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Guideline on clinical investigation of medicinal products in the treatment of depression

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This guideline replaces 'Note for Guidance on clinical investigation of medicinal products in the treatment of Depression' (CPMP/EWP/518/97, Rev. 1).

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List of abbreviations

AEs: Adverse Events

CHMP: Committee for Medicinal Products for Human Use

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

ECG: Electrocardiogram

EMA: European Medicines Agency

EPS: Extrapyramidal symptoms

GABA: Gamma-Aminobutyric acid

GAD: Generalised Anxiety Disorder

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision

ICH: International Conference on Harmonisation

MDD: Major Depressive Disorder

NMS: Neuroleptic Malignant Syndrome

SSRI: Selective serotonin reuptake inhibitors

STAR*D: Sequenced Treatment Alternatives to Relieve Depression

TRD: Treatment Resistant Depression

Executive summary

The present document should be considered as general guidance on the development of medicinal products for acute and long-term treatment of Major Depressive Disorder (MDD). Its main focus is on major depressive episodes that occur in the context of MDD. Despite many approved antidepressants there is still a need for new medicinal products with better efficacy (e.g. faster onset of action, higher rates of response and remission) and improved safety profile in patients with MDD.

The main requirements for the development of medicinal products for the treatment of major depression are reviewed and reconfirmed based on experience with recent clinical development programs. The typical design to demonstrate efficacy and safety of an antidepressant remains a randomized, double-blind, placebo controlled, parallel group study comparing change in the primary endpoint. Inclusion of a well-accepted standard as an active control is strongly recommended. The results must be robust and clinically meaningful. This requires besides statistically significant results the incorporation of responder/remitter analyses to adequately assess clinical relevance. It has to be shown that initial response to treatment is maintained in at least one study following a randomized withdrawal design or an extension study for 6 months.

The update clarifies the requirements in clinical trials for children and adolescents as well as in older people. Special issues in patient populations with treatment resistance or partial response are also addressed. In general the study design in these patient populations will be similar, however, several options are possible and outlined as monotherapy with an antidepressant medicinal product, or add-on or augmentation therapy to a baseline antidepressant therapy.

The need to monitor the degree of suicidal thoughts and behaviour and their change (improvement or worsening) with antidepressant therapy by use of validated instruments is confirmed.

This document should be read in conjunction with other relevant EMA and ICH guidelines.

1. Introduction

1.1. Major Depressive Disorder (MDD)

MDD is one of the most common psychiatric disorders, which is the fourth leading cause of global disease burden and affects about 15 % of the general population. MDD is not a benign disorder, it is associated with substantial psychosocial dysfunction and high individual mental strain as well as with excess morbidity and mortality - the risk of suicide is considerable. Depressive disorders are classified in various classification systems, e.g., currently DSM IV-TR and ICD-10. Both classifications are built principally on severity, features of the current episode, patterns of disease expression over time, as well as persistence and recurrence.

The detection of MDD requires the presence of mood disturbance or loss of interest and pleasure in activities accompanied by at least two (ICD-10) or four other symptoms of depression (DSM IV-TR). These core symptoms may vary from patient to patient, however, they are typically seen for much of the day, almost always every day for at least two weeks and are associated with relevant psychological distress and considerable impairment of psychosocial and work functioning.

Notwithstanding the availability of many compounds with established efficacy and safety there is a high need for new antidepressants. It has been shown that many patients without adequate treatment suffer from a tendency of higher frequency of major depressive episodes together with an increased severity. Therefore pharmaceutical companies are encouraged to foster development of new antidepressants and not only focus on the treatment of acute symptoms and maintenance of the effect during the index episode, but explore also the potential of their compounds in the prevention of new episodes called recurrence prevention. So pharmaceutical companies should not only restrict their development to a claim of acute treatment of major depressive episodes, but should also provide clinical trial data for an additional claim of recurrence prevention. However, prevention of a new episode is not mandatory part of a registration package for treatment of episodes of MDD, but is considered as an additional claim.

1.2. Major Depressive Disorder (MDD) in the paediatric population

For preschool children the condition is very rare (point prevalence is thought to be 0.5%), in adolescents the prevalence is estimated to be approximately 3%. Signs and symptoms of MDD are similar to the adult population; however differential diagnosis in this population is difficult particularly with dysthymic disorder or bipolar disorder. As already mentioned further studies on efficacy and safety of antidepressants in children and adolescents are necessary.

1.3. Partial response and Treatment Resistance

Despite the many treatment options currently available for MDD, a relevant proportion of patients up to one third do not adequately respond to treatment and up to 20% are considered non-responders, even if there is good compliance and the treatment has been taken long enough with an adequate dosage. So there is a clear need for patients, in whom even "state of the art"-antidepressant therapy fails to elicit a sufficient treatment response. Though, despite the clinical picture of treatment resistant depression (TRD) is common in everyday practice, the conceptual elaboration and definition of clear criteria for incomplete response and TRD is still limited. As no specific treatments have been approved for this condition, in clinical practice treatment algorithms have been established for TRD including re-evaluation of the initial diagnosis and, when no correctable cause for TRD is found, optimization of the initial regimen using switching to other antidepressants, augmentation strategies (e.g. combination therapy, lithium and other mood stabilizers, thyroid hormones, atypical antipsychotics, etc.) or even monotherapy with second generation antipsychotics has been considered within the psychopharmacologic options. In many clinical treatment guidelines electroconvulsive therapy is an option for patients suffering from severe TRD.

In a clinical pragmatic view a patient has been considered suffering from TRD when consecutive treatment with two products of different pharmacological classes, used for a sufficient length of time at an adequate dose, fail to induce a clinically meaningful effect (inadequate response). This approach assumes, that inadequate response to two compounds with distinct mechanism of action (e.g. one SSRI and one SNRI) is more difficult to treat than inadequate response to two compounds with the same mechanism of action (e.g. two SSRI's); moreover it assumes that switch of treatment within one class is less effective than switch to a different pharmacologic class. However, this has not been

verified by data from publications and has been recently questioned by the results of the STAR*D program sponsored by the NIMH.

Notwithstanding that no validated clinical criteria and thresholds to define TRD and partial response at present are available, generation of such data would be highly supported. For the purpose of this guideline TRD is considered, when treatment with at least two different antidepressant agents (of the same or a different class) prescribed in adequate dosages for adequate duration and adequate affirmation of treatment adherence showed lack of clinically meaningful improvement in the regulatory setting.

2. Scope

This guideline focuses on antidepressant products developed specifically for major depressive disorder. Recent experience with approval procedures and scientific advices at EMA as well as new results in basic science and clinical guidelines reflecting current medical practice have been taken into consideration with the revision of the guidance document. The need for placebo control and active control is outlined, efficacy and safety issues regarding special populations like children and adolescents, young adults and older people have been addressed.

During the development of this guideline DSM IV and ICD-10 are under revision. As there is a tendency to implement more dimensional aspects to the categorical approach this might have consequences for the definitions of mood disorders as given in this guideline, and may need amending likewise.

Symptoms of major depressive episodes occurring comorbid with other psychiatric disorders (Axis I of DSM IV-TR) or with somatic disorders like Parkinson's disease, Alzheimer's disease, cerebrovascular disorders, cancer and chronic pain syndromes are not in the focus of this guideline.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83 as amended and relevant CHMP Guidelines, among them:

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Note for Guidance on Dose-Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9);
- Note for Guidance on Choice of Control Group in Clinical Trials - CPMP/ICH/364/96 (ICH E10);
- Adjustment for Baseline covariate - CPMP/EWP/2863/99;
- Guideline on Missing Data in Confirmatory Clinical Trials - EMA/CPMP/EWP/1776/99 ;
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety - CPMP/ICH/375/95 (ICH E1);
- Note for Guidance on Studies in support of special populations: geriatrics - CPMP/ICH/379/99 (ICH E7) and the Questions and Answers (EMEA/CHMP/ICH/604661/2009);
- Pharmacokinetic studies in man - EudraLex vol. 3C C3A;
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data - EMEA/CHMP/313666/2005;

- Guideline on the non-clinical investigation of the dependence potential of medicinal products, EMEA/CHMP/SWP/94227/2004;
- Note for guidance on clinical investigation of medicinal products in the paediatric population - CPMP/ICH/2711/99 (ICH E11);
- Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population - EMEA/CHMP/EWP/692702/2008;
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95;
- Note for guidance on clinical investigation of medicinal products for the treatment and prevention of bipolar disorder - CPMP/EWP/567/98.

4. Specific considerations when developing products for the treatment of depression

In developing medicinal products for the treatment of MDD specific problems can be encountered. These include:

4.1. General Strategy

4.1.1. Use of placebo

Clinical studies should provide unambiguous evidence of the antidepressant activity and of the effective dose or dose range. In depression comparisons between a test medicinal product and reference substances are difficult to interpret since there is a high and variable placebo response in depression. Actually in about one-third to two-third of the trials, in which an active control is used as a third arm, the effect of the active control could not be distinguished from that of placebo. As the effect rate in a specific trial is thus uncertain, a non-inferiority margin cannot be determined and a non-inferiority trial is not an option, as the sole basis for demonstrating efficacy.

Therefore, from a scientific point of view, randomised double blind comparisons versus placebo are needed, to permit adequate evaluation of efficacy, though showing superiority over an active comparator would be an acceptable alternative. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions of the medicinal product.

Ethically, however, the use of a placebo is a controversial issue, especially when performing studies during acute episodes and/or in out-patients. On the other hand it would be detrimental to public health and ethically unacceptable to grant a license to a medicinal product to be used in major depression without providing unambiguous evidence of efficacy.

Precautions to minimise the impact of the study should be taken however, e.g., by limiting the duration of the study - generally a duration of about 6 weeks should be sufficient and a longer duration should be justified – and by using a fail-safe provision whereby a serious deterioration of the patient's condition will allow withdrawal from the trial and standard therapy to be given under open conditions.

Three-arm trials including both a placebo and an active control are recommended.

4.1.2. Investigation of relapse and recurrence

Depressive symptoms are occurring in a heterogeneous group of patients and there is a large variance in the natural course of MDD. In the literature a distinction is made between treatment in the acute

phase, the continuation phase and if required the maintenance phase. The purpose of the latter is to prevent new episodes (recurrence prevention), whereas the continuation phase is meant to prevent deterioration during the index episode (maintaining the initial anti-depressive effect). The duration of the continuation phase is usually set at about 6 months, to correspond with the average duration of an episode of depression. In any individual however it should be noted that the duration of an episode varies considerably and may be more (or less) than 6 months. As this might affect the interpretation of the results, the 6 months cut-off point is not used for regulatory purposes. Instead, the guideline focuses on showing effect during the index episode and/or prevention of the next episode.

For authorisation it should be shown that a short-term effect can be maintained during the index episode. For this a randomised withdrawal study, allowing to study relapse prevention is probably the best design. In this design, responders to treatment with the test product of sufficient duration are (re-) randomised to test product or placebo. In the first period, the test product is usually given open, uncontrolled. The duration of either treatment phase is hugely variable in the literature. It will depend among others on the type of patients included and on the time of inclusion. The optimal duration is not known at the moment, but a duration of e.g., 8 to 12 weeks for the first period appears acceptable, whereas the period after (re-) randomisation usually has a duration of 6 months. For such study, the protocol must include specific measures to prevent complication of the disease (especially risk of suicide), like close monitoring and the possibility to use rescue medication or to switch deteriorating patients to appropriate treatment. Special attention is needed to distinguish relapse from withdrawal symptoms, when medication is stopped or tapered off in such a study.

Generally a solely placebo-controlled extension study is not recommended, as there is a risk, that the results will be ambiguous with regard to the question of maintenance of effect. However, in particular cases (e.g. special mechanism of action, populations with very low relapse rate, etc.) this might be an alternative approach to the randomised withdrawal study, but should be justified by the applicant. It is recommended to ask for scientific advice before such an alternative study design is implemented.

Prevention of the next episode(s) or recurrence prevention is not a mandatory part of a registration package for treatment of MDD episodes. When a claim is made, specific studies are needed. Patients in full remission should be randomized to active treatment or placebo. Study duration will be dependent on the frequency of episodes in the study population and should be justified accordingly. Recurrence should be prespecified as a depressive episode that fulfils current DSM criteria and a certain degree of severity on a validated rating scale. In non-bipolar patients, definitive comparisons of the test substance should be performed versus a placebo. For prevention in bipolar patients, the relevant guideline should be consulted.

For a given patient, the duration of treatment depends on the rate of his/her recurrences. Patients with a history of higher frequency depressive episodes should be included and the recent recurrence rate should be taken into account when planning duration and power of the study.

4.1.3. Extrapolations

As is indicated in the introduction, patients included in the trials will be diagnosed as having MDD using accepted diagnostic criteria, e.g., DSM IV. However, depressive symptoms are also seen in other psychiatric disorders or other types of depression. If such specific claims are strived for additional studies to the classical development program for major depression should be provided.

The frequent co-occurrence of depressive and anxious symptoms in MDD requires a specific approach. The issue is twofold: anxiety symptoms may be a part of MDD or due to a co-morbid disorder like Generalised Anxiety Disorder (GAD). In the first situation the anxiety symptoms are seen as secondary

to depression and therefore they will clear with the improvement of the depression. In this case the effect is therefore a part of the antidepressant effect and no additional claim can be granted.

Episodes of MDD can be further classified as mild, moderate and severe. Clinical trials will usually recruit patients, who are moderately ill, as it is difficult to demonstrate an effect in mildly ill patients. Demonstration of an acceptable benefit/risk in moderately ill patients will be considered sufficient for a registration package to get a general license for "Treatment of Episodes of Major Depression" in the context of MDD.

As mentioned in the introduction a major depressive episode may also occur in the framework of a Bipolar Disorder. In general the development of a product in this patient group will be the same as for unipolar depression. However, there are some specific issues, like switching rates, which are addressed in the guideline on bipolar disorder.

4.2. Assessment of Therapeutic Efficacy

Results should be discussed in terms of both clinical relevance and statistical significance. When a statistically significant effect is found and it has been shown that the effect is robust and insensitive to the analysis used, this effect has to be addressed in clinical terms (e.g. rates of responders and remitters), depending on the purpose of the trial. It should be noticed that the relevance of the effect is the primary basis for the benefit/risk assessment. Due to the unreliability of studies in MDD at least 2 pivotal studies are required, however, the whole data package of a development program (e.g. high rate of failed or negative trials in this indication) will be taken into consideration for final benefit-risk assessment. An adequately weighted meta-analysis of efficacy across all clinical studies may improve the precision of the estimates of clinical efficacy. However, the statistical methods to be used and the clinical studies to be included should be agreed to with the regulatory agency, as these may influence the results.

4.2.1. Short-term trials

Confirmatory trials should be double-blind, randomised and parallel group trials. Dosages used should be justified.

The dossier should include parallel group studies against placebo and active comparator (generally accepted standard treatment). Three-arm or multi-arm studies are strongly recommended for pivotal studies in phase III of development, as the trials will be internally validated and the problem of assay sensitivity can be addressed. The aim of the program should be superiority over placebo or active comparator or demonstration of at least a similar balance between benefit and risk of the test product in comparison with an acknowledged standard antidepressant agent (when both are superior over placebo).

The duration of these trials usually is around 6 weeks (at least 4 weeks have been needed to clearly separate active treatment from placebo, in some programs 8 weeks have been studied). Improvement should be documented as the difference between baseline and post-treatment score in signs and/or symptoms, but should also be expressed as the proportion of responders. In MDD a 50% improvement of a patient on a usual rating scale is accepted as a clinically relevant response. Other definitions of responder may be used, e.g. other grades of response or proportion of patients with full remission. Criteria for response and remission must be pre-specified and justified in the study protocol.

4.2.2. Long-term trials

Due to the character of the disorder, longer double blind trials are necessary to demonstrate that the acute effect is maintained during an episode. Studies demonstrating prevention of a new episode are not required for licensing, though of major interest (see also section 4.1.2.).

In randomised withdrawal trials, efficacy usually is expressed as rate of patients worsening (relapsing) and/or time to this event. Both efficacy criteria are of interest and should be submitted. The choice of one of them as primary and the relevance in clinical terms will depend on the type of patients included and the purpose of the trial and have to be justified in the protocol. The analysis should carefully consider the possible biases arising from drop-outs and the statistical methods of dealing with them.

Worsening or relapse has to be defined in the protocol. Usually a clinically relevant increase in symptoms scored on a validated rating scale is used.

4.2.3. Methods to assess efficacy

Efficacy must 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 specifically developed rating instruments are necessary.

Acceptable scales for use as primary endpoint to determine symptomatic improvement include the Hamilton Rating Scale of Depression, preferably the 17 item scale, and the Montgomery Asberg Depression Rating Scale, however other validated scales might be acceptable as well. The protocol should indicate which scale is used as primary variable.

In addition changes in global assessment (e.g. CGI of improvement of the Clinical Global Impression assessment scale) or in social functioning may be used as a key secondary endpoint as long as the assessment tools are validated.

4.2.4. Design features

4.2.4.1. Study population

The disorder should be classified according to an internationally acknowledged classification system, preferably DSM IV-TR (preferable) or ICD-10, using the diagnostic criteria herein. The same classification system should be used for the whole development of the medicinal product. A rating scale alone is insufficient and is not equivalent to a diagnosis.

Further descriptive parameters, like severity of the episode, as well as a detailed history, e.g., duration of the depression and of the index episode, number of episodes per time interval, previous treatment outcome, should also be documented.

In addition cut-off scores, based on an appropriate scale may be used as inclusion criteria.

It is highly desirable that the study population is homogenous with respect to the indication for the dose finding and pivotal studies (see also section 4.1)

Though some of the earlier studies may be done in hospitalised patients, the majority of the database should be in out-patients for better generalizability of the study results.

4.2.4.2. Study design

In principle, to assess the effect of medicinal products parallel, double blind, randomised placebo controlled trials are necessary (see also section 4.2.1). In addition, comparison with a standard product in an adequate dose is needed. The choice of dosages and the comparator should be justified.

Investigators should be properly trained in evaluating the patient. Inter-rater reliability scores (kappa) should be documented for each investigator in advance and if necessary during the study, both with regard to the diagnosis and to rating scales used for efficacy and safety, where relevant.

Prior and concomitant medication has to be documented in detail. Relevant medication has to be washed out. If appropriate, rescue medication should be provided.

If a constant anxiolytic or hypnotic medication cannot be avoided in the beginning of treatment, stratification or at least post hoc analysis may be useful to analyse this effect on the overall treatment effect.

A trial-specific, standardised psychotherapy, psycho-education, support or counselling may be given as supplementary treatment, though it may enhance the placebo effect, but it should be prospectively defined in the protocol. It should be documented in detail and its effect on treatment effect should be analysed. Potential centre effects should be evaluated carefully.

4.3. Clinical Pharmacology Studies

4.3.1. Pharmacodynamics

MDD is a psychiatric syndrome, which is associated with subtle cellular and molecular alterations in a complex neural network. Animal models can be used for screening of antidepressant medicinal products, however, direct transfer to human models is not possible. In humans with MDD brain structural and functional findings (e.g. activation studies using magnet resonance or emission tomography, electrophysiological studies, neuroendocrine circuits, etc.) as well as genomic, proteomic and metabolomic measures have been studied but are incompletely understood and therefore yet still of limited value. So a variety of tests can be performed, but there is no specific model in humans for MDD. Studies on cognition, reaction time and sleep may be helpful to characterize the safety profile of an antidepressant and should be considered based on pharmacological profile/MOA and evolving tolerability profile of the proposed product.

4.3.2. Pharmacokinetics

The usual pharmacokinetic studies should be performed (see guideline on pharmacokinetic studies in man). Especially in dose response studies individual plasma levels may be studied.

4.3.3. Interaction studies

In general the guideline on drug interactions should be followed to investigate possible pharmacokinetic interactions between the test drug and any other drug that may be prescribed simultaneously in clinical practice. Concerning the latter, interactions with alcohol and other CNS active compounds should be investigated. If relevant, pharmacokinetic studies in patients with hepatic and /or renal impairment should be performed. Reference is made to the drug interaction guideline.

4.4. Specific Claims

4.4.1. Trials to study monotherapy in treatment resistant patients

Monotherapy in patients with treatment resistant major depression (TRD) could be a separate but additional claim. This could be granted to compounds with an adequately substantiated general major depression indication. At least one additional short term trial should be performed to support extension of the indication to treatment resistant patients, no additional maintenance studies would be required. Subgroup analyses among treatment resistant patients in trials conducted in a general population with major depressive episodes are not sufficient to obtain the extended indication although they could provide supporting data.

The design of studies in TRD is essentially the same as described for other trials (see section 4.2). The key differences are the choice of control and the definition of the patient population.

Treatment resistance in major depression is defined as lack of clinically meaningful improvement despite the use of adequate doses of at least two antidepressant agents, derived from the group(s) of commonly used first line treatment, prescribed for adequate duration with adequate affirmation of treatment adherence. At least one treatment failure should be shown prospectively.

The choice of active comparator should be clearly justified. The primary objective of a trial of this design would be to demonstrate superiority to the active comparator (which is expected to have insufficient effect in this patient population as shown during the prior treatment with this compound). Demonstrating superiority to placebo in a treatment resistant patient population would not be sufficient to support an indication in TRD.

A comparison with an established standard treatment is considered generally valuable in this condition, however, currently no medicinal product has been approved for TRD. Therefore recommendations as to which active comparator should be included in the third arm cannot be issued at present. Feasibility of study protocols including electroconvulsive therapy or deep brain stimulation techniques as control arm seem to be limited.

4.4.2. Trials to study augmentation/add-on treatment

The use of a compound to augment the activity of another product is worth a specific claim leading to a separate indication statement. This must be substantiated by data demonstrating efficacy in short term and long term trials. Augmentation will be useful in case of insufficient response to monotherapy. Therefore the patient population should consist only of partial responders, patients with TRD (who show no clinically meaningful change from baseline as result of treatment) are not suitable candidates for augmentation. Based on clinical treatment algorithms these patients should be switched to an alternative monotherapy instead and therefore should be excluded from augmentation trials (see 4.4.1). As there is no established consensus on the definition and thresholds of partial responders applicants are encouraged to adjust these criteria via scientific advice before starting a program.

For an augmentation indication short term trial randomised parallel studies will be needed. Patients with partial response to standard medication are randomised to receive active augmentation treatment or placebo in addition to standard medication, which should be blinded if feasible. It is of critical importance that the applicant can establish that the population recruited to the trial are true partial responders. A run-in period alone with assessment of response to standard intervention may not be sufficient since partial response may be driven by other factors than the actual pharmacological treatment in this population. Instead, an initial randomisation to standard medication or placebo would be the best way to characterise the proportion of the population that were partial responders for reasons other than the actual pharmacological treatment. In any case criteria for inclusion should be

carefully defined to best identify "true" partial responders, and relevant data properly documented and critically appraised. Medical history and use of and response to non-pharmacological interventions may help identify the appropriate patient population.

In addition, depending on mechanism of action, inclusion of a monotherapy arm of the test product should be considered for the unambiguous interpretation of the results and estimation of clinical relevance, unless otherwise justified. Trial duration of 4-6 weeks is likely to suffice for demonstration of short term efficacy although typically substantially longer durations may be necessary according to the nature of the test treatment and patient population.

A comparison with an established treatment is generally valuable in clinical trials in patients with major depressive episodes to estimate the clinical value of the test treatment. Inclusion of a treatment arm as active comparator could be of interest for augmentation trials.

Depending on the mechanism of action and already established antidepressant efficacy maintenance studies will be necessary; in case maintenance data are needed, they should be obtained pre-licensing. (again scientific advice is recommended). A randomised withdrawal study is the design of choice to establish maintenance of effect of long term augmentation treatment within the episode. In this case responders to a combination treatment of a known antidepressant and the new compound are randomized to one of the following three treatments: combination therapy, monotherapy antidepressant, and monotherapy new compound (if appropriate).

An alternative might be a long term extension trial with parallel design including test product, placebo and active comparator added to a well established antidepressant. However, such a study would not answer the question whether long-term augmentation is really needed and therefore this is not the favoured option. If chosen, it needs justification and should be verified with scientific advice before starting the study (see 4.1.2.).

Pharmakokinetic or pharmacodynamic drug interactions relevant to the specific characteristics of the new compound should be studied prior to pivotal augmentation studies.

4.5. Special Populations

4.5.1. Older people

Depression in the older people is not uncommon, but certainly not all older people with depressive symptoms will have MDD. In ICH E7 it is indicated that the efficacy and safety for the older people population can be derived from the total database, provided that a sufficient number of elderly patients is included, unless there are specific reasons not to do this.

Recently studies have been conducted in the older people, that could not distinguish between test product and placebo, even though the design of the studies and the dose of the test product were as expected and efficacy of the product had already been shown in adults.

Moreover extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the older people 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 is an analysis of the whole database, whereas the other would be to conduct specific trials in a specified patient 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 a reasonable number of older people (representing sufficiently the growing population of the older people and hence ensuring generalizability) are included to allow a prospective subgroup analysis. As both efficacy and the optimal dose should be addressed, this may be difficult. Specific studies will be more informative and are preferred. Short term studies in older people will be sufficient, if full development in adults is available.

For new products with a new mechanism of action specific trials are usually needed. In case a claim for a product with a new mechanism of action is planned to be based on a pre-planned meta-analysis, this should be discussed with regulatory authorities when setting up the clinical development program.

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

4.5.2. Children and adolescents

Depressive disorders in children and adolescents are phenomenologically equivalent to those in adults, but depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. Early intervention and management is of major importance as depressive episodes may increase in severity and duration with recurrence and are associated with substantial morbidity, poor psychosocial outcome and risk of suicide. Psychotherapeutic approaches are considered first line treatment in this population with MDD and psychopharmacologic approaches should normally be integrated in a stable psychosocial treatment setting. The clinical characteristics may vary somewhat according to age at presentation. Children have a higher rate of physical somatic complaints including headaches and abdominal pains, whilst adolescents are more likely than children to complain of subjective feelings of low mood, and to have a higher rate of suicidal thoughts and self-blame. Extrapolation of adult efficacy and safety data is not considered appropriate. Specific studies are necessary in the paediatric population. Separate studies should generally be conducted in children and adolescents. If a trial includes both children and adolescents, stratification for age group should be employed and the sample size calculation should allow for demonstration of efficacy in each age group independently. Throughout the trials all subjects should receive psychosocial interventions; this should be standardised if possible.

Efficacy in acute treatment should be demonstrated in at least one short term trial of 8 weeks duration (or longer) including a placebo and an active comparator arm. In earlier clinical trials with careful patient selection resulting in a homogeneous patient population a study duration of 8 weeks has been shown sufficient for statistically significant and clinically meaningful separation of active treatment from placebo. If longer study durations are implemented, this should be justified in the protocol and must be balanced against the longer use of placebo control.

Primary endpoint should be the change from baseline in validated, age appropriate rating scales for the core signs and symptoms of MDD. Response and remission should be defined in the protocol. Global and/or functional outcome measures should be estimated as secondary endpoints.

In general maintenance of efficacy data and long term safety data should be generated in the paediatric population as in adults, however, this might depend on the magnitude of efficacy observed in the short term trials and the evidence already available from the studies in adults.

Safety Evaluation

In general the content of ICH E1 should be taken into consideration.

Identified adverse events (AEs), including serious AEs and AEs leading to withdrawal, should be characterised in relation to duration of treatment, dosage, recovery time, age, and other relevant

variables. Adverse event scales should be standardised for use in studies with psychotropic drugs (e.g. UKU scale). Clinical observations should be supplemented by appropriate laboratory tests and cardiac recordings (e.g. ECG). AE rates should be presented for the test treatment, placebo and active comparators.

As treatment durations including the long term open label trials will generally be longer for the test treatment as compared to other treatments (e.g. placebo), the data should be presented in a suitable way for comparisons of event rates.

Special efforts should be made to assess potential AE reactions that are characteristics of the class of drugs being investigated in view of actions on specific receptor sites. Particular attention should be paid to anti-dopaminergic, anti-cholinergic or cholinergic, anti-histaminergic, serotonergic and α-adrenergic, and to glutamatergic or anti-GABAergic AEs, if relevant.

4.5.3. Specific adverse events to be monitored

4.5.3.1. Psychiatric adverse events

Psychiatric adverse events typically represent a large proportion of the AEs reported in trials in MDD patients. These events may be related to the disorder itself as well as the study medication. In order to explore the risk of an adverse effect on the severity of the disorder being treated, the proportion of patients deteriorating during treatment should be documented using the primary efficacy measure.

4.5.3.2. Adverse effects on cognitive functioning

A detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim. Effects on cognition, reaction time, driving and severity of sedation should also be studied. In the adolescent population specific issues such as memory, learning, school performance, etc. should be studied in relation to both the safety and efficacy perspective.

4.5.3.3. Overdose and suicide

Depending on the mechanism of action risks and effects of overdose should be studied particularly with regard to serotonin-syndrome, Qt-prolongation and delirium.

A small increase of suicidal thoughts and behaviour has been described in adolescents and younger adults with use of antidepressants, therefore the potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured using validated rating scales (e.g. InterSePT Scale for Suicidal Thinking, Columbia Suicidality Severity Rating Scale (C-SSRS) or other validated instruments). Rates of suicidal events (from suicidal ideation to completed suicide) should be presented and narrative summaries of suicidal patient statements or behaviours should be provided.

4.5.3.4. Metabolic risk factors

The effects on weight, glucose metabolism and lipid metabolism should be actively measured using standard laboratory measures. The metabolic profile of the test product should be thoroughly characterised in comparison with placebo and active comparator(s).

4.5.3.5. Haematological adverse events

Special attention should be paid to incidence of neutropenia, agranulocytosis and aplastic anaemia.

4.5.3.6. Endocrinological adverse events

Special attention should be paid to effects on sexual functioning, galactorrhoea, gynaecomastia and weight gain. Investigation of neuro-endocrinological parameters relating to prolactin is necessary. In the adolescent population effects on growth and sexual maturation require specific attention and should be closely monitored.

4.5.3.7. Cardiovascular adverse events

Due to the known cardiovascular effects of this class of drugs, cardiac adverse events should be actively monitored. Reported adverse events that might represent orthostatic hypotension or arrhythmia (including syncope, loss of consciousness, etc.) should be presented where relevant. The effect on QT-interval prolongation should be investigated in accordance with the ICH E14 guideline.

4.5.3.8. Sexual dysfunction

Special attention should be paid to the effect on sexual function and libido.

4.5.3.9. Extrapyramidal symptoms (EPS)

There is concern that patients with affective disorders show a higher sensitivity to suffer from acute extrapyramidal side effects and a higher incidence of tardive dyskinesias compared to patients with schizophrenia. Therefore, if antipsychotics are used for augmentation or as treatment option in treatment resistant depressive patients, rates of extrapyramidal symptoms should be presented. In addition the extent and severity of EPS should be actively measured using validated and specifically designed rating scales. Dose – response relationships of EPS should be explored. During the wash out phase prior to acute studies, possible tardive EPS should be measured to distinguish this from acute EPS due to the test treatment.

Tardive dyskinesia occurs late in treatment and is reported for both atypical and typical antipsychotics.

4.5.3.10. Serotonin syndrome / Neuroleptic malignant syndrome

Serotonin syndrome (SS) can be caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors and has been described for many antidepressants. The clinical symptoms include neuromuscular hyperactivity, autonomic hyperactivity and altered mental status.

Neuroleptic malignant syndrome (NMS) consists of similar clinical symptoms and has been reported for all antipsychotics.

4.5.3.11. Rebound / withdrawal phenomena / dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur. Trials should be designed in such a way, that these phenomena can be studied. In some of the short-term and long-term clinical trials, treatment should be stopped abruptly and patients should be followed for a suitable duration, in other studies careful tapering off might be more appropriate depending on the mechanism of action of the compound. Occurrence of rebound and/or withdrawal phenomena should be scored at the appropriate time.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur.

Depending on the results of these studies further studies in humans may be needed.

4.5.3.12. 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.

4.5.3.13. Children and adolescence

Rather than relying on spontaneous AE reporting, potential treatment-emergent adverse events such as somnolence, sexual disturbances, weight gain, affective symptoms such as suicidality, discontinuation/rebound symptoms, etc. should be clearly defined and actively monitored for. Validated questionnaires/scales/tests should be used for the assessment of adverse events.

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.

Definitions

Relapse:

Relapse is defined as re-emergence of depressive signs and/or symptoms within the index episode independent from medication status. It usually indicates that treatment duration was too short or dosage of treatment was insufficient.

Recurrence:

Recurrence is defined as a re-emergence of depressive symptoms after a time without or nearly without symptoms (remission) and without medication. It is seen as the start of a new episode.

Rebound and Withdrawal:

Rebound and withdrawal are phenomena, which are due to tolerance/dependence on and/or discontinuation of the medicinal product. Rebound is defined as an increase of symptoms immediately after treatment is stopped, whereas withdrawal is the development of symptoms different from the original ones. One way to deal with this might be a separate analysis of events immediate after stopping medication (e.g. first week/month) versus events occurring thereafter.

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