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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

This Guideline is intended to provide guidance on the evaluation of new medicinal products in obsessive compulsive disorder (OCD). 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 general anxiety disorder, panic disorder and social anxiety disorder. Those guidelines supersede the previous Note for guidance on clinical investigation of medicinal products in the treatment 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 obsessive compulsive 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

Obsessive-Compulsive Disorder (OCD) is a heterogeneous, chronic and disabling disorder belonging to the anxiety disorders. According to the DSM-IV definition the essential features of OCD are recurrent obsessions and/or compulsions (criterion A) that are severe and time consuming (more than one hour a day) or cause marked distress or significantly interfere with the person's normal routine, occupational functioning, usual social activities or relationships (criterion C). At some point during the course of the disorder, the person has recognised that the obsessions or compulsions are excessive or unreasonable (criterion B).

Obsessions are defined as recurrent and persistent thoughts, impulses or images that are experienced as intrusive and inappropriate and cause marked anxiety or distress. The thoughts, impulses or images are not simply excessive worries about real-life problems, they are recognised by the patient as a product of his own mind (e.g. fear for contamination, symmetry obsession). The person attempts to ignore, suppress or neutralise the obsessions with some other thoughts or actions.

Compulsions are defined as repetitive behaviours (e.g. hand washing, ordering, hoarding, checking) or mental acts (e.g. praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession or according to rules that must be applied rigidly.

1.1 Epidemiology

The course of OCD tends to be chronic, with few remissions. Lifetime prevalence varies from 2 to 4 %. OCD can have its onset in adolescence or early adulthood; however, one third to one half of the patients develop the disorder during childhood. The OCD female/male ratio in adults (0.8 to 3.8) shows an equal representation or a clear predominance in females.

There is some controversy in the literature whether childhood-onset OCD should be considered as a distinct disorder. In contrast to samples in the adult population, early-onset OCD seems to have a male preponderance and to be more commonly characterised by the presence of tics, Tourette syndrome and/or by a family history of OCD. Some authors have also found that childhood onset OCD has a different drug response.

In epidemiological studies, lifetime co-morbidity rates of other psychiatric diseases in patients with OCD range from 75 to 84%. The most frequently associated psychiatric disorders are major depressive disorder, other anxiety disorders (generalised anxiety disorder, social anxiety disorder, panic disorder), substance abuse and eating disorders (anorexia and bulimia).

1.2 Established treatment

In the early 80's OCD was considered as a treatment-refractory disease. It has since been hypothesised that serotonine and dopamine play a role in the pathogenesis of the disorder. It was discovered that SSRI's (Selective Serotonine Reuptake Inhibitors) and clomipramine could be efficacious in 40 to 60% of OCD patients, with a placebo response varying between 5 and 20 %. However, the response to these products is often partial and their long-term efficacy has not been shown unequivocally. In some cases, antipsychotics have shown some effect.

Therefore, there is a clear need for new therapeutic options in OCD.

It should be stressed that OCD is a chronic disorder associated with other psychiatric disorders. Moreover symptoms often fluctuate in severity and intensity, increasing during stress and times of depressed mood.

This guideline deals only with OCD, not with OCD-related disorders.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 Diagnosis and inclusion criteria

It is important that the diagnosis of OCD is based on an internationally acknowledged classification system, preferably using the DSM-IV-TR (or the latest DSM version) and the criteria therein. Other classification systems (e.g. ICD 10) could be used, but should be justified. Diagnosis should be made by a qualified psychiatrist and should be confirmed by the use of a structured diagnostic interview (e.g. SCID).

The use of a severity rating scale alone is insufficient and is not equivalent to a diagnosis.

In addition severity should be documented using a validated scale (e.g. Y-BOCS, NIMH-OC). The inclusion criteria may be based on a justified cut-off score.

2.2 Exclusion criteria

Patients should be screened for psychiatric co-morbidity. It is important to demonstrate that the effect of the agent is specific for OCD and is not due to secondary therapeutic effects on co-morbid conditions.

In order to study the efficacy of new medicinal products in a relatively "pure" OCD population, patients with the following psychiatric disorders should be excluded:

- Current or prior history of psychotic illness (schizophrenia, delusions, etc)
- Bipolar disorder
- Borderline personality disorder
- Social anxiety disorder
- Current or recent history of eating disorders (within the last 6 months)
- Current or recent history of alcohol or substance abuse (within the last 6 months)

Current or recent major depressive episode (within the last 6 months) should preferably be excluded. When the medicinal product under investigation has antidepressant properties, current or recent depressive episode (within the last 6 months) must be excluded.

Other co-morbid psychiatric disorders should be documented and described (including severity assessments).

Concomitant psychotropic treatment should be washed out.

2.3 Baseline characteristics

The following descriptive parameters should be documented:

- Age of onset
- Duration and severity of the disease
- Presence of co-morbid tics (tic disorder, Gilles de la Tourette syndrome)
- Family history of OCD and OCD-related disorders (e.g. tic disorder or Tourette)
- Type of obsessions
- Presence of compulsions
- Degree of functional impairment
- Previous treatment outcome

Even in the absence of major depression, depressive symptoms have to be documented using a validated scale. Special attention is also required towards any anxious symptoms.

This is especially important when the medicinal product that is evaluated has established antidepressant and/or anxiolytic properties.

3. METHODS TO ASSESS EFFICACY

3.1 Definition of the primary endpoints

The choice of the scales and outcome measures and the method of analysis need to be specified in advance. The recommended primary efficacy measure is the change of scores from baseline on the pivotal scale. The choice of the pivotal scale should be justified and its reliability, validity and sensitivity for change should be known. Currently acceptable scales to determine symptomatic improvement in OCD include the Y-BOCS and the NIMH-OC. The Y-BOCS is preferable as the primary endpoint. In advance and if necessary during the study,

investigators should be trained to become and stay interreliable.

Improvement of symptoms should be documented as a difference between baseline and post-treatment score, but should also be expressed as the proportion of responders and /or the proportion of patients in remission.

Responders are defined as patients with a clinically relevant reduction from baseline on the primary outcome scale. The definition of a responder should be justified in relation with its clinical relevance.

Remission is defined as a condition where no or few symptoms of the illness remain. The definition of remission should also be operationally defined and justified in relation with its clinical relevance.

3.2 Definition of the secondary parameters

When the Y-BOCS is used as the primary endpoint, the NIMH-OC can be used as a secondary endpoint.

Because OCD significantly impacts on global social functioning (relationships, work, etc.), it may be useful to measure social and occupational function on a global scale that is independent of the disorder-specific scales. This may provide additional information on the clinical relevance of the treatment. The scales to be used should be validated and the choice should be motivated. Examples of global scales are the Global Clinical Impression Scale (investigator rating scale) and the Sheehan disability scale (self rating scale). A scale for measuring Quality of Life can be used, when validated in the target population.

4. STRATEGY AND DESIGN OF CLINICAL TRIALS

4.1 Pharmacodynamics

A variety of tests can be performed to assess the main and/or secondary pharmacological effects of the medicinal products, as well as their side effects, but the results of these tests will only be indicative since there is no specific model for OCD in humans. Examples of tests that could be useful in the evaluation of medicinal products for the treatment of OCD are cognition and reaction time tests, as they bear on occupational and mental functioning.

4.2 Pharmacokinetics

The usual pharmacokinetic studies should be performed in line with the guidelines on pharmacokinetic studies in man. Especially in dose response studies, plasma levels are informative. Interactions with alcohol and other CNS medicinal products should be investigated.

4.3 Dose response studies

Dose-ranging studies should be preferably performed in a controlled, parallel fixed-dose design, using at least three dosages, to establish the lowest effective dose as well as the optimal dose. When justified, an alternative method of generating adequate dose range studies can be used.

4.4 Therapeutic confirmatory studies

4.4.1 Short term trials

To assess the effect and the safety of a medicinal product in OCD, the conventional parallel group, double blind randomised placebo-controlled trial is recommended. As for other disorders, there could be ethical concerns to treat OCD patients with placebo, especially due to the comparatively long duration of the short-term trials (see below) and the availability of effective treatment in this disorder. However, in the case of OCD, a placebo-controlled trial

seems acceptable due to the lack of evidence that OCD is a progressive disease and considering the low efficacy of established treatments. Moreover some of previous trials on OCD failed to demonstrate superiority of the investigated medicine compared to placebo.

In therapeutic confirmatory studies, it is preferable to use a three-armed, placebo-controlled parallel group design. The choice and dose of the comparator should be justified on the basis of placebo-controlled evidence of efficacy of the comparator.

A placebo run-in period is not advisable, as this might impair generalisation of the study results.

In previous trials on OCD, response to treatment was delayed. For SSRI's and clomipramine, a significant response was only seen around week 8 of treatment. This implies that the duration of short-term trials should be at least 8 weeks and preferably 10 to 14 weeks in order to demonstrate efficacy in an unambiguous way. It is important to note that this duration does not include the titration period.

4.4.2 Long-term trials

Because of the chronic course of OCD, it is necessary to demonstrate long-term efficacy in at least one well-designed study. This might be done by a randomised withdrawal study during extension phases after re-randomisation of responders, when efficacy results are expressed as the number of patients worsening and/or time to this event. Using this design it is important to define relapse as a clinically meaningful deterioration measured on a standard severity scale. In long-term studies on OCD, dropout rates could be high and could lead to a bias. Therefore dropouts should be well documented. The minimal duration of the maintenance treatment in OCD should be six months.

4.4.3 Methodological considerations

It is important to demonstrate that the effect of the agent is specific for OCD and not due to secondary therapeutic effects on psychiatric co-morbid conditions.

Since the primary outcome measure is based on a change from baseline severity, the severity of the disease should be included as a covariate in the primary analyses (see PtC on baseline covariates).

Statistical analysis should be intention-to-treat and per protocol analyses. For superiority trials the ITT analysis is the primary analysis. The handling of dropouts and missing data should be prospectively planned. The reasons for dropouts should be well documented. The impact on the estimated effect of different methods of handling missing data due to dropouts should be evaluated. (See NfG on statistical principles and PtC on missing data.)

Sample size should be calculated based on the effect size that is clinically relevant.

Any kind of external non-medical support or counselling should be prospectively defined in the protocol and should remain constant during the study. Formal psychotherapy with proven efficacy on OCD (e.g. cognitive behavioural therapy) should be excluded.

4.5 Studies in special populations

4.5.1 Studies in children and adolescents

OCD can be characterised starting from the age of 6 years. OCD in children differs from OCD in adults: the obsessions are different, the compulsive symptoms are more pronounced and children may not recognise symptoms as a problem.

Therefore, separate trials for obsessive-compulsive disorder (OCD) in children and adolescents are necessary.

Obsessive-compulsive symptoms (OCS) are often seen in developmentally delayed children

and adolescents. In this patient population, specific trials are needed to demonstrate efficacy in this particular situation.

Studies in children and adolescents with OCD should be supported by adequate pharmacokinetic and dose response studies.

Diagnosis should be made by a well-trained child psychiatrist because of the complexity of diagnosing OCD in children and adolescents (progression and co-morbidity). Diagnosis should be based on the diagnostic criteria of the DSM-IV TR (or the latest version).

The CY-BOCS should be preferably used for defining the primary endpoint. General scales (e.g.; CGI, Children's Global Assessment Scale) should be used as secondary endpoints.

Main co-morbidities in children are Gilles de la Tourette syndrome, ADHD (Attention-Deficit/Hyperactivity Disorder) and developmental disorders. Co-morbid depression and other anxiety disorders are frequent in adolescents. These co-morbid disorders should preferably be excluded.

The duration of short-term efficacy trials in children should take into account the possibility of a late response.

Once maintenance of efficacy has been demonstrated for adults, long-term efficacy studies are optional in children and adolescents.

For methodological reasons, it would be preferable to exclude psychotherapy during the studies. However, it is ethically difficult to do so. Therefore the use of psychotherapy should be monitored and remain constant during the trial.

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

Children and adolescents are particularly likely to experience "behavioural" symptoms and psychiatric adverse events. Therefore, irritability, hostility, agitation and suicide-related events (e.g. suicidal ideation, self-harm and suicide attempt) should be closely monitored during the course of the trial.

4.5.2 Studies in the elderly

The available data indicate that treatment efficacy is similar in the elderly and in adults below the age of 60. In ICH E7 it is indicated that the efficacy and safety for elderly can be derived from the total database, unless there are specific reasons not to do.

Nevertheless, the extrapolation of the adult dose to the elderly may be difficult due to the pharmacokinetic properties of the product and/or to a different sensitivity of the elderly for the pharmacodynamics of the product. Therefore defining a safe dose range in these patients may be necessary.

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.

Adverse reactions 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 *4.5.1 Children* and *4.5.2 Elderly)*.

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

5.2 Specific adverse events

5.2.1 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 OCD increases the risk of dependence. Based on the results of the animal studies, in vivo studies in humans may be required.

5.2.2 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. 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.

5.2.3 Haematological adverse reactions

Special attention should be paid to agranulocytosis, aplastic anaemia and reduction in platelet count.

5.2.4 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).

5.2.5 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.