Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD)

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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

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Executive summary

Attention Deficit Hyperactivity Disorder (ADHD) is among the most common disorders in child- and adolescent psychiatry. Its impact on learning and development is considered substantial. The benefit of pharmacotherapy has empirically been proven, and several products are on the market. Although primarily a disorder diagnosed in childhood and adolescence, signs and symptoms may not be self-limiting but may persist into adulthood. These new insights in the ADHD syndrome are a challenge in the field of drug development. However, this Guideline is intended to provide guidance on the evaluation of new medicinal products in ADHD with focus on the childhood onset. It is the first guideline written in psychiatry to address a (child) psychiatric disorder from this perspective, and it should be read in conjunction with other EMA and ICH guidelines, which may apply to similar conditions and patient populations.

1.   Introduction

Attention Deficit Hyperactivity Disorder, ADHD, is a well defined disorder with core features of inattention, hyperactivity, and impulsivity, but also impairment in executive functions. It has its origin in childhood and is often diagnosed for the first time in school-aged children because of learning problems and problems with social behaviour. Treatment is therefore directed towards improvement of attention and reduction of hyperactivity/impulsivity in order to be able to focus on tasks and performance, and improve associated behavioural and relational problems. Methylphenidate is among the first effective drugs reported to treat the 'hyperkinetic syndrome' in the 1950s. Although often regarded as the standard of treatment, new products have come to the market, e.g. atomoxetine with a different mode of action. Psycho-education, and psycho-education in combination with pharmacotherapy are usually the standard of care in Europe, and behavioural treatment is often provided to sustain success of pharmacotherapy, and to modify conduct problems. In the context of non-pharmacological interventions, cognitive treatment, neurofeedback training and dietary measures[1] can be regarded as potential, but not yet evidence based strategies.

It has long been assumed that the core symptoms of ADHD ameliorate with age. It has recently been recognized that symptoms and impairments may persist into adulthood, thereby extending treatment to this age group. Usually, inattention and restlessness predominate at adult age, interfering with work and social functioning.

As ADHD is a chronic disorder, long term treatment can be foreseen, thereby emphasizing the need for long term safety data in a group of patients that does include many otherwise healthy individuals.

1.1   Diagnosis

ADHD usually first comes to attention in children and adolescents, and is characterized by a persistent pattern of inattention, hyperactivity/impulsivity that causes impairment in school performance and social functioning. In adults, symptoms may experience a shift from inattention and hyperactivity/impulsivity into inattention and restlessness, and not be dominated by hyperactivity. According to DSM-IV-TR, six out of nine symptoms of either the inattention or hyperactivity/impulsivity domain should have persisted for 6 months (criterion A). Some symptoms should present before the age of 7, and some impairment in school, work or social environment should be present at the time of diagnosis (criterion B-D). Symptoms should not be secondary to other psychiatric disorders (criterion E). The majority of cases present with criteria for both inattention and hyperactivity/impulsivity, but either symptom domain may predominate, justifying classification in subtypes, i.e. combined type, predominantly inattentive and predominantly hyperactive/impulsive.

The ICD-10 classifies ADHD among the hyperkinetic disorders. The presence of symptoms in both domains (inattention and hyperactivity/impulsivity) is necessary to qualify for an ICD-10 diagnosis. Therefore, the diagnosis is more restrictive, which makes prevalence rates different when applying ICD or DSM classifications

There are no diagnostic tools other than the rating of symptoms that are characteristic for ADHD. Morphological differences observed with magnetic resonance imaging techniques (MRI[2]) and functional

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[1] Pelsser LM, Frankena K, Toorman J et al. 2009. A randomised controlled trial into the effect of food on ADHD. Eur Child and Adolesc Psychiatry, 18 (1): 12-9

[2] Hutchinson A, Mathias J et al. 2008. Corpus callosum morphology in children and adolescents with Attention Deficit Hyperactivity Disorder: A meta-analytic review. Neuropsychology 22 (3): 341-9

imaging (fMRI[3]) as well as electrophysiological differences, differences in cognitive performance, and DNA polymorphisms[4] are all subject of thorough investigation, yet far from potential use as valid (bio) markers.

1.2   Differential diagnosis

ADHD should be discriminated from otherwise 'normal' behaviour in active children, but also from disruptive behaviour in children due to low- (mental retardation) or high intelligence (gifted children) when there is no 'match' between demands and capabilities. Although often co-morbid to Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), ADHD should be discriminated from oppositional behaviour due to repeated failure in performance and the incapability of living up to expectations. Differentiation should be made between ADHD and Stereotypic Movement Disorder (tic-disorders), where the hyperactivity is more focussed to specific body parts. ADHD, if not co-morbid, should be discriminated from other mental disorders that share similar symptoms, e.g. mood and anxiety, and personality disorders. In particular, bipolar disorder in children should not be mixed up with ADHD. The age (younger than 7 years) of onset of first symptoms should be kept as one of the hallmarks for differentiation. ADHD should not be diagnosed if symptoms present in the context of a pervasive developmental or psychotic disorder. Nor should symptoms be due to the use of medication.

For adults, ADHD should be discriminated from disorders where inattention or other cognitive impairments are present, such as in bipolar disorder, depression and anxiety disorders or other cognitive impairment complaints.

1.3   Epidemiology and co-morbidity

ADHD is one of the most prevalent disorders of childhood, its worldwide prevalence being estimated at approximately 5-6%[5]. Prevalence rates, however, vary with the source referred to. The DSM-IV-TR states a slightly higher rate (3-7%), due to the inclusion of ratings of both subtypes. Prevalence rates in adolescents separately, and adults have been less investigated. For adults, an average prevalence rate of 3.4% has been reported in a cross-national survey[6], with the lowest rate in lower-income countries (1.9%) compared to the higher- income countries (4.2%).

At least in children, ADHD is more frequent in boys than in girls. In clinical samples, the average male-to-female ratio of 5:1 has been found, but in epidemiological samples ratios of 3:1 or 2:1 are mentioned[7]. The figures often depend on the (sub)type investigated. For the inattentive type, gender difference is less clear.

In child psychiatry, co-morbidity is almost inevitable in diagnostics[8,9]. As a result, co-morbidity is high in ADHD. Only 30% of cases are pure ADHD. The most apparent co-morbid conditions are Oppositional Defiant Disorder and Conduct Disorder. A variety of other disorders may be co-morbid (e.g. mood, and anxiety disorders, learning disorders, Tourette's syndrome), but should also be differentiated from ADHD. In older subjects, substance abuse is often found to be co-morbid, whereas in the adult population also Borderline and Antisocial Personality Disorders are prevalent co-morbid conditions.

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[3] Rubia K, Halari R et al. 2008. Dissociated Functional Brain Abnormalities of Inhibition in Boys with Pure Conduct Disorder and in Boys with Pure Attention Deficit Hyperactivity Disorder. Am J Pychiatry in press.

[4] Waldman ID, Nigg JT et al. 2006. The adrenergic receptor alpha-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. Cog Affect Behav Neurosci 6 (1): 18-20

[5] Polanczyk G, Silva de Lima M et al. 2007. The worldwide prevalence of ADHD: A Systematic Review and Metaregression Analysis. Am J Psychiatry 164:942-948

[6] Fayyad J, De Graaf R et al. 2007. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. British J Psychiatry 190: 402-09

[7] Staller J, and Farone SV 2006. Attention-deficit hyperactivity disorder in girls: epidemiology and management. CNS Drugs 20 (2): 107-23.

[8] Caron C and Rutter M. 1991. Comorbidity in Child Psychopathology: Concepts, Issues and Research Strategies. J Child Psychol and Psychiat 32 (7): 1063-80.

[9] Gillberg C, Gillberg IC etal. 2004. Co existing disorders in ADHD: implications for diagnosis and intervention. Eur Child Adolesc Psychiatry Suppl 1: 180-92

2.   Scope

This Guideline is intended to assist applicants during the development of medicinal products intended for the treatment of attention deficit hyperactivity disorder (ADHD), independent of the class of product under investigation. Therefore, it is only guidance for the purpose of registration trials. While diagnosis and study design recommendations apply to drugs under development at the time the guideline was developed, consideration must always be given to the evolution of clinical practice and guidelines with time.

3.   Legal Basis

This Guideline is intended to provide guidance on the evaluation of new medicinal products in attention deficit hyperactivity disorder (ADHD). This guideline has to be read in conjunction with the introduction, general principles (4) and the Annex I to Directive 2001/83 as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- 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),

- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH E11),

- Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, Directive 2001/20/EC,

- Pharmacokinetic studies in man (EudraLex vol. 3C C3A),

- Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (CHMP/SWP/169215/2005),

- Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M 3 (R2)/ CPMP/ICH/286/95).

4.   Patients characteristics and selection of patients

4.1   Diagnosis and inclusion criteria

The disorder should be classified according to an internationally acknowledged classification system, preferably to the latest version of the DSM or ICD, using the diagnostic criteria herein. The inclusion of subtypes should be specified. The use of a severity rating scale or cognitive performance task is additional, but should not replace a clinical diagnosis. Diagnosis should be made by a (child) psychiatrist or by a non–psychiatrist physician experienced in ADHD and co-morbid diagnoses, and who is trained in the use of (semi)structured interviews to confirm the diagnosis and exclude relevant co-morbid disorders.

The diagnosis of ADHD in adults should be similar to that in children and exerted by trained psychiatrists or physicians with comparable experience in that area. Mandatory for the diagnosis in adults is the verifiable presence of first symptoms in (early) childhood (e.g. by medical records/school reporting etc).

The age for inclusion should cover the range from 6 to 18 years in the case of children. Children and adolescents should be separated or stratified. For adults, patients older than 18 years of age can be included. Primary studies for dose finding should include patients with ADHD *without* significant co-morbidities. Otherwise, interpretation of study results may be inconclusive, e.g. treatment effects of a psycho-stimulant on ADHD with co-morbid disrupted behaviour or treatment effects of an antidepressant on ADHD with co-morbid mood or anxiety disorder. In confirmatory trials, the inclusion of subjects with ADHD and co-morbid conditions such as ODD/CD (Borderline and Antisocial Personality Disorders in adults) is acceptable, as it enables generalization of the results to the wider population. In addition, ongoing behavioural treatment, provided controlled for and stratified, is

accepted.

Further descriptive parameters, like severity (e.g. differentiated according to subtype), as well as a detailed history, e.g. of the duration of ADHD, presentation of first symptoms, degree of functional impairment and previous treatment outcome, should be recorded. Other characteristics such as male-to-female ratio, the predominant symptoms of inattention or hyperactivity/impulsivity related to age and course of disease, as well as the predominant out-patients status of patients should be reflected in the study population. Co-morbid symptoms (e.g. anxiety, depression) should be rated with proper scales. Referred to are the respective guidelines for Depression and Anxiety Disorder (CPMP/EWP/518/97; CHMP/EWP/484366/09, and CPMP/EWP/4284/02).

Information should be obtained from a reliable informant (either parent/caretaker or teacher), but also from the respective subject, i.e. child/adolescent. In addition to the diagnostic criteria, cut-off scores, based on appropriate scales, may be used to include patients with a certain degree of severity to assure sensitivity to change. In pre-pubertal children, self-report may not be a reliable method for symptom rating. Across the a ge span of school-aged children (6-18 years), observer ratings of both parents/caretakers and informants (teachers) should be used in addition to the clinician ratings. In the case of adolescents, the teacher ratings are not mandatory.

For adults, information should be obtained from the individual, and a significant other, if necessary.

4.2   Exclusion criteria

Excluded should be patients with:

- A current diagnosis of another Axis I disorder (co-morbidity), i.e. within 6 months prior to inclusion, with the exception of ODD/CD (as mentioned for confirmatory trials), albeit that ADHD should be the primary diagnosis

- Severe co-morbid symptoms such as anxiety, depression

- A primary Axis II disorder, including mental retardation (personality disorder in the case of adults, except for borderline/antisocial personality disorder in confirmatory trials)

- A current or recent history of substance abuse disorder (within 6 months of study entry)

- Newly initiated formal behavioural, cognitive or cognitive-behavioural therapy or change in frequency of sessions within the prior 3 months or during the course of the study, that are not part of the study design. Stratification according to treatment is necessary

- Ongoing relevant psychotropic co-medication indicated for ADHD. Such medication should be washed out, whereas duration of washout time should bear relevance to the mode of action of the drug

- Relevant somatic/neurological disorders that exclude participation because of the pharmacology of the study drug (e.g. epilepsy).

5.   Methods to assess efficacy

5.1   Primary efficacy endpoints

Efficacy should be assessed by rating scales. For ADHD many symptom rating scales are available[10], the most prominent being the Conner's Rating Scales, and the ADHD Symptoms Rating Scale (ADHD-SRS). The choice of rating scales should be justified from the test quality criteria (reliability, validity). The sensitivity for change should be known. Obviously, rating scales should be validated for the specific age cohorts (children/adolescents/adults). Clinician ratings (using 'observer' scales), with the help of reliable informants (parents/caretakers/teachers or patient in the case of adolescents/adults) should be taken as primary. Not only a reduction of symptoms should be assessed, but also a functional outcome should be measured (school performance/social/occupational functioning). For adults, efficacy trials should be performed separately, and not be extrapolated from data in children and adolescents. A similar trial design as in children/adolescents can be used. Symptoms may, however, present differently, and should be assessed with scales validated for this specific age group (see earlier).

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[10] www.neurotransmitter.net/adhdscales.html

Two primary endpoints should be stipulated reflecting the symptomatic and the functional domain. Since functional outcome is an outcome observed over time, there are two options to meet these requirements; *either* the primary endpoint for the short term trials should be a reduction of symptoms, supported by an improvement in global functioning, e.g. CGI, whereas the primary endpoint for the long term trials should be both a reduction of symptoms *and* an improvement in functioning, *or* the primary endpoint should be both a reduction of symptoms and an improvement in functioning in a short-term trial followed by a maintenance of effect study (see also section 6.2.2). The choice to follow either strategy will depend on the feasibility to define a functional outcome measure that allows separation from placebo and relevant responder definition after a relatively short time of treatment. Improvement should be documented as a difference between baseline and post-treatment score. In order to allow an estimate of clinical relevance the proportion of responders should be presented for both endpoints. For this, appropriate cut-off points on validated rating scales should be defined and justified. The functional outcome scales should be representative for true (psycho)social functioning, achievement, (peer) relations etc., and not merely be reflected in (sub)domains of chosen instruments. The use of the same rating scale for inclusion, efficacy and responder definition is recommended.

In advance and if necessary during the study, raters (e.g. either parents/caretakers or teachers in the case of children) should be properly trained for assessment of patients with the applied rating scales. Methods should be foreseen to assess inter-rater reliability.

5.2 Secondary efficacy endpoints

Ratings from reliable informants (either parent/caretaker, or teachers in the case of children/adolescents) should be taken as key secondary endpoint. Depending on the choice of the assessment used as primary efficacy endpoint, further, additional, assessments may be used as secondary efficacy endpoints, e.g. 'subject' rating scales (self-report) in the case of adolescents. In adults, self-report is the assessment tool of choice. A patient diary card may also be suitable in this respect.

5.3 Other supportive efficacy criteria

Exploratory measures, i.e. brain function (fMRI), electrophysiological measures (Evoked Related Potentials, ERP, and (neuro)cognitive performance are encouraged.

6. Strategy and design features of clinical trials

6.1 Early studies in man

6.1.1 Pharmacodynamics

Although there is no specific human model for ADHD, the pharmacodynamics of products can be tested relative to methylphenidate that has a fast dose-dependent effect on ADHD symptoms. This may be done e.g. in a laboratory classroom setting for children and adolescents, where time to onset and time to offset can also be captured through evaluation of symptoms by teachers and observers with proper scales. For adults, comparable test situations are not available. Any development in this respect is encouraged, if considered helpful by the investigator. Beyond PD in humans, there are several animal models that can serve as a pharmacological model for ADHD[11,12].

6.1.2 Pharmacokinetics/interactions

The usual pharmacokinetic studies should be performed (see note for guidance on pharmacokinetic studies in man). Pharmacokinetic studies may start with adults for safety reasons, i.e. first experience. Yet, the pharmacokinetic profile of the drug should be investigated for each age cohort separately. The principle of sparse sampling and modelling techniques should be applied where possible.

The note for guidance on drug interactions should be followed to investigate possible pharmacokinetic and pharmacodynamic interactions. Special interest should be taken in interactions with stimulant medication, as well as with alcohol and other CNS active products that are relevant from a safety perspective.

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[11] Kostrewa RM, Kostrewa JP et al. 2008. Pharmacological models of ADHD. J Neural Transm 115 (2) 287-98.

[12] Rusell VA. 2007. Reprint of 'Neurobiology of animal models of attention-deficit hyperactivity disorder'. J Neurosci Methods 166 (2): I-IV.

6.1.3 Dose response studies

As far as possible the lower end of the clinically effective dose range and the optimal dose should be determined in one or more dose-finding studies, usually with a randomised, controlled, parallel-group, fixed-dose design, evaluating at least 3 separate dose levels. It is generally recommended to include placebo. The use of an additional active comparator arm may be considered. In cases where the PK characteristics are similar across all age cohorts, dose response studies may be performed in a combined pediatric population (6-18 years). Yet, it should be explored whether PK/PD is similar in the different age cohorts. The treatment duration in dose-finding studies may vary depending on the expected mode of action of the investigational product (i.e. fast or slow onset) and the active comparator. Treatment duration of 4 weeks on stable medication may be sufficient to inform the evaluation of dose response in subjects with ADHD

6.2   Therapeutic confirmatory studies

6.2.1 Short-term trials

For confirmatory trials randomised, double-blind, parallel-group studies are necessary. In general three-arm-studies including placebo and active comparator are required. The duration of the studies should be at least 6 weeks on stable dose, dependent on the mode of action of the drug. The trial duration may need to be extended to, e.g. 8-12 weeks on stable dose, in the case the strategy of short-term efficacy is followed by the demonstration of maintenance of effect through a randomised withdrawal design. (see 6.2.2). Separate studies are needed in children and adolescents, or at least those groups should be studied in a single trial that is powered to allow for analyses in the different age groups. Diagnostic instruments should be adjusted likewise.

- ### Choice of control group

As stated above the test product should be compared with both placebo and an active comparator, using a three- or multi-arm design. Three-arm studies are highly recommended for internal validation of the trial. The aim of the study may be superiority over placebo or active comparator, non-inferiority against active comparator, or at least demonstration of a similar balance between benefit and risk of the test product in comparison to an acknowledged standard agent. In the case separate studies are performed in children and adolescents, it is recommended that the three-arm design is at least applied in the age cohort where the lowest sensitivity to treatment is expected.

- ### Run-in period/wash-out period

When patients are already treated with a psychoactive compound with impact on ADHD, a wash-out period is necessary. Generally a placebo run-in period to exclude placebo responders is not useful as it may impair generalisation of the results[13]. Any reason to exclude placebo responders should be discussed.

- ### Methodological considerations

It is important to demonstrate that the effect of the medicinal product is specific for ADHD and is not due to secondary therapeutic effects on psychiatric co-morbid conditions (see 4.1). Sample size should be calculated based on a treatment effect that is clinically relevant. For details on the statistical analysis refer to the statistical guideline (ICH 9) as well as the Points to Consider document concerning missing data (CPMP/EWP/1776/99).

Efficacy should be demonstrated on ADHD in general. Analysis of effects on subtypes may be secondary. Whether this may lead to specific claims depends on the acknowledgement of the subtypes as separate entities, and progress in scientific insight in this field. In the latter case the development of specific assessment scales for the different subtypes may be needed. A separate claim in adults can be obtained either after, or in parallel with a claim in children.

6.2.2 Long-term trials

Because of the chronic course of ADHD, in addition to the short-term trials demonstration of long-term efficacy has to be established in at least one well-designed study. A 6 month-, double-blind, placebo-

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[13] Senn, S.1997. Are placebo run ins justified? BMJ 314: 1191

controlled study is recommended to meet both the symptomatic and functional endpoint (see earlier). However, if both endpoints can be met during short-term treatment, e.g. 8-12 weeks, the randomised withdrawal design can be used to demonstrate maintenance of effect. In the latter case patients are treated open-label for a sufficient period of time to meet both endpoints, whereafter responders are randomised to continue treatment or receive placebo for at least 6 months in a follow-up. A responder definition for both endpoints is needed, and relapse should be defined likewise. Time to relapse of symptoms and function are considered the principal outcome.

6.3 Studies in special populations

6.3.1 Elderly

Since there is no experience with the elderly, the age of inclusion is in principle unlimited in adults. Yet, it may be felt that the elderly could be a target population. In this case, the benefit/risk may be different, and special attention should be paid to the dosing and related safety of CNS active drugs in this population. The diagnosis should be similar to the diagnosis in adults. There are no data available with regard to the presence of co-morbid conditions. Although efficacy/safety may be worth exploring, this is not encouraged.

6.3.2 Pre-school children

Similarly, there is little experience with pre-school children (younger than 6 years of age). However, it is generally accepted that ADHD can be diagnosed in children from the age of 4 years, and pharmacotherapy may be worth exploring. Adjusted assessment tools are needed. Alternative strategies for dose finding may be necessary in the young age group. Mere extrapolation of pharmacokinetic data from older children may not be sufficient, and may depend on the nature of the product.

The benefit/risk may also be different considering the safety of psychotropic drugs on brain development and maturity, as well as the improved functioning that is the objective of the treatment.

Special care should be taken for safety assessment. A prospective cohort design for a long-term safety follow-up should be a part of the Risk Management Plan.

7. Clinical safety evaluation

7.1 General recommendation

Identified adverse events should be carefully monitored and should be characterised in relation to the duration of treatment, dose and/or plasma levels, recovery time, age and other relevant variables.

All adverse events should be fully documented with a separate analysis of adverse drug reactions, dropouts and patients who died during the trial.

Side effects that are characteristic of the class of the product being investigated should be carefully monitored. In this respect, both parents/caretakers or significant others and children should contribute to reports.

Clinical observations should be supplemented if necessary by appropriate tests (blood pressure, cardiac rhythm etc.).

Beyond the regular assessment of adverse events special attention should be paid towards effects, short- and long-term, on the developing brain (see 7.3) and bodily functions (see 7.2.5).

7.2 Specific adverse events

7.2.1 Rebound/withdrawal/dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur. Therefore, rebound and/or withdrawal phenomena should be systematically investigated.

For new candidate compounds, patients should be followed for a suitable time to detect possible rebound and withdrawal symptoms and differentiate them from recurrence of symptoms. This should be performed both after short- and long-term exposure to the compound.

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 (CHMP/SWP/94227/2004). Based on the

results of the animal studies, in vivo studies in humans may be required (preferably in healthy adult subjects).

7.2.2 Central nervous system (CNS) adverse reactions

Depending on the class of the investigated medicinal product and the possible interactions with various receptors, effects on cognition, reaction time and/or driving, and the extent of sedation should be studied. Likewise, sleep disturbances should be assessed. Neurocognitive measures in the different age cohorts (children/adolescents/adults) should be considered as standard for the (long-term) safety assessment. Similarly it may be necessary to monitor psychiatric side effects (e.g. depression, mania, psychotic symptoms, excitability, agitation, and mood changes). In addition, the need to assess seizure potential should be justified.

Special attention should be paid to attempted and completed suicides by using a suitable suicide rating scale or review of relevant AE data. Suicidality should be prospectively assessed by using proper instruments, e.g. the C-CASA method20, or the C-SSRS, which is an existing documentation system that allows documenting according to the C-CASA categories. However, alternative approaches that may be less cumbersome can be used as well.

7.2.3 Haematological adverse reactions

Special attention should be paid to agranulocytosis, aplastic anaemia and reduction in platelet count, if relevant for the drug under investigation.

7.2.4 Cardiovascular adverse reactions

Special attention should be paid to cardiotoxicity, i.e. hypertension, arrhythmias and conduction disorders, repolarisation disorders, in particular QT interval prolongation, if the medicinal product belongs to a class associated with cardiovascular effects. The need for ECG tracing before starting stimulants should be investigated, and cardiac safety in cardiovascular-compromised patients (e.g. congenital abnormalities) should be monitored. Likewise special attention should be given to cardiotoxicity in the compromised adult population.

7.2.5 Endocrinological adverse reactions

Special attention should be paid to growth, alterations in weight, and sexual maturation. In adolescents and adults, disturbance in libido should be assessed.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (prolactin secretion, hypothalamic-pituitary-adrenal hormones (HPA) etc).

7.3 Extent of population exposure to assess clinical safety including 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 (ICH E1A).

Long-term safety trials are required in ADHD as childhood-onset disorder. Special attention should be drawn towards the effects on the developing brain (e.g. adverse cognitive effects) and body, and the susceptibility to the 'known' side effects of psychotropic drugs in children, which may be altered or enhanced. Often, enhanced or altered sensitivity is reported in children and adolescents compared to adults.[14] Advantage can be gained from safety data in young animals[15]. Long-term safety can be generated in open extension studies of short-term studies and/or by specific long-term trials. Studies should last for at least 1 year, and prospective follow-up for a longer period of time should be part of the Risk Management Plan (RMP) post-licensing. A prospective cohort design is recommended (see safety section).

Long-term follow-up of safety in children should be part of the Risk Management Plan.

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[14] Correll CU. 2008. Monitoring and management of antipsychotic related metabolic and endocrine adverse events in paediatric patients. Int Rev Psychiatry 20 (2): 195-201.

[15] Advokat C. 2007. Update on amphetamine neurotoxicity and its relevance to the treatment of ADHD. J Atten Disorder 11 (1): 8-16.