European Medicines Agency

London, 18 December 2008
Doc. Ref. EMEA/CHMP/EWP/431734/2008

COMMITTEE FOR MEDICAL PRODUCT FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

DRAFT AGREED BY EFFICACY WORKING PARTY	November 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 December 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2009

Comments should be provided using this template to EWPSecretariat@emea.europa.eu

KEYWORDS	*ADHD, children, adults, psychostimulants*

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ATTENTIONAL DEFICIT HYPERACTIVITY DISORDER (ADHD)

TABLE OF CONTENTS

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 restricted to childhood and adolescence, signs and symptoms may not be self-limiting but to 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 psychiatric disorder from this perspective, and it should be read in conjunction with other EMEA 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. 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. Within this context, cognitive treatment, neurofeedback training and dietary measures[1] can be regarded as potential, but not yet evidence based strategies.

It has long been acknowledged that the core symptoms of ADHD ameliorate with age. It has recently been recognized that symptoms 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 an otherwise healthy patient group.

1.1 Diagnosis

ADHD 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. 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 that is 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.

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 MRI (fMRI[3]) as well as electrophysiological differences, differences in cognitive

[1] Pelsser LM, Frankena K, Toorman J et al. 2008. A randomised controlled trial into the effect of food on ADHD. Eur Child and Adolesc Psychiatry, to be completed

[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

[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.

performance, and DNA polymorphisms[4] are all subject of thorough investigation, yet far from potential use as (bio)marker.

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- and Conduct Disorder, 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 specific bipolar disorder in children should not be mixed up with ADHD. The age of onset of first symptoms (< 7 years of age) 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.

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 and adults have been less investigated. In a Finish Cohort Study, the prevalence rate for ADHD in adolescents was as high as 8.5%, the majority of cases being the inattention subtype[6]. Comparable rates are reported in other studies. For adults, an average prevalence rate of 3.4% has been reported in a cross-national survey[7], 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 ratio's of 3:1 or 2:1 are mentioned[8]. 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[9,10]. 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.

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

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[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] Smalley SL, McGough JJ et al. 2007. Prevalence and psychiatric comorbidity of Attention Deficit Hyperactivity Disorder in an adolescent Finish population. J Am Acad Child and Adolesc Psychiatry 46 (12): 1575-83

[7] 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

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

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

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

product under investigation. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

3. LEGAL BASIS

This Guideline is intended to provide guidance on the evaluation of new medicinal products in attention deficit hyperactivity disorder (ADHD). It should be read in conjunction with Directive 2001/83/EC, 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),
- 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)

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, 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 psychiatrist or by a non–psychiatrist physician experienced in ADHD and co-morbid diagnoses, and who is trained in the use of structured interviews to confirm the diagnosis and exclude relevant co-morbid disorders.

The age for inclusion should cover the range from 6 to 18 years of age, and children and adolescents should be separated or stratified.

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 ODD/CD is acceptable, as it enables generalization of the results to the general population.

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.

Information should be obtained from a reliable informant (parent/caretaker/teacher). 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 age 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.

4.2 Exclusion Criteria

Excluded should be patients with:

- another Axis I disorder (co-morbidity) 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 (personality disorder in the case of adult diagnosis)
- mental retardation
- a current or recent history of substance abuse disorder (within 6 months of study entry)
- ongoing formal behavioural, cognitive or cognitive-behavioural therapy that is not part of the study design
- ongoing relevant psychotropic co-medication for ADHD (such medication should be washed out)
- 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[11], the most prominent being the Connors' 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). 'Observer' scales, assessed by clinicians 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 functioning). Beyond health related quality of life scales, appropriate goal-oriented scales should be developed in this area.

Two primary endpoints should be stipulated reflecting the symptomatic and the functional domain. 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 this, appropriate cut-off-points on validated rating scales should be defined and justified. 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. parents/caretakers and teachers) should be properly trained for assessment of patients with the applied rating scales. Methods should be foreseen in the study protocol to assess inter-rater reliability.

5.2 Secondary Efficacy Endpoints

Ratings from reliable informants (parent/caretaker, and teachers) should be taken as primary 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. global assessments, and 'subject' rating scales (self-report) in the case of adolescents (for the issue of teacher ratings, see II.I).

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.

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

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. Beyond PD in humans, there are several animal models that can serve as pharmacological model for ADHD[12,13].

6.1.2 Pharmacokinetics/Interactions

The usual pharmacokinetic studies should be performed (see note for guidance on pharmacokinetic studies in man). Pharmacokinetic studies should be performed 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 bet taken in interactions with alcohol and other CNS active products that are relevant from a safety perspective.

6.1.3 Dose Response Studies

Randomized, controlled, parallel fixed dose studies, using at least 3 dosages are needed to establish as far as possible the lower end of the clinical effective dose range as well as the optimal dose. Generally it is recommended to add a placebo arm as well as an active comparator. When taking methylphenidate as reference, the duration of trials can be short, i.e. 6 weeks on stable medication, but the duration may very dependent on the mode of action of the drug that is expected (fast or slow onset).

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. Separate studies are needed in children and adolescents, and 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.

- **Run-in Period/Wash-out Period**

When patients are already treated with a psychoactive compound with impact on ADHD, a washout period is necessary. Generally a placebo run-in period to exclude placebo responders is not useful as it may impair generalisation of the results. 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

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

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

due to secondary therapeutic effects on psychiatric co-morbid conditions. Sample size should be calculated based on an effect size that is clinically relevant. The clinical relevance of the effect (responders) should be taken into consideration. For details on the statistical analysis refer to the statistical guideline (ICH 9) as well as the Points to consider document concerning missing values.

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. In the latter case the development of specific assessment scales for the different subtypes is needed.

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. This might be done by prolonging the time of double blind or by a randomised withdrawal design. In the latter design, all patients receive active treatment. Responders to treatment are subsequently randomized to continue the investigational drug or to placebo. Patients are followed by at least 6 months for maintenance of effect.

In these studies efficacy usually is expressed as number of patients worsening (relapsing) and/or time to this event. Both efficacy criteria should be submitted. Nevertheless, in the study protocol it has to be justified whether one or both are used as primary endpoint. The analysis should carefully consider the possible biases arising from drop-outs (not because of relapse) and the statistical methods of dealing with them.

Worsening or relapse has to be defined in the protocol and should be a clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits.

For withdrawal studies, the protocol should include specific measures to prevent complications of the disease (e.g. serious worsening, discontinuations symptoms) like close monitoring and the possibility to use rescue medication or to switch deteriorating patients to appropriate treatment with reference compounds.

6.3 Studies in Special Populations

ADHD is recognized to be persistent into adulthood. Symptoms may experience a shift from inattention and hyperactivity/impulsivity into inattention and restlessness. Yet, the syndrome is considered to have had its origin in childhood. Symptoms and co-morbidity may be different, and there is no experience with elderly. Hence, the special population is limited to adults (<65 years of age), and efficacy and safety should be demonstrated in this population separately.

Similarly, there is little experience with pre-school children (< 6 years of age). Yet, pharmacotherapy may be worth exploring. Adjusted assessment tools are needed, as well as proper dosing that can not always be extrapolated from older age groups. The benefit/risk may be different considering the safety of psychotropic drugs on brain maturity and development, and the improved functioning that is the objective of treatment.

6.3.1 Adults

The diagnosis of ADHD in adults should be similar to that in children, and exerted by trained psychiatrists or comparable health care professionals. Mandatory for the diagnosis in adults is the verifiable presence of first symptoms in early childhood. Borderline- and antisocial personality disorder are often found co-morbid[14,15]. The presence of other axis I diagnoses (e.g. Major Depression) should be excluded as well as substance abuse and alcoholism. Depressive and anxiety *symptoms* should be assessed with proper scales for adults.

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[14] Kooij JJS, Boonstra AM et al. 2006. Coexistence of borderline and antisocial personality disorder, and role of childhood sexual abuse in adults with ADHD. Thesis

[15] Miller TW, Nigg JT et al. 2007. Axis I and II comorbidity in adults with ADHD. J Abnorm Psychol 116 (3): 519-28

As in children, dose finding and exploratory studies should preferably be performed in patients without co-morbidity. In confirmatory trial, a more easy position can be taken, i.e. allowing the predominant co-morbidities to enable generalization of result to target population. Efficacy trials should be performed separately in this patient group, 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 adults. Clinician ratings should be primary, whereas ratings by a significant other and/or subject ratings, i.e. self report, can be made secondary.

6.3.2 Pre-school children

The diagnosis of ADHD in the very young children < 6 years of age may be similar as in the young school aged children. However, diagnostic instruments should be validated for this age group, as well as assessment scales.

Alternative strategies for dose finding may be necessary in this young age group. In small children, often higher doses are required. Therefore, mere extrapolation of pharmacokinetic data from older children may not be sufficient, and dependent on the nature of the product.

Special care should be taken for safety assessment. A prospective Cohort design for long-term safety follow-up should be 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 and bodily functions.

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, at least one short-term and one long-term trial should incorporate a short withdrawal period to look for withdrawal symptoms. This could be done in a randomised withdrawal study where treatment is abruptly stopped in responders and patients are followed for a suitable time to detect possible rebound and withdrawal symptoms.

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. Differentiation between pre- and post pubertal status and adulthood is needed, because of ongoing brain development across the age span of 6-18 years, and the matured brain in adulthood. Based on the results of the animal studies, in vivo studies in humans may be required.

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. 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, and mood).

Suicidal ideation and behaviour should be monitored carefully. Special attention should be paid to attempted and completed suicides. The Columbia Suicide Severity Rating Scale by Posner et al[16] is currently used in many studies, but alternative scales may 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, in particular QT interval prolongation, if the medicinal product belongs to a class associated with cardiovascular effects. 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 (prolactine secretion, adrenal hormones 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 mandatory in ADHD as childhood onset disorder. Special attention should be drawn towards the effects on the developing brain and body, and the susceptibility to the 'known' side effects of psychotropic drugs in children, that may be altered or enhanced. Often, enhanced or altered sensitivity is reported in children and adolescents compared to adults.[17] Advantage can be gained from long-term safety data in young animals[18]. Long-term safety can be assessed in open extension studies after the double blind. Studies should last for at least 1 year, and prospective follow-up for a longer period of time should be pat of the Risk Management Plan (RMP) post-licensing. A prospective cohort design is recommended (see safety section).

Long-term safety trials in adults may not need follow-up in the RMP, unless safety signals emerge from the phase III trials. The assessment of dependence and abuse potential after prolonged exposure is mandatory, and interaction with other psychotropic drugs needs to be investigated

Long-term safety assessment for the different age cohorts, should be part of the Risk Management Plan.

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[16] Posner K, Oquendo MA et al. 2007. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in de FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 164 (7): 1035-43.

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

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