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

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

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Abbreviations

AEs: Adverse Events

BD: Bipolar disorder

CHMP: Committee for Medicinal Products for Human Use

C-SSRS: Columbia-Suicide Severity Rating Scale

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ECG: Electrocardiogram

EMA: European Medicines Agency

EPS: Extrapyramidal symptoms

GABA: Gamma-Aminobutyric acid

GAD: Generalised Anxiety Disorder

HAMA: Hamilton Anxiety Scale

HDRS: Hamilton Depression Rating Scale

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

ICH: International Conference on Harmonisation

MADRS: Montgomery-Asberg Depression Rating Scale

MDD: Major Depressive DisorderMINI: Mini-International Neuropsychiatric Interview

NMS: Neuroleptic Malignant Syndrome

RAAD: Rapid acting antidepressant

SmPC: Summary of Product Characteristics

SCID: Structured Clinical Interview for DSM Disorders

Sheehan-STS: Sheehan Suicidality Tracking Scale

SIBAT: Suicide Ideation and Behaviour Assessment Tool (SIBAT)

SSRI: Selective serotonin reuptake inhibitors

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). It updates and replaces the previous guideline (EMA/CHMP/185423/2010 Rev. 2). The main focus is on major depressive episodes that occur in the context of MDD. Bipolar and related disorders are separated from depressive disorders in DSM-5 and possible extrapolations in alignment with the bipolar guidance document will also be addressed.

Up to two thirds of MDD patients do not achieve remission following an initial adequate trial of antidepressant therapy.

Despite many approved antidepressants there is 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.

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. The results must be robust and clinically meaningful. This requires incorporation of rates of response/remission to adequately assess clinical relevance, in addition to statistically significant results. It has to be shown that the initial response to treatment is maintained in at least one study following an adequate design. The emergence of new antidepressants with rapid onset of effect and recent clinical developments of psychedelics require separate design strategies. The requirements for clinical trials in partial and non-responders (i.e. treatment resistant depression) with MDD are revisited.

Nearly 70% of patients with MDD experience residual symptoms with first line standard of care. These may include anxiety, impaired cognition, fatigue and sleep disturbance. A separate claim in specific domains or symptom clusters within MDD (e.g. cognitive dysfunction either as specific claim or additional claim on top of MDD treatment) will need a solid justification for the therapeutic rationale. Specific studies should be performed.

The update specifically addresses:

- Several aspects for trial designs in difficult to treat patients (partial responders or non-responders to treatment) including the definition and identification of those patients, the role of augmentation and combination strategies
- Clinical development requirements for new rapid acting therapies
- Issues to consider for the development of psychedelic medications
- Clinical development requirements to target sub-domains of depression
- Requirements for clinical trials in children and adolescents and possible extrapolation from adult data
- Sex-related differences and considerations in MDD

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 (see also section 4.6.1.3.).

1. Introduction (background)

Major Depressive Disorder (MDD)

MDD is one of the most common and disabling psychiatric disorders and the fourth leading cause of global disease burden. An estimated 3.8% of the population worldwide is affected by MDD, including 5.0% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years. Approximately 280 million people in the world have depression. Depression is about 50% more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression. MDD is not a benign disorder. More than 700 000 people die due to suicide every year (World Health Organization webpages, accessed 2023), and MDD is a leading precipitating factor for suicide. Depression frequently occurs with comorbid psychiatric disorders. For preschool children MDD is very rare (point prevalence is thought to be 0.5%), in adolescents the prevalence is estimated to be approximately 8%. Meta-analytic analyses suggest a higher prevalence of MDD in adolescents than in the general global population, but the paucity of youth-specific epidemiologic studies of MDD across regions warrants further investigation. 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. Studies on efficacy and safety of antidepressants in children and adolescents are necessary (section 4.5.2).

Depressive disorders are classified in various classification systems, e.g., currently the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)[1]. 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 depressed mood or loss of interest and pleasure in activities accompanied by at least two (ICD-10) or five (DSM-5) symptoms of depression. 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 in social, occupational, or other important areas of functioning.

A shift in the definition of MDD in DSM-5 to distinguish it from other disorders e.g. bipolar and anxiety disorder has been noted. Despite the common features of MDD (unipolar) with Bipolar Disorder (BD), there are differences in duration, timing, phenomenology, family history and genetics (section 4.2.5.).

Despite the many treatment options currently available for MDD, up to 50% of patients do not adequately respond to the first antidepressant prescribed and up to two thirds do not achieve remission, even if there is good compliance and the treatment has been taken for a sufficient length of time at an adequate dosage.

In clinical practice, treatment algorithms have been established including re-evaluation of the initial diagnosis and, when no correctable cause is found, optimization of the initial regimen or switching to other antidepressants or augmentation strategies (e.g. combination therapy, lithium and other mood stabilizers, atypical antipsychotics, etc.) or monotherapy with second generation antipsychotics have been considered as psychopharmacologic options. However, treatment approaches are not standardised. The approval of a treatment for TRD in an add-on setting with conventional SSRIs or SNRIs after at least two treatment failures has resulted in adjunctive treatment trials being considered a valid approach for TRD (section 4.4.1.).

Notwithstanding the availability of many compounds with established efficacy and safety there is a high need for new antidepressants. Recent studies have stimulated new basic research in the

[1] We are aware that ICD-11 is currently being developed and will replace ICD-10 as soon as it comes into force.

antidepressants field and have identified new neural signalling circuits in antidepressant response and novel antidepressant mechanism (section 4.4.3.). Conventional antidepressants usually require 4 to 6 weeks to exert their therapeutic effects. Rapid acting antidepressants (RAADs) can have different pharmacokinetic and pharmacodynamic characteristics and may require different studies (section 4.3.2.3.). Psychedelics are currently being recognised in psychiatry as potential treatment options to treat various medical conditions including MDD. Psychological support /Psychotherapy in conjunction with the use of psychedelics faces several challenges mainly related to standardisation, training, monitoring and safety that need to be addressed in specific study designs (section 4.3.2.4.).

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 to focus not only on the treatment of acute symptoms and maintenance of the effect during the index episode, but also to explore the potential of their compounds in preventing new episodes called recurrence prevention. However, prevention of a new episode (recurrence prevention) is not a mandatory part of a registration package for treatment of episodes of MDD, but is considered as an additional claim (section 4.2.3.).

2. Scope

This guideline focuses on antidepressant products developed specifically for MDD. Recent experience with approval procedures, PRIME allocations and CHMP 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. Specific methodological issues as well as efficacy and safety issues regarding special populations including children and adolescents, young adults and older people are addressed.

After the release of DSM-5 the implementation of more dimensional aspects has consequences for the definitions of mood disorders as given in this guideline. With the transition of DSM-IV into DSM-5, bipolar and related disorders have been separated from depressive disorders, and bipolar II disorder (BD II) is no longer considered a milder form of bipolar I disorder (BD I). Since there is a separate Guideline for bipolar disorder, bipolar depression is not in the scope of this guideline (section 4.2.5).

Symptoms of major depressive episodes occurring in comorbidity with other psychiatric disorders or with somatic disorders including Parkinson's disease, Alzheimer's disease, cerebrovascular disorders, cancer and chronic pain syndromes are not in the focus of this guideline.

In many clinical treatment guidelines electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) are options for patients suffering from severe TRD. However, non-medicinal approaches and non-pharmacological interventions are not within the scope of this guideline.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83 as amended. Further is referred to the EMA and ICH guidelines on pharmaceutical development, PK/PD topics, clinical trial design, special populations including the elderly and paediatric population:

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines

Among them those of specific interest for depression are:

CPMP/EWP/567/98 Note for guidance on clinical investigation of medicinal products for the treatment and prevention of bipolar disorder

ICH E11 (R1) Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population

ICH E11A on paediatric extrapolation

ICH E7 Studies in Support of Special Populations: Geriatrics, including Questions and Answers

EMEA/CHMP/SWP/94227/2004 Guideline on the non-clinical investigation of the dependence potential of medicinal products.

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

4.1. *Clinical Pharmacology Studies*

4.1.1. 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.

There is also no specific MDD model in humans as the relationship between structural and functional findings as well as genomic, proteomic and metabolomic changes in MDD is not well elucidated. However, 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/mechanism of action (MOA) and evolving tolerability profile of the proposed product. In addition, safety profiling should include studies providing data informing the probability of adverse events to be monitored as described in section 4.6.

It is expected that appropriate preclinical studies (e.g. in vitro and receptor binding studies) should be able to support the MOA , potential effective dose and where appropriate the positive effects in specific domains, and forecast the effect in humans based on accepted theoretical constructs.

4.1.2. Pharmacokinetics

Studies should be performed to characterise the pharmacokinetics of the new medicinal product (see the relevant guidelines on pharmacokinetic studies in man, including special populations, drug interactions, etc.) and where possible this information should be used to study the relationship between dose, exposure and response (including efficacy and safety). Population PK analyses may be used to investigate pertinent covariates, e.g. weight, age, sex assigned at birth, gender, healthy vs patient population, concomitant medications including those relevant to targeted patient subpopulations, etc. that may influence the pharmacokinetics of the drug. The choice of dose for the clinical program should be adequately justified.

4.1.3. Interaction studies

In general, the guideline on drug interactions should be followed to investigate possible pharmacokinetic interactions with other drugs and food. Interactions with alcohol and other relevant CNS active compounds should be investigated which may include pharmacokinetic as well as pharmacodynamics interactions. Where applicable pharmacokinetic studies in patients with hepatic and/or renal impairment should be performed.

4.2. *Assessment of Therapeutic Efficacy*

It is acknowledged that there are several methodological issues being discussed in the scientific community when conducting clinical trials in depression, including the potential reasons for an increased placebo response and proposals to address this issue (section 4.2.2.).

Clinical studies should provide unambiguous evidence of the antidepressant efficacy and of the effective dose or dose range. It is generally preferred to establish the dose-response relationship in a phase II multiple arm parallel fixed dose study to maximise confidence that the doses(s) studied in phase III are optimal. The minimum effective dose and the dose at which most efficacy is achieved should be established when possible. Rapid acting antidepressants including psychedelics might not follow a classic chronic dosing paradigm, so single course treatments or single-dose intermittent treatments should be justified.

Due to variable observed treatment effects in MDD studies, at least two pivotal short-term studies are required. A relapse prevention study should also be conducted (section 4.2.3.).
In MDD, comparisons between a test medicinal product and reference substances are difficult to interpret since there is a high and variable placebo response in depression. 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 two-arm non-inferiority trial is not an option, as the sole basis for demonstrating efficacy. Hence, randomised, double blind, placebo- controlled trials are the gold standard to permit adequate evaluation of short-term efficacy. A placebo arm in at least one of the studies is required to evaluate the true effect size of a new antidepressive agent.
Additionally, a two-arm trial establishing superiority of the test product over an active comparator is considered acceptable as one of two required pivotal short-term studies to establish an antidepressant effect of the new test product. However, it does not necessarily allow claiming better efficacy than the comparator as in absence of a placebo arm it cannot be determined whether the response of the active control may approach that of the putative placebo.

Results should be discussed in terms of both clinical relevance and statistical significance, and the effect should be shown to be robust and insensitive to the analysis used. When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool, response and remission rates should also be provided. Usually, an improvement of 50% or more on a usual depression rating scale is applied to define individual treatment response (section 4.3.2.1.). An adequately weighted meta-analysis of efficacy across all clinical studies may improve the precision of the pre-defined responder-based estimates of clinical efficacy.

4.2.1. Target of estimation in depression

The scientific question(s) of interest, i.e. what the trial seeks to address, and consequently the target(s) of estimation (estimand) should be clearly specified. Trial planning, design, conduct, analysis, and interpretation must be aligned with the estimand. Reference is made to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials (EMA/CHMP/ICH/436221/2017).

Relevance and (expected) frequency of intercurrent events may differ between different therapeutic settings and consequently influence the definition of a relevant (primary) estimand. Different estimands may be warranted depending on the type of treatment such as monotherapy, add-on treatment or rapid acting antidepressants as well as depending on the therapeutic goal: treatment of acute symptoms in current (index) episode, long-term efficacy (relapse/recurrence prevention) (see also section 4.2.3.). All estimands should be clearly aligned with the scientific question of interest.

With a considerable number of alternative treatments available in the MDD setting, relevant intercurrent events to be considered include, but are not limited to, treatment discontinuation and changes in medication such as use of alternative anti-depressants or other medications and changes in background therapy (e.g. psychotherapy, anxiolytic medication, hypnotic medication) and/or dose. In addition, depending on the population selected, death due to suicide might require incorporation into the estimand definition.

Irrespective of the setting and unless an alternative strategy is duly justified, 'treatment discontinuation' should be handled with a treatment policy strategy addressing the treatment effect regardless of discontinuing treatment. Similarly, a treatment policy strategy is relevant for changes in background therapies, which is equivalent to considering them as part of the treatment regimen of interest.

Handling the use of alternative anti-depressants that are not considered part of the treatment regimen of interest (i.e. therapies that could not be co-administered with the investigational treatment) is challenging and discussions on the most appropriate estimand are still ongoing. A treatment policy strategy could be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, might be more relevant. Still, the downside of this hypothetical strategy is that a theoretical treatment effect – not existing in the real world - is estimated, as alternative treatments are available in real life. Furthermore, the use of alternative medications generally follows patients' discontinuation from the treatment regimen of interest, and appropriate methods should be used to handle these co-occurring events with different strategies. As another option, considering the use of alternative medications as failure, they could be incorporated in the endpoint with a composite strategy (e.g. in a dichotomized responder definition). However, if this strategy is implemented through dichotomization, the loss of information would suggest that this estimand should rather be considered as a secondary estimand, at least for short term trials. Additionally, the treatment effect assuming all patients adhered to the treatment regimen (i.e. hypothetical strategy for both intercurrent events 'treatment discontinuation' and 'changes in medications not considered part of the treatment regimen') could be of interest as a secondary estimand only. This may be included merely as a means to compare effect estimates to past trials.

For binary or time to event endpoints such as relapse instead of or in addition to the strategies discussed above, it may be warranted to apply a composite strategy for the (primary) estimand definition, e.g. the intercurrent events such as treatment discontinuation or use of alternative medications could be integrated into a composite variable with relapse. In any case, intercurrent events that are included as part of a composite endpoint definition need to be clinically relevant in themselves.

Overall, the choice of estimand and the aligned methods of estimators (section 4.3.3.) are still areas of ongoing discussion and research. Sponsors are encouraged to discuss the estimand and aligned trial design and method of estimation (analytical approach) at CHMP scientific advice or protocol assistance.

4.2.2. Placebo response and strategies to address high placebo response

A high placebo response has been observed in trials that were submitted for approval in MDD. Several factors are thought to contribute to high placebo response and applicants may account for these factors during the process of screening, population selection and conduct of the trial. Appropriate training of investigators may help to reduce a high placebo response caused by overrating of patients at baseline.

Enrichment strategies with a placebo run-in are only acceptable in phase II but not for phase III studies, since the external validity of the studies may be affected (section 4.3.2.).

4.2.3. Investigation of relapse and recurrence

Depressive symptoms occur 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 treatments in the acute phase, the continuation phase and if required, the maintenance phase. Relapse defined as re-emergence of depressive signs and/or symptoms within the index episode has to be distinguished from recurrence after remission. The latter occurs in the context of a new depressive episode (see Definitions).

For marketing authorisation it should be shown that a short-term effect can be maintained during the current (index) episode in so-called relapse prevention studies (section 4.3.2.).

Prevention of the next episode(s) i.e., recurrence prevention is also a worthwhile treatment goal. It is encouraged to evaluate this in specific studies (section 1.). CHMP scientific advice is recommended if a claim for recurrence prevention is pursued.

For a given patient in the everyday clinical practice, the duration of treatment depends on the rate of his/her recurrences. Patients with a history of higher frequency depressive episodes should be included in the recurrence prevention investigation and the recent recurrence rate should be considered when planning the duration and power of the study.

4.2.4. Study population and entry criteria

MDD should be classified according to an internationally acknowledged classification system, preferably DSM-5 or ICD-10, using the diagnostic criteria therein. 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.

Episodes of MDD can be classified as mild, moderate and severe. Clinical trials will usually recruit patients, who are moderately or severely ill, as it is difficult to demonstrate an effect in mildly ill patients. Demonstration of an acceptable benefit/risk ratio in moderately ill patients will be considered sufficient for a registration package to get a general indication for "Treatment of Episodes of Major Depression" in the context of MDD. However, an appropriate number of patients with severe depression should be included in the clinical development program allowing the evaluation of a potential effect modification.

In addition, cut-off scores, based on an appropriate scale may be used as inclusion criteria. In studies where the main aim is to show an agent is effective at all, i.e. dose-finding phase II studies, a more homogeneous population more sensitive to detect such effect needs consideration.

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, unless patient safety considerations render the conduct of trials in out-patients impossible.

4.2.5. Extrapolations

Patients included in the trials will be diagnosed as having MDD using accepted diagnostic criteria, DSM-5 or ICD-10. However, depressive symptoms are also seen in other psychiatric disorders or other types of depression. If such specific claims are strived for, specific studies should be conducted.

As already mentioned in the introduction, a major depressive episode may also occur in the framework of bipolar and related disorders. Extrapolation of short term and maintenance of efficacy in adults from unipolar depression to bipolar depression need to be considered on a case by case basis. Some specific issues, like duration of the episodes, switching rates and population selection and safety data, are addressed in the guideline on bipolar disorder.

For studies required in paediatric patients and possible extrapolations reference is made to section 4.5.2.

4.3. *Efficacy endpoints and considerations for study designs*

4.3.1. Efficacy endpoints

The choice of rating scales should be justified based on test quality criteria (reliability, validity) and the sensitivity to change should be known.

Acceptable scales to determine symptomatic improvement include the Hamilton Rating Scale of Depression (HDRS), preferably the 17-item scale, and the Montgomery-Asberg Depression Rating Scale (MADRS), however other validated scales might be acceptable as well. For rapid acting antidepressants it is anticipated that specific scales, other than the most commonly used MADRS, will be developed and validated, in order to be able to fully capture the rapid onset of effect.
The protocol should indicate which scale is used as primary assessment tool.

In addition, changes in other aspects of the disorder, including, but not limited to changes in global assessment (e.g. Clinical Global Impression assessment scale) or social functioning may be used as a key secondary endpoint if the assessment tools are validated for MDD.

Investigators and raters should be properly trained in evaluating the patient. Inter-rater reliability scores (e.g. by using kappa statistics) should be documented for a group of raters sufficiently sized for such analyses. The use of independent and blinded central raters can be used in particular cases provided that the central reading assessments have been validated (section 4.4.2.4.).

Because the patients' perspective on the relative importance of symptoms of their disorder is relevant, self-rated symptoms scales can also be used. The development and validation of new patient-reported outcome (PRO) measures is encouraged. If PROs are to be considered as primary or key secondary endpoints, CHMP scientific advice is recommended.

Despite recent advances in the field, specific biomarkers have not yet been established in MDD. It is considered essential that sufficient data are collected before any biomarker can be used for prognostic or predictive purposes or is sufficiently sensitive to changes in the course of the condition/disorder. Applicants are encouraged to seek CHMP scientific advice/qualification procedure to discuss adequacy of the proposed biomarker.

4.3.2. Study design

Two randomised, double blind, controlled trials are required to allow adequate evaluation of short-term efficacy in MDD. At least one of the trials should be placebo-controlled (section 4.2.). Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions of the medicinal product.

Precautions to minimise the impact of the use of placebo on the potential deterioration of the patients' condition should be taken, e.g., by limiting the duration of the study.

Maintenance of effect (relapse prevention) should be shown in a long-term study (section 4.2.).

The following general design aspects should be considered for trial planning.

Assessment of success of blinding should be included in all trials at the last visit and methods predefined in the trial protocol to assess the effect of functional unblinding. Blinding success should be reported using suitable statistics that account for correct guesses by chance.

Use of a placebo run-in period (single- or double-blind) and potential subsequent patient selection in confirmatory phase 3 studies is considered problematic with regard to the generalizability of the results to the population treated in clinical practice, since patients included in the trials may not correspond to the target population (e.g. non-responders to placebo run-in). With respect to placebo response reference is made to section 4.2.2.

If a constant anxiolytic or hypnotic medication cannot be avoided, a corresponding subgroup analysis should be pre-specified to assess consistency of the treatment effect in each relevant subgroup. Stratifying randomization by use of anxiolytic or hypnotic medication in combination with study treatment should be considered, in particular, if this subgroup is considered of special relevance.

A trial-specific, standardised psychotherapy/psychological support (psychoeducation, motivational support or counselling) may be given as supplementary treatment, though it may enhance the response in both treatment groups, but it should be prospectively defined in the protocol. It should be documented in detail and its influence on treatment effect should be analysed.

For any trial, potential centre effects should be carefully evaluated.

4.3.2.1. Short-term trials

Depending on the mechanism of action, pivotal trials should be long-enough to demonstrate a treatment effect.

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 programmes 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 or remitters. 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.

4.3.2.2. Long-term trials

Due to the character of the disorder, longer trials are necessary to demonstrate that the acute effect is maintained during an episode (relapse prevention). For this, a randomised withdrawal study is the preferred design. In this design, stable responders to treatment with the test product are (re-) randomised to test product or placebo. In the first period, the test product is usually given open-label, 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. 6 to 12 weeks for the first period appears acceptable, whereas the period after (re-) randomisation usually has a duration of 6 months. The duration of 6 months is not strictly necessary when a time to event approach is chosen. 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.

A long-term placebo-controlled parallel group study (e.g. expanding the short-term efficacy study) is not recommended, as there is a risk, that, due to a high dropout, the results are not interpretable regarding 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 generate long-term efficacy and safety data but should be justified by the applicant.

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 target population which is selected based on pre-defined criteria and will need to be justified.

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. In long-term maintenance trials impact of intercurrent events may be higher as compared to short-term trials. Furthermore, for randomized withdrawal trials, additional considerations on the target population are required. Usually, patients responding to short-term active treatment (pre-defined response criteria) are recruited and this restriction of the population needs to be reflected in the estimand definition for the withdrawal part.

4.3.2.3. Rapid acting antidepressants (RAAD)

For antidepressants with a rapid onset of effect, both rapid efficacy and sustainability of effect will have to be characterised keeping in mind the natural course of a depressive episode. At least one of the pivotal trials should be double blind, randomised, parallel group, placebo-controlled, as is the case with conventional antidepressants. Depending on the mechanism of action, an earlier efficacy endpoint could be appropriate, but the acute onset of action should be clearly predefined and measured accordingly with a validated scale. CHMP scientific advice is recommended if a rapid onset of effect indication is pursued to achieve agreement on the most appropriate measurement timepoints and trial duration to establish efficacy and safety. Rapid acting antidepressants may be studied as monotherapy and/or add-on treatment. The following treatment situations can be foreseen a) as monotherapy, where the rapid acting antidepressant is administered alone in patients initiating therapy or replacing a conventional antidepressant b) initiation of treatment with a RAAD followed by maintenance treatment with a conventional antidepressant agent in a sequential way and c) maintaining the conventional antidepressant and initiate treatment with a RAAD followed by a maintenance dose of RAAD as add-on approach. Each situation requires a different study design. In any case durability of effect beyond the initial treatment response should be characterized, dependent on the chosen treatment situations mentioned before.

4.3.2.4. Psychedelics

Psychedelics include various psychoactive compounds of different chemical classes such as classical hallucinogens that act as 5-HT2A agonists (e.g. psilocybin, LSD, DMT, mescaline) and "atypical" psychedelics including dissociative anaesthetics (e.g. ketamine, esketamine) and entactogens (e.g. MDMA). Psychedelics alter perception, mood and affect numerous cognitive processes via different mechanisms of action; those relevant in the context of therapeutic use remain to be definitely established. They can however also acutely induce anxiety and other psychiatric adverse events including suicidal ideation and behaviour (section 4.6.1.). These as well as cardiovascular effects (particularly for MDMA) require careful monitoring and further investigations.

Several studies with psychedelics in the field of depression are currently ongoing. As with all other antidepressants, to establish a positive benefit/risk ratio randomized, double-blind placebo-controlled short-term trials are needed, as well as extended or long-term trials to determine the maintenance of effect, optimal psychological support and the impact of these treatments on recovery and functioning

over time. Due to potential significant alterations of perception and behaviour, it is recommended to start development in a more severely affected population, such as patients with treatment resistant depression (section 4.4.1.).

The psychoactive effects of currently investigated psychedelic agents present several challenges for the design, conduct, and interpretation of clinical trial data:

- placebo and/or comparator. Due to the obvious and easily detectable subjective effects induced by an active dose of a psychedelic substance the choice of appropriate comparator while maintaining the blinding can be challenging. Different strategies such as low dose or active placebo, i.e. alternative substances with a distinct mechanism of action but with a similar psychoactive effect have been considered to make it more difficult to guess the treatment arm.

- expectancy and unblinding. Positive expectancy might lead to overestimation bias while disappointment with treatment (negative expectancy) might lead to symptom worsening or safety issues (nocebo effect). Here, it is particularly important to assess and report success of blinding with appropriate methods, predefined ín the trial protocol (section 4.3.2.) and to take measures of expectancy. An effective strategy might involve systematically assessing participants' awareness of their treatment allocation to ensure the reliability of blinding. The use of independent and blinded external raters could help to mitigate the effects of unblinding and expectancy. Conducting trials with different designs, e.g. offering open label treatment after the double-blind placebo-controlled phase for those in the control group or including different doses (low, middle and high) without placebo could help addressing these challenges and provide complementary information to estimate the nocebo effect.

- dosing. As in every application, the justification for the adequate therapeutic dose is an important aspect of the MA submission dossier. The dose-effect relationship needs to be characterised. In particular, the relationship between characteristics of the acute psychedelic experience and clinical improvement, as well as the need for dose adjustments should be investigated. This includes individualised dosing due to inter-individual variability in drug metabolism, age, sex, personality as well as extra-pharmacological factors (so called "set and setting").

- maintenance of effect. Endurance of effect needs to be demonstrated. Also the efficacy of re-treatment needs to be demonstrated if recurrent dosing is foreseen in the posology. The experience and the available information on the sustainability of the action and the long-term effects, both desirable and undesirable of psychedelics and the efficacy of re-treatment are very limited.

- safety. The ability to change the perception of reality can have unknown implications for depressed patients. Therefore, psychedelics need to be administered in a controlled environment. Although classical serotonergic psychedelics do not appear to show potential for addiction this cannot be ruled out for all products, depending on the mechanism of action. Headaches, elevated blood pressure and tachycardia have also been reported to be associated with the use of psychedelics. The safety profile of the psychedelic should be taken into account to ensure appropriate safety mitigations are in place. Drug-drug interactions in case of regular co-administration need to be characterised. Also, long half-life psychedelics may require long surveillance which can be burdensome for patients, physicians and health care systems. The exact time course for long-term surveillance depends on the MOA of a certain psychedelic and could be needed up to one year.

- Psychological support /Psychotherapy. The monotherapy setting with psychedelics alone may not be applicable or feasible. The application of psychedelics is usually embedded in a non-directive psychological support. Trials need to be able to demonstrate that the effect of the psychedelic assisted therapy is not due to the psychological intervention alone. The framework of operation (protocol) as well as preparatory and post-dose integration sessions and whether this needs to be adapted to the type of psychedelic need to be clearly defined. Type, length and frequency of the psychological intervention and training need to be standardised to the maximum possible effect, despite ethnic and cultural differences. Extrapolation from the trial setting to clinical practice or the plan to provide specific training to therapists needs to be addressed.

Due to the diversity of compounds and actions of psychedelics, potential safety issues and the need for a case-by-case approach, applicants are encouraged to seek CHMP scientific advice, prior to initiating their clinical development program.

4.3.3. Statistical considerations

Generally, efforts should be made to collect all relevant data for the primary and important other estimands (e.g. follow-up regardless of intercurrent events) to minimize the need to rely on untestable assumptions in the analysis and interpretation of the trial results.

Still, handling of missing data is of particular concern, as a relevant amount of missing data (often differential across treatment arms) has to be expected based on trial results from the past. Furthermore, some data points after occurrence of an intercurrent event may need to be regarded as 'missing' (or at least not used as they are) for estimation of a specific estimand, even though data were collected after the intercurrent event and may be relevant for other estimands. For example, data collected following the start of alternative anti-depressants need to be considered missing when a hypothetical strategy is targeted for this intercurrent event (section 4.2.1.).

When missing data follows treatment discontinuation, the analysis should not implicitly assume that all the benefit from treatment is retained. Hence, methods based on the missing-at-random assumption are not acceptable if (primarily) based on data collected while on treatment - for estimation of the treatment effect regardless of treatment discontinuation. This similarly applies when targeting the effect had patients not used alternative anti-depressants (hypothetical strategy), as patients likely discontinued treatment prior to changing to an alternative. Hence, the disease course after the intercurrent event has to be modelled and/or imputed and may rather reflect treatment failure.

Multiple-imputation-based approaches can be considered for analysis as they provide sufficient flexibility for estimation (e.g. missing data may be handled differently for different intercurrent events incorporated in the targeted estimand). Missing data for patients discontinuing treatment could be imputed based on data of patients that were followed beyond treatment discontinuation in a retrieved-dropout approach. Alternatively, placebo-based imputations (with a justified assumption on the amount of benefit retained, if any) could be considered. Similar considerations apply for estimation of the effect regardless of treatment changes (treatment policy strategy for 'change in background treatment'). When estimating the effect had no alternative treatment been initiated after treatment discontinuation, retrieved dropout or placebo-based imputations could be an acceptable approach. However, different handling of missing data may be warranted as patients who initiate an alternative treatment may relevantly differ from patients simply discontinuing treatment.

In any case, assumptions underlying the primary analysis should be examined through pre-specified and justified sensitivity analysis (e.g. tipping point analyses) addressing the same estimand. Analyses

estimating other estimands can also assist in the interpretation of trial data and may supplement benefit-risk assessment.

4.4. *Specific claims*

4.4.1. Treatment resistance and partial response

Treatment resistance in depression develops in a continuum with progressively higher resistance depending on the number and nature of interventions failed. Nevertheless, the distinction between partial response and TRD is still valid for indication claims and the type of patients to be included in clinical trials. The classical distinction between add-on or augmentation trials in partial responders versus monotherapy trials for non-responders, however, is no longer valid since efficacy for TRD has been shown in an add-on setting (section 1.). If a claim for treatment of MDD in patients with partial response is intended, the setting, i.e., monotherapy or add-on, will need to be justified.

Treatment resistance

Typically, TRD trials recruit patients with demonstrated history of failure of at least two antidepressants deriving from the group(s) of products commonly used as first line treatment (of the same or a different class) prescribed at an adequate dosage for an adequate duration, with adequate affirmation of treatment adherence. However, the inclusion of patients with one failed treatment at a maximum tolerated dose and for an adequate duration can also be considered. The population included in the trials should be pre-specified and justified. For the purpose of this guidance, previous non-pharmacological treatment attempts are not part of the TRD definition.

Retrospective assessment of partial response or lack of response could be a reasonable approach. Retrospective assessment of treatment failure should be primarily based on medical records of previous treatment if such records can be obtained, and not on the patient's recollection of symptom improvement, which may be biased. Relevant data including use of and response to non-pharmacological interventions need to be carefully documented. Patients should be carefully screened for previous episodes of mania, hypomania or sub-threshold bipolarity and this would increase the accuracy of population selection, because it is desirable to have such population excluded.

Partial response

Sponsors should provide and justify clear criteria for partial response to antidepressant treatments (e.g. improvement of symptoms between ≥25% and <50%). CHMP scientific advice on detailed criteria should be sought.

4.4.1.1. Studies in TRD and partial response

Short-term trials

For treatment resistance and partial response short-term randomised, parallel group studies will be needed, as in the case of general MDD population (section 4.3.2.). Depending on the mechanism of action the trial duration may vary considerably. Usually 4-6 weeks are 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. In the case of RAADs it is recommended that CHMP scientific advice is pursued prior to fixing the study design (section 4.3.2.3.). Pharmacokinetic or pharmacodynamic drug interactions relevant to the specific characteristics of the new compound should be studied prior to pivotal augmentation studies.

TRD

Monotherapy as well as add-on trials are acceptable trial options in TRD.

a. Monotherapy

Demonstration of efficacy should be superiority over placebo or an appropriate comparator. Feasibility of study protocols including ECT or rTMSas control arm seems to be limited and is out of the scope of this guideline (section 2).

b. Add-on treatment

Add-on treatments in TRD are a feasible approach. The test product is compared to placebo on a background of a stable dose of an antidepressant therapy.

The choice of an add-on setting over a monotherapy setting should be justified as a rationale for the product's mechanism of action in respect to the available alternatives is needed.

Partial response

Study designs should be conducted in an add-on setting to the antidepressant for which partial response is shown or in a monotherapy setting if justified. In the add-on setting, the comparator should be the antidepressant to which the new product is added plus placebo in a superiority design.

Maintenance of effect

Depending on the mechanism of action and already established antidepressant efficacy, maintenance of effect studies may be necessary (CHMP scientific advice is recommended). A randomised withdrawal study is the design of choice to establish maintenance of effect of monotherapy and augmentation /add-on treatment within the index episode. In the latter case responders to a combination treatment of (a) known antidepressant (s) and the new compound should be randomized to one of the following two treatments: combination therapy of the test product and the known antidepressant(s) versus the known antidepressant (s) plus placebo. A long-term extension trial with parallel design is not encouraged since it will not answer the question whether long-term augmentation is really needed. If such study is chosen, it needs justification and should be verified with CHMP scientific advice before starting it. As the relapse rate under the known antidepressant (s) plus placebo may be different than with placebo alone, this has to be taken into account in the duration of the randomized observation period (section 4.3.2.2.).

4.4.2. Specific symptoms in MDD

Specific symptoms and domains within MDD, such as sleep disturbance, cognitive dysfunction, and anhedonia, are reflected in the diagnostic criteria of the DSM-5. Impairment of specific domains or symptom clusters in MDD (e.g. cognitive dysfunction) is of major importance to patients. The development of targeted therapies to address symptom clusters which persist despite current treatment and are mediated by known neurocircuitry are being proposed. The efficacy in the targeted (cluster of) symptoms should be specific for depression. Thus, a pathophysiological justification for the claimed mechanisms of action to treat specific symptoms will be required. If this approach is taken, trials designed to test the specific hypothesis of efficacy in the context of a separate symptom, domain or dimension are required as well as adequate endpoints. The patient population studied should not be artificially narrowed. If both a claim for treatment of depression overall and that of specific symptoms is sought, the effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.

4.4.2.1. Improvement in cognitive function

Cognitive dysfunction is considered a core feature in the psychopathology of MDD during both the acute phase and the residual period and represents one of the symptoms for which a clinical need has been identified. Sufficient evidence exists indicating that patients suffering from MDD exhibit deficits in multiple domains of cognitive function, including learning and memory (verbal and nonverbal), attention, psychomotor speed, executive function, emotional processing and social cognition. Cognitive dysfunction may persist as residual symptom, despite resolution of the depressive symptoms in the acute phase. An effect on cognition may affect the time course of a depressive episode and this would be beneficial and clinically relevant for patients.

If an effect on cognitive function in patients with MDD is claimed, specific effects on cognitive function need to be shown that could clearly be disentangled from the overall depressive symptoms. It depends on the robustness of the results whether a separate indication statement can be pursued or whether the data should rather be mentioned in section 5.1. of the SmPC. To support a separate claim for efficacy on cognitive aspects in patients with MDD or the improvement of cognitive impairment associated with MDD, ideally specific and dedicated studies should be performed to demonstrate such an effect.

There is a lack of consensus on best tools to accurately and efficiently assess cognition in clinical settings, although performance-based outcomes (PerfO) measures could provide satisfactory measurement objectivity. No single test or series of tests have been established as the gold standard for the evaluation of cognitive function in MDD. As a general rule, tools for measuring/rating the improvement in cognitive dysfunction in MDD should be validated, pertinent in terms of realistically reflecting symptomatic severity, sufficiently sensitive to detect changes related to treatment and reliable (inter-rater; test/retest reliability). Applicants are encouraged to seek CHMP scientific advice before initiating an exploration of a claim in cognitive dysfunction in MDD.

Demonstration of improvement in cognitive dysfunction and/or cognitive deficits will not be sufficient as the sole demonstration of efficacy for the indication of MDD.

4.4.3. Depression with specifiers

The DSM-5 includes a number of specifiers for depressive disorders with defined diagnostic features. If a claim for a sub-population as defined in a specifier is pursued, a dedicated trial with specific inclusion criteria and adequate endpoints is required.

Anxious distress

The frequent co-occurrence of depressive and anxious symptoms in MDD requires a specific approach. Anxiety symptoms may be a predominant part of MDD and depending on the criteria for the definitions can identify depression with anxious distress. From a regulatory perspective the population in which benefit/risk is demonstrated will be described in the label. The Structured Clinical Interview for DSM Disorders (SCID) and the Mini-International Neuropsychiatric Interview (MINI) are examples of suitable diagnostic instruments for assessing co-occurrence of depressive and anxious symptoms in MDD. The severity of symptoms can be assessed with the use of more specific tools such as the Hamilton Anxiety Scale (HAMA).

Post-partum depression

The specifier 'with peripartum onset' in the DSM-5 refers to depressive episode with an onset either during pregnancy or in the four weeks following delivery. Whether post-partum depression is distinct from major depressive episodes without peripartum onset is still a matter of debate, however based on identified differences in for example hormone contributions and symptomatology, a claim in post-

partum depression should be supported by specifically designed studies in this specific population. The Edinburgh Postnatal Depression Scale (EDPS) is an example of a patient-reported screening instrument that can be used in addition to the usual depression assessments.

4.5. *Special Populations*

4.5.1. Older patients

Depression in 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 older patients (e.g. 65 years of age or older) is included, unless there are specific reasons not to do so.

Studies have been conducted in older people, which 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. This suggests a different pattern of response to first line antidepressants in the older population. In addition, depression with onset in the older age can be treatment refractory.

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. Potential different sensitivities to pharmacological targets in older compared to younger adults need to be considered to achieve an appropriate drug response.

Therefore, not only efficacy, but defining a safe dose (range) in these patients is a main concern. Usually this should be addressed before licensing. Pharmacokinetic studies or population pharmacokinetics may support the choice of the dose.

Extrapolation of efficacy from studies in younger adults to older patients is not encouraged. 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 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. These studies in older people should be adequately designed and powered to take into account the high drop-out rates and the high placebo response in the older age group.

The following three subgroups of older patients are of interest: age 65-74, 75-84 and 85+. If a sufficient number of patients over 75 years of age are not included in the clinical development program, Phase IV studies in this patient group are recommended.

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 and/or patient-reported outcome measures should be included as secondary endpoints. The input of carers may help to interpret the severity of symptoms.

For new products with a new mechanism of action specific trials are usually needed.

4.5.2. Children and adolescents

Depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. Hence, the relevant age groups for juvenile depression are children (7-11 years of age) and adolescents (12-17 years of age).

Early intervention and management are 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 pain, while adolescents are more likely to complain of subjective feelings of low mood, and to have a higher rate of suicidal thoughts and self-blame.
There is inadequate evidence to conclude which type of treatment approach is most effective in preventing relapse or recurrence of depressive episodes in children and adolescents and there is still not enough evidence to support the implementation of depression prevention programmes.

Extrapolation of adult efficacy and safety data based on PK data alone is not considered appropriate. Therefore, short-term efficacy data should be generated in the paediatric population as in adults, separately for children 7 to 11 years of age and for adolescents 12 years of age and older.
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. In addition to stratification, an age-staggered approach may also be appropriate. If throughout the trials all subjects receive psychosocial interventions, this should be standardised —wherever possible.

Efficacy in acute treatment should be demonstrated in at least one short-term placebo-controlled trial. The study duration should be long enough to show statistically significant and clinically meaningful separation of active treatment from placebo. Trials of 4-6 weeks duration are usually recommended but this might need to be adapted depending on the mechanism of action (section 4.3.2.). 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 and/or patient-reported outcome measures should be included as secondary endpoints. The input of carers may help to interpret the severity of symptoms.

Maintenance of effect and long-term efficacy studies may not be necessary in the paediatric population and extrapolation from adults could be acceptable, provided that robust evidence of short term-efficacy is available from both adults and the paediatric population (adolescents and children), and the effect size is comparable or analogous across trials.
Long-term safety data still need to be generated. Post-marketing long-term safety studies in children and adolescents could be structured to include also efficacy endpoints to support extrapolation of long-term efficacy.

4.5.3. Sex-related differences and considerations

Serotonergic neurochemical responses which were differently affected in males and females have been observed in animal models, consequently causing sex-dependent effects in behaviour. In addition,

certain animal species have exhibited a sexually dimorphic response to chronic antidepressant treatment.

There is higher prevalence of MDD in women. A number of publications have identified sex differences in patients with MDD. In women, the risk for suicide attempts is higher whereas the risk for suicide completion is lower compared to men. However, at present, these differences cannot be considered sufficient for specific recommendations for trial populations, which should be an accurate reflection of the patient population in clinical practice. Predefined analyses of sex specific groups are welcomed. Data should be presented specific for sex and ideally for gender as well, age, race etc. to allow an estimate of potential differences.

4.6. *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, frailty and other relevant variables. After discontinuation of treatment, AEs should be reported for an adequate time (e.g., 5 half-lives). Adverse event scales should be standardised for use in studies with psychotropic drugs. 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 a-adrenergic, and to glutamatergic or anti-GABAergic AEs, if relevant.

4.6.1. Specific adverse events to be monitored

Some of the below mentioned adverse events are typical for some drug classes or MOA but may not apply to all MOAs. Applicants should justify the safety monitoring during the clinical trial.

4.6.1.1. 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 to the study medication. These may include but are not limited to anxiety, dysphoria, agitation, aggression, insomnia, dissociation, hallucinations, confusion (see also section 4.6.1.3.). 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, preferably for both the active treatment and placebo.

4.6.1.2. Adverse effects on cognitive functioning

If relevant, a detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim (section 4.4.2.1.). 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. The use of additional scales is especially required if an effect has been identified in early trials or is related to the MOA. The use of additional scales should be carefully considered since increased interactions with caregivers might increase placebo response.

4.6.1.3. Overdose

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

4.6.1.4. Suicide

The potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured in all age groups using validated rating scales (e.g. InterSePT Scale for Suicidal Thinking, Columbia Suicidality Severity Rating Scale (C-SSRS), the SIBQ (Suicidal Ideation and Behaviour Questionnaire) 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 if available.

4.6.1.5. 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).

4.6.1.6. Haematological adverse events

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

4.6.1.7. Endocrinological adverse events and sexual dysfunction

Special attention should be paid to the effect on sexual function and libido. The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale.

In case anti-dopaminergic substances are tested, effects on galactorrhoea and gynaecomastia should also be evaluated and the 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. Thyroid dysfunction can affect mood and should also be monitored.

4.6.1.8. Cardiovascular adverse events

Due to the known cardiovascular effects associated 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/QTc-interval prolongation should be investigated in accordance with the ICH E14 guideline.

4.6.1.9. 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 with a strong dopaminergic mode of action 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.

4.6.1.10. Serotonin syndrome / Neuroleptic malignant syndrome

Serotonin syndrome can be caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors and has been described for many antidepressants. Serotonin syndrome is typically caused by the use of two or more serotonergic medications or drugs. The clinical symptoms include neuromuscular hyperactivity, autonomic hyperactivity and altered mental status. Diagnosis is based on a patient´s symptoms and history of medication use.

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

4.6.1.11. 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 evaluated 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.

4.6.1.12. Long-term safety

Since a depressive episode can have a duration of up to 2 years, the total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure of at least 12 months.

4.6.1.13. Older patients

Certain adverse events such as anticholinergic effects, delirium, sedative effects, cardiovascular and hypotensive effects, dizziness, falls, effect on food intake and functional decline, have been observed in older patients treated with certain antidepressants and these should be monitored in the trials designed for older patients.

4.6.1.14. Children and adolescents

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

Response: clinically relevant improvement in terms of symptom reduction (to be defined in advance of the study).

Responder: a patient with clinically relevant and pre-defined improvement.

Remission: Remission is defined as no or only few signs of a specified condition.

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.

Specifier: extension to a diagnosis that further clarifies the course, severity, or special features of the patient's disorder. More than one specifier may be applied on a patient.

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