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DRAFT

GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF INSOMNIA

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GUIDELINE ON MEDICINAL PRODUCTS FOR THE TREATMENT OF INSOMNIA

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EXECUTIVE SUMMARY

The present document should be considered as general guidance on the development for medicinal products for the treatment of acute and chronic forms of insomnia. Its main focus is on primary insomnia, however, some issues on secondary or comorbid insomnia will be mentioned as well. This document should be read in conjunction with other relevant EMEA 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). 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 this requires a different approach, particularly with regard to long-term studies (patient population, study duration, choice of endpoints, risk of tolerance and dependence, etc.). 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 randomized, double-blind, placebo-controlled, parallel group study comparing change in the primary endpoint. The results must be robust and clinically meaningful.

If an indication for long-term treatment of chronic insomnia is sought, the absence of tolerance, abuse and dependency 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-individual and intra-individual variation across the life span in the need for sleep, sleep problems are among the most frequent symptoms presented in medical practice. Sleep disorders include hypersomnias, parasomnias, sleep-wake-schedule disorders, and –most commonly – insomnias. Primary insomnia may be transient/situational or persistent and occurs despite an adequate opportunity to sleep. It is characterised by one or more of the following main criteria that last for at least one month (DSM-IV-TR):

– difficulties in initiating sleep;

– disorders of maintaining sleep (frequent awakening);

– premature awakening;

– feeling of nonrestorative sleep,

with subsequent impaired daytime functioning.

The term insomnia can be further characterized by acute or chronic sleep disturbance, which creates daytime fatigue, 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 patients with a normal sleep pattern. Originally insomnia was regarded as a symptom, not a disease 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 and substance use disorders (secondary or comorbid insomnia). However recent findings from basic and clinical research are questioning this approach.

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, increased basal metabolic rate, increased body temperature, increased heart rate, increased levels of CNS metabolic rates, 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 there are not many well conducted epidemiological studies available. Population surveys indicate a 1-year prevalence of insomnia complaints of 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 the patients suffer from chronic insomnia and 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 disturbed.

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

2. SCOPE

The previous guidance was mainly driven by experience with hypnotic agents. The current guidance takes into consideration other approaches based on different mechanisms of action and recent results from basic research. The rapid increase of sleep problems in the adult population and particularly in the increasing 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 the treatment of acute and chronic insomnia incorporating new research data and experience from recent clinical trials and development programs. The present document addresses not only acute primary insomnia, but chronic forms of primary insomnia and some issues relating to secondary insomnia as well. 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)
- Missing data (CPMP/EWP/177/99)
- 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)

4. DIAGNOSTIC CRITERIA

4.1 *Diagnosis of Primary Insomnia*

In most development programs the clinical diagnosis of primary insomnia has been based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR of the American Psychiatric Association): difficulty initiating or maintaining sleep or nonrestorative 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 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 comorbidities. Diagnosis can be supported by neurophysiological data from, for example, multichannel polysomnography. Recently, both research diagnostic criteria for insomnia and quantitative insomnia diagnostic criteria have been reported to increase the homogeneity of study populations. In order to reduce the amount of variance of clinical signs and symptoms, patients with primary insomnia and patients with insomnia associated with non-psychotic mental disorders are considered appropriate for such studies. Insomnia associated with major affective or psychotic disorders seems less appropriate because of the amount of variance.

The definition of chronic insomnia requires symptoms to be present for at least one month (previously 6 months).

The diagnosis must be established at screening and confirmed at study randomisation. Prior and concomitant medication should be documented in detail. If a placebo wash-out period is successfully accomplished, the need for further treatment with a hypnotic medicinal product has to be made plausible. In interpretation of such wash-out results regard must be paid to the half life of the substance which is being 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 use of ICSD-II criteria may be more appropriate to define the patient population for clinical efficacy and safety trials for secondary insomnia.

There are only limited data on the epidemiology of secondary insomnia as 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 primary 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.

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. If such differences have been confirmed this would strengthen a separate claim of secondary insomnia.

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. Pseudospecific claims of secondary insomnia in many disorders 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 clinical trials are required to demonstrate efficacy: (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:

– 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. 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 addition sleep architecture can be measured by multichannel polysomnography.

The measurement techniques for the evaluation of anti-insomnia effects indicative of therapeutic efficacy include psychometric methods and neurophysiological measurements (sleep laboratory studies). However, in principal, establishing efficacy will be based on clinical relevant improvements of subjective sleep parameters of the patients in their natural setting. These results should be supported by data obtained in specialized settings or by neurophysiological evaluations.

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. Separate studies in children and adolescents are always considered mandatory. In the elderly population, separate studies or a significant proportion of patients to allow for a prospective subgroup analysis is mandatory. 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 etc., but clearly establish an artificial setting for the patients. Therefore 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 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 or actigraphy could be added to the patient reported subjective outcomes as supportive evidence for consistency.

5.2 *Study design and methods*

5.2.1 Run-in period

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. Patients with major short term fluctuations of their condition should be excluded. Placebo can be given during this period to assess compliance with medication.

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, availability of normative data for the population in question.

a) Sleep questionnaires/visual analogue scales

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).

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 a 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, information processing. For tests that are prone to learning and memory effects on repeated administration (e.g. digit-symbol-substitution tasks), parallel forms 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 control subjects.)

Visual classification of sleep EEG studies should follow internationally acknowledged rules. If automatic classification systems are used, the validity of classification criteria should be critically discussed.

- **Health related quality of life**

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

6.1 *Early pharmacology and pharmacokinetic studies /pharmacodynamic studies*

Initial studies of a potential hypnotic agent 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, 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 hypnotics (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 risk of tolerance, abuse and dependency 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 three arm parallel group trials with placebo and an active comparator. Dose response-relationships should be established and reproduced in clinical endpoints.

The minimum effective dose and the maximum recommended dose should be determined. The sample size should be justified. The performed analyses should include the intent-to-treat population and the observed-case population.

Control of compliance as well as screening for psychotropic drugs are recommended during the placebo run-in period, the treatment phase and any placebo discontinuation phase.

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 preferred. 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.

6.2.2 Long term Trials

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 randomized withdrawal design, responders to the investigational treatment of sufficient duration are re-randomized to investigational drug or placebo. This is done in two time periods, in the first open and uncontrolled period the stabilized responders continue with the test treatment for 2 to 4 weeks, thereafter they are re-randomized and followed by at least 6 months depending on the mechanism of action of the studied medicinal product. The alternative of a double-blind placebo-controlled extension study should last for 6 months as well.

Efficacy is usually expressed as number of patients worsening (relapsing) and/or time to this event. Both criteria should be included. Worsening or relapse should be defined in the protocol based on a clinically relevant increase of symptoms of insomnia, scored on a validated rating scales at one or more visits.

The choice of (co)primary parameter(s) has to be justified.

In addition to efficacy and safety, the long-term trials should address tolerance, rebound insomnia, abuse and dependence.

The analysis should be carefully consided 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.

6.3 *Concomitant treatments*

Any treatment likely to impair alertness, intellectual function and behaviour should be excluded in order to eliminate any interference or bias, particularly in exploratory 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, the acceptable level of use of such medicinal products should be specified in the protocol and remain constant throughout the trial.

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, persistent insomnia refractory to usual behavioural and licensed pharmacological 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 their 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 homogenous patient group, such as patients with autism/learning difficulties, ensuring that patients are age matched, matched for cognitive level and not treated with concomitant drugs that may interfere with sleep.

Pivotal efficacy trials should establish dose-response in specific paediatric subgroups compared to placebo, however, three-arm studies including placebo and an active comparator are preferred. Trials should include a run-in period with standardised behavioural interventions. Only patients non-

responsive to an adequate period of standardised behavioural interventions should be randomised to treatment. In general clinical outcome measures as primary endpoint are preferred in the paediatric population as well. However, based on expert recommendation results might be more reliable with the use of objective primary outcome measure criteria (e.g. actigraphy or polysomnography) in this population. In such cases next day performance or school performance should be explored 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 emergent after treatment discontinuation.

Secondary endpoints should be clearly defined and should include the effect of the medication upon neurocognitive/neurobehavioural parameters. Assessment of functioning at school (concentration and academic performance) and of mood and general wellbeing should be performed using validated methods. Effects on quality of life for the care giver, 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*

The prevalence and frequency of primary and secondary insomnia increases with age. In older adults sleep onset latency is increased, however, particularly sleep maintenance and sleep efficiency is impaired with a different pattern of sleep architecture compared to younger adults.

Moreover, the optimal dose in the elderly might be different to the younger adults based on 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 usually should be addressed before licensing.

In principle two approaches are possible. One is an analysis of the whole database, whereas 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 a prospective subgroup analysis (subjective clinical endpoints and objective polysomnographic measures). As both efficacy and the optimal dose should be addressed, this might be difficult.

Therefore specific studies will be more informative and are needed, particularly in the growing elderly population over 75 years. 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, however, particularly in the older patients (>75 years old) alternative endpoints for efficacy and safety may be justified.

For new medicinal products with a new mechanism of action always specific trials are always needed.

In both situations pharmacokinetic studies may support the choice of the dose and should be conducted.

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, abuse and dependency must be addressed in the clinical trials. The use of validated questionnaires for eliciting side effects is encouraged.

8.1 *Specific adverse events to be monitored*

Hang over/Increased Alertness

Improved sleep disturbances may be followed by different consequences for daytime functioning. An impaired daytime functioning or increased rate of spurious actions by hang over effects or an unphysiological overalertness should be monitored.

Rebound/Withdrawal/Tolerance/Abuse/Dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena/discontinuation syndrome may occur. Trials should be designed in such a way that these phenomena can be studied. In some of the short-term and long-term clinical trials, treatment should be stopped abruptly and patients should be followed for an adequate period of time. 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.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur. Depending on the results of the animal studies more data may be necessary, including well-designed studies in humans.

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 hang over-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.

Haematological adverse reactions

Special attention should be paid to the incidence of leukopenia, agranulcytosis, aplastic anaemia and reduction in platelet count.

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.

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 hyperexcitability 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 nonrestorative 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 and does not occur exclusively during the course of another sleep disorder and 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: Psychic dependence implies a craving for a medicinal product which is measured by animal drug taking behaviour models. Assessment of positive reinforcing properties of medicinal products leading to craving is best performed using self-administration techniques in rats or monkeys. Among the suitable screening methods are the various self-administration techniques which assess generalisation of substance taking behaviour over different classes of dependence producing substances in substance experienced animals. Continuous self-administration studies using substance naive animals should be performed in addition. Further assessment of the substance in a substance discrimination paradigm is extremely helpful. Generalisation effects of the agent in animals trained for known dependence producing compounds can be used to classify whether the agent will belong to such a group of compounds.

Narcolepsy (DSM-IV-TR)**:** is characterized by irresistible attacks of refreshing sleep that occur daily over the last 3 months (crierion 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).

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