European Medicines Agency
Evaluation of Medicines for Human Use

London, 26 January 2006
Doc. Ref. CHMP/EWP/3635/03

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF SOCIAL ANXIETY DISORDER (SAD)

DRAFT AGREED BY THE EFFICACY WORKING PARTY	January – July 2004
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	November 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	May 2005
AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP	26 January 2006
DATE FOR COMING INTO EFFECT	1 August 2006

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF SOCIAL ANXIETY DISORDER (SAD)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Guideline is intended to provide guidance on the evaluation of new medicinal products in social anxiety disorder (SAD). 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),
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7),
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH11),
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A).

Three separate guidelines are available for obsessive compulsive disorder, general anxiety disorder and panic disorder. Those guidelines supersede the previous Note for guidance on clinical investigation of medicinal products in the treament of general anxiety disorder, panic disorder and obsessive compulsive disorder (EudraLex vol. 3C C28A).

This Guideline is intended to assist applicants during the development of medicinal products intended for the treatment of social anxiety disorder, independent of the class of product under investigation. This note is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

1. INTRODUCTION (background)

Until recently Social Anxiety Disorder (SAD) was termed “Social Phobia” and in general it was seen as an infrequent disturbance without meaningful psychosocial impairment. New epidemiological and clinical data changed this view and at present it is seen as a highly prevalent disorder associated with serious impairment, which significantly affects an individual’s quality of life. To emphasize the recent developments and findings the DSM-IV Task Force on Anxiety Disorders and leading researchers of the field recommended to use the term Social Anxiety Disorder instead of Social Phobia as it more appropriately connotes the burden, pervasiveness and impairment of this disorder.

Today SAD is seen and defined as an disorder, which involves marked, persistent, and unreasonable fear of being observed or evaluated negatively by others in social performance or interaction situations (e.g. public speaking, eating in front of others, talking to strangers, meeting people in authority, being tested, expressing disagreement) and is linked with somatic, cognitive and behavioural symptoms. The feared situations are avoided or else are endured with intense anxiety and distress. However, the longer SAD is not diagnosed and treated the more the disorder affects functioning and quality of life and due to chronicity and comorbidity leads to heavy social and economic burden.

The primary goals of psychopharmacological treatment for SAD are:

- decrease and control of anxiety related to social performances or interaction situations
- reduction of phobic avoidance of feared situations or performances.

Both psychopharmacological and psychological treatments are effective but not much is known about which approach is superior for which patient. Drug classes, which have been evaluated in SAD consist of selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclics, benzodiazepines, and beta-blockers.

Diagnosis

SAD or rather "social phobia" first appeared as a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders III (DSM-III) in 1980, and overall the diagnostic criteria remained largely consistent with those put forth in DSM-IV-TR. Main changes were the inclusion of a generalized type of SAD with DSM-III-R and the modification to include children with DSM-IV. The core feature of SAD is an excessive fear of humiliating or embarrassing oneself while being exposed to public scrutiny or to unfamiliar people, resulting in intense anxiety upon exposure to social interactions or performance situations. In addition to the occurrence of social anxiety, the DSM-IV-TR diagnostic criteria require that the frightening situations are either avoided as much as possible, leading to significant impairments in normal routine, social activities or relationships and work functioning, or create at least marked distress.

This allows distinction of SAD from "normal" forms of shyness and performance anxiety on a qualitative and quantitative basis. Because shyness is usually self-defined, it probably corresponds to a more heterogeneous group than SAD, including people that would not meet diagnostic criteria of the disorder. On the other end of the severity spectrum of SAD is avoidant personality disorder. As defined in the DSM-IV-TR diagnostic criteria of SAD and avoidant personality disorder are overlapping, and the latter is sometimes seen as a more severe form of SAD. In DSM-IV-TR it is recommended that in patients with SAD a diagnosis of avoidant personality disorder should also be considered. However, the diagnosis of avoidant personality disorders can be misleading and has not been supported by recent studies. As a result, some researchers recommend to delete avoidant personality disorder from the DSM as was done with the diagnoses of avoidant disorder of childhood or overanxious disorder in children and adolescents.

In some patients, anxiety is associated with most social situations (including both formal performance situations such as presenting a lecture, and informal social interactions such as initiating conversations, attending parties or dating) and then will be specified as "generalized" type of SAD. In others, anxiety occurs only in one or a few specific social situations, e.g. public speaking, or eating/drinking in public leading to a diagnosis of a "non-generalized" or "limited" type of SAD.

Physical symptoms of anxiety in the feared situations consist of shaky voice, clammy hands, tremor, sweating, palpitations, nausea and most commonly, blushing. Associated features of SAD commonly consist of hypersensitivity to criticism or rejection, a lack of assertiveness, and low self-esteem or feelings of weakness.

The ICD-10 diagnostic criteria are less strict, requiring the presence of a fear of social situations or fear of humiliation or avoidance in order to make the diagnosis, rather than all three.

Thus the diagnostic criteria of SAD as outlined by DSM IV-TR are clearly preferred for clinical trials.

Differential diagnosis

Social anxiety is associated with several other DSM-IV-TR disorders. Similarly, a variety of disorders other than specific phobia are linked with fear and avoidance of specific stimuli. As outlined earlier SAD should be distinguished from "normal" fear and anxiety based on the quantitative differences in level of severity and impairment. Sometimes other anxiety disorders may be misdiagnosed as SAD, e.g. panic disorder or generalized anxiety disorder. When symptoms of major depression and SAD coexist, it is essential to determine which disorder is primary and which is predominant. As has been reported, many patients with SAD develop major depression and up to thirty percent of patients with primary major depression suffer from symptoms of SAD.

Severity and Burden of Disease

Due to its early onset SAD damages the acquisition of educational and social skills at critical phases in adolescence or young adulthood. SAD is associated with diminished overall emotional health, reduced school and work performance, decreased employment and impaired social life (e.g. limited friendships, half of the patients single, divorced or separated, few recreational activities), increased use of psychotropic medication, increased suicidal thoughts, financial problems, and more help seeking from medical and mental health professionals and low ratings of life satisfaction. Therefore SAD is often associated with severe psychosocial impairment and substantial negative effect on quality of life.

Epidemiology and Comorbidity

Findings from epidemiological studies show lifetime prevalence rates of up to 6 to 8 % for SAD. Relatively convergent cross-sectional lifetime estimates of 7 to 12 % and 3 to 4 % for current (4 weeks to 12 months) prevalence have been reported from several recently published studies based on DSM-IIIR- or -IV-criteria. Recent studies revealed that the typical onset of SAD is in childhood and adolescence (mean age between 10 and 16 years) and that onset after the mid-20s is highly uncommon. Preliminary data have shown that an isolated fear of public speaking occurs later than other social fears, and that generalized SAD appears earlier than non-generalized SAD. Females are affected twice as frequently as males in the community, however, in clinical populations the gender distribution is more balanced. Other results from the Epidemiological Catchment Area Study have shown that SAD is associated with high levels of subjective distress, impaired social functioning, substance abuse and a higher rate of suicide attempts.

All major community and clinical studies have found elevated rates of comorbidity in patients with SAD. It has been shown that 50 to 80 % of clinical patients with SAD have at least one other mental disorder, the comorbidity rates are especially high for other anxiety disorders (up to 50 %, most common with other specific phobias, but also with generalized anxiety disorder, panic disorder, or obsessive compulsive disorder) and depressive disorders (up to 45 % in community samples; up to 80 % in clinical samples). Based on several retrospective and prospective epidemiological studies it was highlighted that SAD starts in childhood and adolescence and may be a trigger of a cascade of comorbidity secondary to SAD (see section 4.3.2 Children and adolescents).

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 Diagnosis and Inclusion Criteria

The disorder should be classified according to an internationally acknowledged classification system, preferable to the latest version of DSM, using the diagnostic criteria herein. The use of a severity rating scale alone is insufficient and is not equivalent to a clinical diagnosis. Diagnosis should be made by an psychiatrist or by a non–psychiatrist physician experienced in anxiety disorders and who is trained in the use of structured interviews to confirm the diagnosis and exclude relevant psychiatric comorbid disorders.

Further descriptive parameters, like severity (e.g. degree of anxiety, degree of phobic avoidance), as well as a detailed history, e.g. duration of SAD, degree of functional impairment and previous treatment outcome, should be recorded.

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.

For the dose finding and pivotal studies it is recommended to include patients with SAD without significant comorbidities. Otherwise interpretation of study results may be inconclusive, e.g. treatment effects of an antidepressant on SAD with comorbid major depression.

As the majority of SAD patients are out-patients this should be reflected in the study population.

2.2 Exclusion criteria

Excluded should be patients with:

- a current or recent history of major depression (within 6 months of study entry).
- predominant depressive symptoms (not meeting the DSM IV MDD criteria), patients should have low severity scores, e.g. <2 on item 1 of the Hamilton Depression Rating Scale
- predominant or severe symptoms of another anxiety disorder
- schizophrenia or other disorder with psychotic symptoms
- bipolar disorder
- a current or recent history of substance abuse disorders (within 6 months of study entry).
- a primary or severe Axis II disorder (personality disorders)

- formal behavioural, cognitive or cognitive-behavioural therapy (these therapies have been empirically validated and in general have been proved effective for SAD treatment. They have been shown to be more effective than no treatment, psychosocial “placebo” intervention and even some psychopharmacological interventions. Therefore, patients with ongoing specific psychotherapy for SAD should not be included in confirmatory trials.
- with ongoing relevant psychotropic co-medication for SAD (such medication should be washed out).

3. METHODS TO ASSESS EFFICACY

Results should be discussed in terms of both statistical significance and clinical relevance. When a statistically significant effect is found and it has been shown that the effect is robust with respect to the assumptions underlying the primary analysis, this effect should be addressed in terms of clinical relevance (responders, remitters), depending on the purpose of the trial. It should be noticed that the clinical relevance of the effect is a basis for the benefit/risk assessment. The sample size of the studies should take this into account.

3.1 Primary Efficacy Endpoints in confirmatory trials

Efficacy will be assessed by rating scales. The choice of rating scales should be justified from the test quality criteria (reliability, validity) and the sensitivity for change should be known. For the assessment of improvement in SAD specifically developed rating scales are necessary.

Several scales have been developed for measurement of specific symptoms according to the diagnostic criteria of SAD, which may be appropriate for use in clinical trials. Some of them are clinician-administered, e.g. the Liebowitz Social Anxiety Scale (LSAS; 4-point scale) and the Brief Social Phobia Scale (BSPS; 5-point scale). In the LSAS anxiety and avoidance for 11 social interaction and 13 performance situations is quantified, while the BSPS evaluates fear and avoidance for seven social situations and the severity of four physiological symptoms of anxiety. The LSAS has been applied in many studies on SAD and can be considered as a standard rating scale in SAD. A specialized version of the LSAS for use in children and adolescence has been developed.

Improvement of symptomatology should be documented as a difference between baseline and post-treatment score, however, in order to allow an estimate of clinical relevance the proportion of responders or remitters should be presented. For this appropriate cut-off-points on validated rating scales should be defined and justified in the protocol.

In advance and if necessary during the study investigators should be properly trained for diagnostic criteria and for assessment of patients with the applied rating scales. Methods should be foreseen in the study protocol to assess inter-rater reliability.

3.2 Secondary Efficacy Endpoints

Depending on the choice of the assessment used as primary efficacy endpoint, other assessments may be used as secondary efficacy endpoints.

In addition to the clinician-administered assessment scales several self-rating tools for SAD are available. The 45-item Social Phobia and Anxiety Inventory (SPAI; 7-point scale; 32 items for social phobia; 13 items for agoraphobia) offers information on cognitive, behavioural and physiological responses to several social situations. A more recent developed scale is the 17-item Social Phobia Inventory (SPIN; 5-point scale; 6 items severity of fear; 7 items for avoidance; 4 items somatic symptoms), which has demonstrated good psychometric characteristics.

Moreover global assessments (e.g. a score 1 and 2 on the Clinical Global Impressions Scale of Global Improvement) and changes from baseline in the Sheehan Disability Scale may be used as well.

3.3 Other supportive efficacy criteria

- Clinical Global Impressions Scale - Severity of Illness

- QoL may be used when validated for the patient population

4. STRATEGY AND DESIGN FEATURES OF CLINICAL TRIALS

4.1 Early Studies in Man

Pharmacodynamics

Etiology and pathogenesis of SAD is not known. However, during the last decade research on the etiology and pathophysiology of SAD has increased. A variety of tests have been performed in patients with SAD using several pharmacological active substances. However, none of the symptoms provoked by these anxiogenic stimuli was similar to the individual patient's typical phobic symptomatology. Tests on peripheral markers as plasma neurotransmitter or hormone levels as well as tests on autonomic reactivity showed no conclusive results.

Clinical studies using functional neuroimaging like functional magnetic resonance techniques or emission tomography have been initiated to confirm the involvement of specific brain structures in the experience of anxiety or fear, particularly the circuits of the limbic system seem to be involved. However, there is no specific model in humans for SAD.

Studies of cognition, reaction time or on sleep architecture may be informative concerning the side effect pattern of the tested product.

Pharmacokinetics/Interactions

The usual pharmacokinetic studies should be performed (see note for guidance on pharmacokinetic studies in man). Especially in dose response studies individual plasma levels should be investigated.

Moreover in general the note for guidance on drug interactions should be followed to investigate possible pharmacokinetic and pharmacodynamic interactions. Concerning the latter, interactions with alcohol and other CNS active medicinal products should be analysed.

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.

Usually the duration of these trials is between 8 and 12 weeks.

4.2 Therapeutic Confirmatory Studies

4.2.1 Short-term trials

In principle, to assess the effect of medicinal products randomised, double blind, parallel-group studies are necessary. In general three-arm-studies including placebo and active comparator are requested. The dose of the new compound as well as the dose of the active comparator has to be justified.

A duration of at least 12 weeks is recommended for these trials.

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. The choice of active comparators should be justified. They should be chosen from one of the compounds already approved in this indication. If several compounds of proven efficacy in this indication are available, the pharmacological properties of the test productcompared to the active comparator may be taken into consideration.

Though a placebo might be seen as an ethical problem in studies by some investigators, from a scientific point of view the use is necessary to show the effect of the new product unequivocally, as the effect in the placebo group may be high in patients with SAD and rather variable between studies

Run-in period/Wash-out period

When patients are already treated with a psychoactive compound with impact on SAD, a wash-out period may be necessary. Generally a placebo run-in period to exclude placebo responders is not useful and 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 SAD and is not due to secondary therapeutic effects on psychiatric comorbid conditions. Sample size should be calculated based on an effect size that is clinically relevant. It may be useful to take the clinical relevance (responders/remitters) into consideration. The statistical analysis should include various analyses, among others intention-to-treat (ITT) and per protocol. However, the ITT analysis is the primary analysis. The handling of dropouts and missing data should be prospectively planned in the study protocol. The impact on the estimated effect of different methods of handling missing values due to drop out should be evaluated. See further the statistical guideline (ICH 9) as well as the Points to consider document concerning missing values. However, it may be considered that clinical assessment of significant effects is done by inspection of the clinical relevant improvement from baseline on the primary outcome measure defined by remitters/responders.

4.2.2 Long-term trials

Because of the chronic course of SAD, in addition to the short-term trials demonstration of maintenance of effects has to be established in at least one-well-designed study. This might be done by a randomised withdrawal design. The design of the randomized withdrawal study in responders is characterised by a first phase where patients are treated (open label usually) and a second phase where predefined responders/remitters from the first phase are randomised to either placebo or to one or more active treatment arms. The duration of the open phase should be at least 2 months and may be up to 6 months. The duration of the randomised phase is usually 6 to 12 months. At the start of the randomised phase the medication may need to be tapered off to prevent withdrawal phenomena.

In such studies efficacy usually is expressed as number of patients worsening (relapsing) and/or time to this event. Both efficacy criteria are of interest and 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 be 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.

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

4.3 Studies in special populations

Elderly

In comparison to other anxiety syndromes SAD has been reported to be rare in the geriatric population and seldom arise for the first time in older people. In ICH E7 it is indicated that the efficacy and safety for the elderly can be derived from the total database, unless there are specific reasons not to do.

The extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the elderly for the pharmacodynamics of the product. Therefore not only efficacy, but defining a safe dose (range) in these patients is a main concern. Usually this should be addressed before licensing. In principle two approaches are possible. One in an analysis of the whole database, whereas the other would be to conduct specific trials in a specific patients population. The optimal design would be a placebo-controlled dose response study.

The first approach may be accepted as pivotal information for agents of known pharmacological classes, provided that sufficient elderly patients are included to allow a prospective subgroup analysis.

For new products with a new mechanism of action specific trials may be needed. In both situations pharmacokinetic studies may support the choice of the dose and should be conducted.

Children and adolescents

Usually SAD starts in childhood or adolescence and is in follow-up often comorbid with other anxiety disorders, depressive disorders, substance abuse and eating disorders. Epidemiological and patient sample studies suggest that the mean age at onset of SAD is in the early -teens to the early 20s with onsets after

age 25 relatively uncommon. Longitudinal studies concerning comorbid conditions with SAD revealed that SAD generally precedes mood, substance use and eating disorders. In a recent prospective study it was shown that the presence of SAD in adolescence was associated with a higher risk to develop a subsequent depressive disorder in adulthood. Accordingly, SAD may be a trigger for later development of other psychiatric disorders and early treatment of SAD in children and adolescents holds theoretical promise for reduction of long-term morbidity. This emphasizes the importance of clinical studies to establish the efficacy of early treatment strategies for symptomatic improvement in patients with SAD and as well as a preventive measure.

Previously, children who showed symptoms resembling SAD were categorized to diagnoses of avoidant disorder of childhood or overanxious disorder. Specifically, DSM-IV advised that SAD might be expressed differently in children than in adults and that children may not feel their reactions to social situations as being unreasonable or excessive.

Unfortunately only a few small treatment studies provided preliminary support to the efficacy of psychopharmacological approaches, nevertheless, at present the place of psychopharmacological treatment of SAD in children and adolescents remains unclear.

Trials should be conducted in children (6-12 years) and adolescents (> 12 years) separately. For both age categories studies are needed, as presentation of symptoms and natural course may be different. Rating scales should be specific for and validated in the age groups (e.g. Liebowitz Social Anxiety Scale for Children and Adolescents). Development of the product solely in adolescents could also be considered, but the results would not be generalisable to young children. Differences in impact of adverse effects seen in children and adolescents in comparison to adults should be considered, particularly attention should be paid to suicidal ideations and behavioural abnormalities in children and adolescents. In line with the paediatric guideline (ICH E11), trials may be conducted after a licence for adults is obtained.

Moreover, in line with the relevant guideline, effects on cognition, learning, development, growth and endocrine functions should be addressed; cognition and learning should be studied pre-licensing using recognised tests, validated for the age and patient group. Also the direct effect on endocrine functions in adolescents should be studied before licensing. Long-term effects on learning, development, growth and sexual function may be studied post-marketing, but appropriate protocols should be available when the use in children is applied for.

5. CLINICAL SAFETY EVALUATION

5.1 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. As both serotonine and dopamine seem to play a role in the pathophysiological process of the disease, possible side effects related to these neurotransmitter systems should be investigated, preferably using specific scales (e.g. serotoninergic syndrome, extrapyramidal symptoms). Interactions with other neurotransmitter systems (e.g. noradrenergic, cholinergic and histaminergic receptors) should also be monitored.

Clinical observations should be supplemented if necessary by appropriate tests.

Specific monitoring is needed in children/adolescents and the elderly (see sections 4.3.1 Elderly and 4.3.2 Children and adolescents).

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self poisoning should be provided.

5.2 Specific adverse events

Rebound/ withdrawal/dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur.

Rebound and/or withdrawal phenomena should be investigated. Short term and long-term study designs should contain at least one visit after treatment discontinuation in order to assess the occurrence of withdrawal and rebound symptoms.

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. The chronic nature of SAD increases the risk of dependence. Based on the results of the animal studies, in vivo studies in humans may be required.

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. Similarly it may be necessary to monitor psychiatric side effects (e.g. depression, mania, mood).

Suicidal behaviour should be monitored carefully. Special attention should be paid to attempted and completed suicides.

Haematological adverse reactions

Special attention should be paid to agranulocytosis, 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, if the medicinal product belongs to a class associated with cardiovascular effects or in studies in which the active comparators with such profiles are used (e.g. clomipramine).

Endocrinological adverse reactions

Special attention should be paid to sexual disturbance, libido and weight gain.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (e.g. SIADH, prolactine secretion).

5.3 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).

Relevant data from other indications could be used as supportive safety information in the present indication.