analyses should be included to explore the impact of missing data on the primary analyses. In general, the common guidelines (e.g. see ICH E9, Points to consider on Switching between Superiority and Non-inferiority and Guideline on missing data in confirmatory clinical trials) should be followed.

Control of compliance as well as screening for psychotropic drugs, including drugs of dependence, are recommended during the placebo run-in period, the treatment phase and any placebo discontinuation phase. With regard to the selection of patients (some will be tested, some will not be) and the timing of these tests, the choice of checks should be random. Special attention should also be paid to limited consumption of alcohol and caffeine during the trials.

6.2.1. Short term Trials

Randomised, double blind, parallel-group fixed dose studies are required. Three-arm-studies including placebo and active comparator are strongly recommended. The dose of the new compound as well as the dose of the active comparator should be justified.

For pivotal studies in insomnia, the treatment duration should be at least 2 to 4 weeks of active treatment. If products with a new mechanism of action are studied, longer study durations may be necessary based on this mechanism (longer studies would be required for agents demonstrating a latency to full clinical effect).

6.2.2. Long term Trials

In principle, a long-term study is needed unless there are compelling safety reasons not to conduct such trials. In this situation, the indication would be “short-term treatment”.

This might be done by a double-blind placebo-controlled extension study or, preferably, by a randomised withdrawal design. In the randomised withdrawal design, responders to the investigational treatment of sufficient duration are randomised to continue the investigational drug or switch to placebo. This is done in two time periods. In the first open and uncontrolled period the stabilised responders continue with the test treatment for 2 to 4 weeks, thereafter they are randomised and followed for at least 6 months depending on the mechanism of action of the studied medicinal product. The alternative, a double-blind placebo-controlled extension study, should equally last for at least 6 months. Those subjects not coming into the maintenance phase should have their medication withdrawn under placebo control to detect any possible dependence.

Regarding the design of a double-blind placebo-controlled extension study, the demonstration of efficacy is based on effect sizes of the chosen endpoints and on drop-out rates. With respect to the randomised withdrawal design efficacy is usually based on the number of patients worsening (relapsing) and/or the time to this event; however, both criteria should be included. Worsening or relapse should be defined in the protocol, based on a clinically relevant increase of symptoms of insomnia that are scored on validated rating scales at one or more visits.

Subjective endpoints alone are considered acceptable. The choice of (co)primary parameter(s) has to be justified.

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. Analyses should carefully consider the possible biases arising from drop-outs (not because of relapse) and the statistical methods of dealing with them should be defined in the protocol (Guideline on missing data in confirmatory clinical trials (CPMP/EWP/177/99 Rev. 1).

6.3. Concomitant treatments

Any treatment likely to impair alertness, intellectual function and behaviour should either be excluded or be given in unchanged dosage in order to eliminate any interference or bias, particularly in pivotal/confirmatory trials. This includes (but is not limited to) other hypnotic, anxiolytic, antidepressant, antipsychotic, anticholinergic and memory enhancing drugs. If concomitant use of such drugs cannot be avoided e.g. in secondary insomnia, the acceptable level of use of such medicinal products should be specified in the protocol, be optimised and remain constant, beginning at least 4 weeks before entering the study and continuing throughout the trial. Stratification of the randomisation with respect to the use of concomitant medication and the inclusion of this factor into the analysis model should be considered.

Given the high co-morbidity with psychiatric disorders, concomitant cognitive behavioural therapy (CBT) and other psychological treatments should be documented. These therapies often target processes that could have an effect on sleep.

7. Special Populations

7.1. Paediatric population

Sleep problems are common in paediatric populations. Prevalence rates are reported to be as high as 20-40% depending on the age group and geographical location of the epidemiological studies. Children and adolescents with neurodevelopmental disorders, psychiatric disorders and chronic illness or disorder (e.g. those causing pain or discomfort) have high rates of sleep disturbance that do not always respond to sleep hygiene interventions. Insomnia in children and adolescents is not as well understood as in adult populations and it is therefore usually impossible to extrapolate risk-benefit data from adult studies to paediatric populations. Consequently, separate trials in the paediatric population are required. These should be conducted in severe, chronic insomnia refractory to usual behavioural strategies, where possible causative or maintaining medical disorders have been excluded.

As children do not usually complain of sleep problems, diagnosis should be made by a paediatrician experienced in child and adolescent sleep disorders and include a detailed sleep history from the child and the child´s carer. Formal diagnosis should be possible in most cases. As ICSD-II has many more sub-classifications it is considered a better choice for children and for research than other classification

systems such as the DSM-IV or ICD-10. Any extrapolation of efficacy results across paediatric sleep disorders must be justified depending on the nature of the sleep disorders.

Proof of concept should be established in a homogeneous patient group, such as patients with autism/mental retardation, ensuring that patients are age matched, matched for cognitive level and not treated with concomitant drugs that may interfere with sleep.

If a Phase II dose-response study is conducted, then Phase III studies need to confirm efficacy and safety in a wider group of paediatric insomnia patients than in the proof of concept study. Three-arm studies including placebo and an active comparator should be performed once there is an approved insomnia drug for the relevant age groups under study. Trials should include a run-in period with if possible standardised behavioural interventions. Only patients non responsive to an adequate period of behavioural interventions should be randomised to treatment. Clinical outcome measures as primary endpoint are preferred in phase III studies in the paediatric population. However, based on expert recommendation the use of objective primary outcome measure criteria (e.g. actigraphy or polysomnography) in this population would also be valid. In such cases next day performance or school performance should be included as co-primary endpoint. The duration of efficacy trials should be as for the adult population. A follow up period should be included to assess withdrawal/rebound reactions and adverse events emerging after treatment discontinuation.

Secondary endpoints should be clearly defined and should include the effect of the medication on neurocognitive/neurobehavioural parameters. Assessment of functioning at school (concentration and school performance) and of mood and general well-being should be performed using validated methods. Effects on quality of life for the caregiver, impulsivity, attention, vigilance, learning (memory consolidation), verbal fluency, complex/divergent/creative thinking, functioning at home and behavioural problems are also of interest.

As sleep disturbances in children may adversely affect the pulsatile growth hormone release, effects of treatment on height, weight and pubertal status should be assessed. Rather than relying on spontaneous AE reporting, potential treatment-emergent adverse events such as somnolence, affective symptoms such as suicidality, depression, etc should be clearly defined and actively monitored for. Validated questionnaires/scales should be used for monitoring AEs. The duration of long-term safety trials should be adequate to assess any effects on sexual development or growth.

7.2. Elderly

Elderly people tend to exhibit a different pattern of sleep architecture compared to younger adults and the prevalence and frequency of primary and secondary insomnia increases with age. In older adults sleep onset latency is increased, and sleep maintenance and sleep efficiency tend to be impaired.

Moreover, the optimal dose in the elderly might be different from that in younger adults due to differences in the pharamacokinetic properties of the product and/or to a different sensitivity in the elderly for the pharmacodynamics of the product.

Therefore, not only efficacy, but also defining a safe dose (range) in the elderly is a main concern and should usually be addressed before licensing.

In principle two approaches are possible. One is an analysis in a subgroup of the whole trial-database, and the other would be to conduct specific trials in the elderly.

The first approach might be acceptable as pivotal information for products of known pharmacological classes, provided that sufficient elderly patients are included to allow for prospectively planned subgroup analyses (of both subjective clinical endpoints and objective polysomnographic measures). As both efficacy and the optimal dose should be addressed, this might be difficult. It cannot be assumed that efficacy is the same in the elderly as in younger adults. Therefore, specific studies will be more informative. For new medicinal products with a new mechanism of action, specific trials are always needed. It is also recommended to obtain data and to assess safety and efficacy in elderly patients over 75 years of age. A placebo-controlled dose response study is considered as an optimal design for such a trial in the elderly population. In general efficacy and safety should be established by using the same endpoints as in the younger adults, although alternative endpoints for efficacy and safety may be justified, particularly in the older patients (>75 years old). In the elderly, psychological performance tests should additionally be carried out 2-6 hours after administration (dependent on the mode/onset of action), to identify how impaired these patients are during the night. Demented patients should be separately assessed.

For products with a known mechanism of action as well as products with a new mechanism of action, pharmacokinetic studies in the elderly are essential.

8. Safety Evaluation

In general the content of ICH E1 should be taken into consideration.

Identified adverse events should be characterised in relation to time to onset, dose, the recovery time, and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and electrophysiological recordings (e.g. electrocardiogram).

All adverse events occurring during the course of a clinical trial must be fully documented with separate analysis of serious adverse drug events, adverse events leading to drop-outs and patients with a fatal outcome.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated depending on the action on distinct receptor sites, e.g. benzodiazepine-like effects. The risk of tolerance and dependence must be addressed in the clinical trials. Moreover, where appropriate, the abuse potential should be investigated. Disinhibitory and paradoxical effects need documenting in detail. The use of validated questionnaires for eliciting side effects is encouraged.

The elderly are particularly susceptible to unwanted CNS effects and these should be studied fully.

8.1. Specific adverse events to be monitored

Hangover/Increased Alertness

A treatment effect on sleep disturbances may be followed by different consequences for daytime functioning. The possibility of impaired daytime functioning or increased rate of spurious actions by hangover effects or an unphysiological over-alertness should be monitored (please refer to section 5.2.2).

Potentially serious outcomes such as falls and fractures in the elderly should be routinely monitored.

Rebound/Withdrawal/Tolerance and Dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena/discontinuation syndromes may occur. 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. Placebo control is helpful wherever feasible. Occurrence of rebound and/or withdrawal phenomena should be evaluated at the appropriate time depending on pharmacokinetics and mechanism of action of the medicinal product.

Investigations of the dependence potential in animals will be required in case of new classes of compounds or when there are indications that dependence may occur. In this regard, the recommendations of the pertinent guideline should be followed (EMEA/CHMP/SWP/94227/2004).

Central Nervous System (CNS) adverse reactions

Taking into consideration the class and the interactions with various receptors, effects on cognition, reaction time and/or driving, the extent of sedation or hangover-effects etc. should be studied. Specific claims have to be based on specific studies. Effects on cognition and neurobehavioural parameters should be assessed in children/adolescents.

Interaction with alcohol is a particular problem and can be associated with disinhibition, paradoxical reactions and drug-facilitated assaults.

Haematological adverse reactions

Special attention should be paid to the incidence of leukopenia, agranulcytosis, aplastic anaemia, reduction in platelet count as well as to liver parameters.

Cardiovascular adverse reactions

Special attention should be paid to arrhythmias and conduction disorders, in particular QT-interval prolongation and dispersion in a class associated with cardiovascular effects, as well as postural hypotension.

Endocrinological adverse reactions

Special attention should be paid to sexual disturbances, libido and weight gain and to sexual development in the paediatric population.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuroendocrinological parameters may be necessary over an adequate period of time, particularly in children/adolescents.

Extent of population exposure to assess clinical safety

Recommendations should be consistent with ICH E1A.

Long term safety

The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure (ICHE1A).

Definitions

Physical dependence: Development of physical dependence is characterised by manifestation of withdrawal phenomena occurring after discontinuation of medicinal product administration. There are characteristic patterns of withdrawal symptoms depending on class and mechanism of action of a therapeutic agent. Early signs of withdrawal are often characterised by changes in REM-sleep duration and autonomic dysregulation. Later hyper-excitability and convulsions, tremor and vomiting may occur. Withdrawal phenomena are easily assessable especially in rats, dogs, and monkeys.

Dyssomnias: Primary disorders of initiating or maintaining sleep or of excessive sleepiness characterized by a disturbance in the amount, quality or timing of sleep**.**

Primary Insomnia: (DSM-IV-TR): Complaint of difficulty initiating or maintaining sleep or of non-restorative sleep that lasts for at least 1 month (criterion A), which causes clinically significant distress or impairment in social occupational, or other important areas of functioning (criterion B). The disturbance of sleep does not occur exclusively during the course of another sleep disorder (criterion C) or mental disorder (criterion D) and is not due to the direct physiological effects of a substance or a general medical condition (criterion E).

Primary Hypersomnia: (DSM-IV-TR): Complaint of excessive sleepiness for at least 1 month (or less if recurrent) as evidenced by either prolonged sleep episodes or daytime sleep episodes that occur almost daily (criterion A), which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion B). The excessive sleepiness is not better accounted for by insomnia, does not occur exclusively during the course of another sleep disorder, cannot be accounted for by inadequate amount of sleep (criterion C) or mental disorder (criterion D) and is not due to the direct physiological effects of a substance or a general medical condition (criterion E).

Psychic dependence: Psychological or psychic dependence refers to the experience of impaired control and implies a craving for a medicinal product.

Dependence or physical dependence is also used in the psychopharmacological context in a still narrower sense, referring solely to the development of withdrawal symptoms on cessation of drug use. Dependence potential is determined by those intrinsic pharmacological properties that can be measured in animal and human drug testing procedures.

Narcolepsy: (DSM-IV-TR)**:** Characterized by irresistible attacks of refreshing sleep that occur daily over the last 3 months (criterion A). One or both of the following are present: (1) cataplexy (i.e. brief episodes of sudden bilateral loss of muscle tone, most often in association with intense emotion) (2) recurrent intrusions of elements of rapid eye movement (REM) sleep into transition between sleep and wakefulness, as manifested by either hypnopompic or hypnagogic hallucinations or sleep paralysis at the beginning or end of sleep episodes (criterion B). The disturbance is not due to the direct physiological effects of a substance (e.g. drugs of abuse, a medication) or a general medical condition (criterion C).

Otherwise the WHO glossary should be used for definitions.
(http://www.who.int/substance_abuse/terminology/en/)

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