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Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia

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This guideline replaces NfG on clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95).

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Guideline on clinical investigation of medicinal products, including depot preparations, in the treatment of schizophrenia

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Executive summary

This document is intended to provide general guidance for the development of medicinal products, including depot preparations, for the treatment of schizophrenia. The guideline has been developed during a transitional period in which the DSM IV classification and diagnostic criteria for schizophrenia (and other psychotic conditions) are being revised in the preparation for DSM 5.

This guideline will not address development of medicinal products for the treatment of psychotic conditions other than schizophrenia.

The main requirements for the development of medicinal products for the treatment of schizophrenia, with regard to study design, patient population and outcome measures are described. Specific issues, including treatment resistant patient populations and other specific patient groups (children and adolescents) are addressed. Attention is focused on alternative treatment options such as add-on, augmentation, and combination therapy. The importance of specific domains in schizophrenia including cognition and negative symptoms are also discussed.

The change in outcomes of clinical studies performed in patients with schizophrenia in the last decades (e.g. higher placebo response, stability of clinical response) has triggered a broad discussion. Possible study designs in terms of use of placebo, study duration, and patient population have been reviewed and have been redefined where needed. The main scope is to provide guidance on the choice of clinical studies that are feasible and likely to produce interpretable results.

For convenience and harmonization of documents, guidance for the development of depot preparations is added as appendix.

This document should be read in conjunction with other relevant EMA and ICH guidelines (see section 3).

1. Introduction (background)

1.1. Schizophrenia

Schizophrenia is a severe psychiatric disease with a heterogeneous course and symptom profile. The personal tragedy associated with schizophrenia is extreme, since it attacks the human properties considered most precious and distinguishing. The worldwide lifetime morbidity risk of the disorder is about 1 percent across diverse geographic, cultural, and socio-economic regions and has not changed over the years. The age of onset of the first psychotic episode is typically in the late teens, but can be as late as into the mid thirties. Onset prior to adolescence is rare. Age of onset is earlier in men than in women. In most patients the disease follows a chronic course with lasting impairment.

Schizophrenia presents clinically with so-called positive and negative symptoms. The positive symptoms include delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours. Negative symptoms include affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms appear to reflect a diminution or loss of normal function.

In addition, cognitive deficits (defects of working memory, information processing, attention/vigilance, learning, reasoning and social cognition) are common. Whether these should be considered to belong to the core symptoms is currently under discussion. Cognitive deficits generally show poor improvement with current antipsychotic treatment.

Besides these predominant symptoms, schizophrenia is associated with an increased incidence of other psychiatric symptoms such as manic and depressive symptoms, anxiety or obsessive-compulsive symptoms, substance abuse and dependence, and personality disorder. Schizophrenia with co-morbid symptoms should be distinguished from other psychotic disorders (see also section 1.3).

The current diagnostic criteria are made explicit in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM IV) and in the International Classification of Diseases, (ICD 10). These criteria are valid for the purpose of case identification. According to DSM IV (1994) the essential features of schizophrenia are a mixture of characteristic signs and symptoms (both positive and negative) that have been present for a significant proportion of time during a 1 month period, with some signs of the disorder persisting for at least 6 months.

1.2. Schizophrenia in the paediatric population

Schizophrenia is very rare in pre-pubertal children and is more likely to be associated with chromosomal/cytogenetic variations. However, when it does occur, schizophrenia in pre-pubertal children is comparable at the symptom level to schizophrenia in adults.

Fleeting hallucinations and delusions are common in paediatric subjects and therefore a high rate of misdiagnoses is reported. The differential diagnosis includes affective disorders (major depressive episodes and bipolar disorder), psychosis secondary to medical conditions, side effects of medication and/or substance abuse, autism spectrum disorder, conduct disorders, post-traumatic disorders and personality disorders under development.

Schizophrenia in adolescents may be preceded by prodromal cognitive impairment at a young age but these abnormalities have neither diagnostic specificity nor predictive value. A deterioration in functioning is often associated with the schizophrenic prodrome. With increasing age, symptoms increasingly resemble those of adults. However, negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning in adolescent patients. In addition the disease tends to follow a more severe course, has lower response to treatment and a worse long-term prognosis than adult onset schizophrenia.

Because of these characteristics in children and adolescents, for registration purposes only patients with a definitive diagnosis of schizophrenia would be eligible for inclusion in clinical studies.

1.3. Other psychotic disorders

Several other psychotic conditions are recognised. However, their classification and diagnostic criteria are being thoroughly revised within the preparation of DSM 5. The diagnosis and treatment of psychotic conditions other than schizophrenia will not be discussed in the current guideline (see also section 2).

1.4. Treatment

1.4.1. Medical treatment

The aim of conventional antipsychotic treatment can be categorised into: 1) acute treatment primarily to control positive symptoms, and 2) maintenance treatment to consolidate stabilized control of symptoms and to prevent exacerbations. In addition to the traditional emphasis on positive symptoms, a number of clinical trial programmes have investigated products specifically for their possible effects on negative symptoms, cognitive function, and on depressive symptoms seen in schizophrenia.

The effectiveness of the so-called first generation or typical antipsychotic agents, on symptoms in schizophrenia is mostly attributed to their anti-dopaminergic effect, particularly at the D2 receptors. The so-called second generation or atypical antipsychotic agents show in addition a varying degree of affinity for serotoninergic (notably 5-HT 2A), dopaminergic, muscarinic, cholinergic, α1 adrenergic and histamine H1 receptors, which are thought to be involved largely in the negative symptom presentation.

Recently, compounds that modulate glutamate receptor activity are being studied in line with theories that dysregulation of the glutamatergic system might contribute to the pathophysiology of schizophrenia. Other targets including but not limited to acting on the GABA (γ-Aminobutyric acid) system, on alpha-2 adrenergic receptors and on various serotoninergic and dopaminergic receptors including D1 receptor agonists as well as acetylcholinesterase inhibitors and muscarinic acetylcholine receptor agonists are being studied for their impact on either cognition or other symptoms not directly linked to the positive symptoms.

For patients whose psychotic symptoms are not sufficiently controlled with one medicinal product there are a number of possible augmentation strategies with various treatment objectives. Although such strategies are quite widely used in clinical practice there are no products currently approved in the EU (European Union) for use in this way at the time of writing of this document, and there is a general lack of supporting evidence.

1.4.2. Supportive treatment

In most EU countries, patients with schizophrenia are offered supportive treatment, such as standardised psychotherapy, psycho-education, social support, and counselling. These supportive treatment practices vary considerably among EU member states but have their value for sustainability of drug effects.

2. Scope

This guideline focuses primarily on products developed specifically for schizophrenia. Some comments are also made about treatment of psychosis as a part of other disorders. However, data requirements to support an indication for other disorders are out of the scope of this guideline.

During the development of this guideline DSM IV is under revision, and it is expected that it will be replaced by DSM 5. This might have consequences for the definitions of the disorders as given in this guideline, and these may need amending accordingly.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 (as amended) and relevant CHMP and ICH guidelines, in particular:

- Dose-Response Information to Support Drug Registration (CPMP/ICH/378/95 , ICH E4)
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A).
- Points to Consider on the Clinical Requirements of Modified Release Products Released as a Line Extension of an Existing Marketing Authorisation (CPMP/EWP/1875/03).
- Note for guidance on clinical investigation of drug interactions (CPMP/EWP/560/95)
- The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs (CHMP/ICH/2/04, ICH E14)

- Guideline On The Non-Clinical Investigation Of The Dependence Potential Of Medicinal Products (EMEA/CHMP/SWP/94227/2004)
- Statistical Principles for Clinical Trials (CPMP/ICH/363/96, ICH E9)
- Choice of Control Group in Clinical Trials (CPMP/ICH/364/96, ICH E10)
- Points to Consider on Adjustment for Baseline covariate (CPMP/EWP/2863/99)
- Guideline on Missing data in confirmatory clinical trials (CPMP/EWP/177/99)
- Note For Guidance On Population Exposure: Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95, ICH E1)
- Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU population (EMEA/CHMP/EWP/692702/2008)
- Note For Guidance On Clinical Investigation Of Medicinal Products In The Paediatric Population (CPMP/ICH/2711/99, ICH E11)
- Note For Guidance On Studies in support of special populations: geriatrics (CPMP/ICH/379/95, ICH E7)
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)
- Note for Guidance on the evaluation of the pharmacokinetic of medicinal products in patients with impaired renal function (CHMP/EWP/225/02)
- Guideline on the evaluation of the pharmacokinetic of medicinal products in patients with impaired hepatic function (CHMP/EWP/2339/02)

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

In developing medicinal products for the treatment of schizophrenia, specific issues should be considered. These include:

4.1. General strategy

4.1.1. Use of placebo

There is a debate about the use of placebo in clinical trials in the treatment of schizophrenia. Concerns about ethical issues and feasibility have been raised. However, assay sensitivity cannot be guaranteed even in well designed and conducted trials if a placebo arm is not included. Historical controls are not useful for current clinical trials, since the concept of the disorder, the diagnostic criteria and the efficacy criteria have changed. In recent trials in schizophrenia, the difference in efficacy between active treatments and placebo has tended to be smaller than the differences seen in the past. Therefore, a placebo control has been considered necessary for internal validation of non-inferiority trials comparing new drugs to an active control and is also highly desirable so that the 'absolute' effects (both therapeutic and adverse) of a product can be ascertained.

To avoid unnecessary risks for patients and others, placebo controlled studies should be performed in a highly controlled setting, with stringent follow-up to apply predefined escape criteria, rescue medication and stopping rules. Provided these safeguards are in place, the benefits of using a placebo arm will generally override any ethical reservations in short term controlled efficacy trials (see section 4.4.3.1) Long term administration of placebo to patients in need of active treatment is ethically problematic and is associated with a high rate of premature withdrawals, making interpretation of the

data difficult. For demonstrating maintenance of effectiveness of treatment in the long term, the use of a placebo arm is however possible and appropriate in a randomised withdrawal study in which patients stabilised on open label test treatment for at least 12 weeks are randomised to active test treatment or placebo. Patients who relapse meet study endpoint criteria and can receive active treatment immediately without compromising the study requirements. Provided the study is appropriately designed and conducted patients in the placebo group who become in need of active treatment will not be denied it and hence there should not be ethical problems.

4.1.2. Specific claims

For first and second generation antipsychotics an effect on schizophrenia should be demonstrated before efficacy on specific domains (such as cognition or negative symptoms) can be claimed. This is to avoid unnecessary polytherapy. For other compounds with different mechanisms of action that target a specific domain and for which no antipsychotic effect is expected, specific claims could in principle be made without a general indication for treatment of schizophrenia. Each of these claims should be supported by robust evidence and this will require trials specifically designed to test the specific aspect of efficacy for which a claim is to be made. The patient population studied, the comparator that is chosen, and the usefulness (validity, relevance) of the rating scales used to measure efficacy for that situation should all be justified (see section 4.5).

4.1.3. Extrapolation to other psychoses

As stated in sections 1.3. and 2, psychotic symptoms may occur in other disorders which may either be syndromes distinct from schizophrenia or prodromal to the development of full schizophrenia. Diagnostic criteria can be found in DSM IV and ICD 10. As such disorders may differ substantially in terms of patient characteristics and their natural course, it is not possible to extrapolate data from a specific psychotic disorder (e.g. schizophrenia) to another (e.g. delusional disorder). Therefore, it is not acceptable to perform studies in order to support a broad indication for treatment of psychosis.

4.2. Assessment of therapeutic efficacy

To support an indication for the treatment of schizophrenia, efficacy on a broad range of schizophrenia symptoms, as captured by the total score on instruments such as the PANSS or BPRS, has to be demonstrated in short-term studies (see section 4.4.3.1.) and maintenance of treatment effectiveness has to be shown in at least one long term study (see section 4.4.4.). Both types of data should be part of the package submitted for marketing authorisation.

Cognitive impairment in schizophrenic patients may be part of the chronic illness or may be due to other causes such as transient exacerbations of acute psychotic symptoms, medications (especially anticholinergic agents), depression, or understimulation of the patients (as a result of hospitalization). In order to support an indication for the treatment of cognitive symptoms of schizophrenia, a treatment effect should be shown on cognitive symptoms that are clearly a core part of the syndrome of schizophrenia. The effect of treatment on cognitive function should be documented even if no specific indication is sought, for the purpose of characterizing the safety of the drug product.

4.2.1. Choice of efficacy outcomes and assessment tools

Efficacy has to be measured with the use of accepted, reliable and valid measurement scales. In some cases alternative assessment tools may be appropriate, but the choice of other tools should be fully justified based on standard test quality criteria.

The primary efficacy measure should be a composite measure of the symptoms of schizophrenia. For this, the widely accepted measurement scales are the PANSS (Positive and Negative Symptom Scale) and BPRS (Brief Psychiatric Rating Scale), which are still considered to be reliable and validated. However the use of other valid, more recently developed instruments is encouraged, provided reference can be made to the well known instruments, PANSS/BPRS.

In addition secondary efficacy measures should be presented to assess the effect of the test product on further aspects of the disease. Clinical global impression (CGI) data should also be presented, both CGI-severity and CGI-improvement.

For assessment of negative symptoms in particular, the use of specially designed rating scales is necessary. Older assessment scales such as the BPRS give little emphasis to negative symptoms and are not suitable for this purpose. Satisfactory reliability and validity has been demonstrated for the negative symptoms subscale of the PANSS and for the SANS (Scale for the Assessment of Negative Symptoms). Due to the limitations of available scales as mentioned, the development of new scales is encouraged. This also applies to instruments used to assess treatment effects on cognition.

4.3. Clinical Pharmacology studies

4.3.1. Pharmacodynamics

The use of biomarkers such as receptor occupancy PET studies (e.g. D2 and 5HT 2A receptor occupancy) and imaging techniques to detect structural changes in the brain may be useful in dose finding and proof of concept studies in early drug development. However, specific claims will be obtained based on results from clinical outcomes and not on biomarkers, which can provide only supportive evidence.

4.3.2. Pharmacokinetics

No specific requirements for medicinal products in schizophrenia are necessary (see Guidelines on pharmacokinetic studies in man, modified release products, and on evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic and renal function). The extent to which the drug crosses the blood-brain barrier should be established. For depot preparations, see appendix.

4.3.3. Interactions

All pharmacodynamic interactions between the test drug and other drugs that may be prescribed simultaneously in clinical practice and have potential PD interaction, should be studied, as well as potential pharmacodynamic interactions with alcohol and CNS (Central Nervous System) active substances. Reference is made to the drug interaction guideline.

4.4. Clinical efficacy trials

4.4.1. Exploratory trials

For exploratory or proof of concept studies various designs are acceptable. In these studies the emphasis tends to be maximization of the power of the study to detect a treatment effect, rather than on broad applicability of the findings. Methods of achieving this include using narrow inclusion criteria or other selection of patients considered most likely to respond, and excluding placebo responders (enrichment design). These design aspects are only acceptable for exploratory trials, and should not be applied to provide confirmatory pivotal evidence of efficacy.

4.4.2. Demonstration of dose response relationship

It is essential that the proposed doses for the SmPC are robustly justified. Preliminary data on the dose range anticipated to be therapeutic can be obtained from non clinical data such as animal models and receptor occupancy studies. However dose-response relationships need to be established in clinical trials using validated efficacy endpoints. The minimum effective dose and the dose at which best efficacy is obtained should be established. Flexible dose designs are unsuitable to provide this information and therefore designs with multiple fixed doses and a placebo control are required. It is preferred to make direct dose comparisons of multiple doses in a single study. Dose response is typically established in short-term studies, and this information serves as a basis for dose selection in both additional short-term phase 3 studies and the longer term maintenance study. It is strongly recommended to establish the dose-response of the investigational drug prior to the start of confirmatory trials (Phase 3) as the use of inadequately justified doses may hamper interpretation of the latter trials. In addition, the study population in the dose finding studies should preferably reflect the entire targeted patient population. For general strategy and design refer also to section 4.4.3. Refer to ICH E4 regarding dose-response estimations and the utility of modelling.

4.4.3. Confirmatory trials

The purpose of short term confirmatory trials is to demonstrate the efficacy of the medicinal product and obtain initial information on safety in the wide patient population.

4.4.3.1. Study design for short term trials

Crossover designs are unsuitable for trials in patients with schizophrenia. Confirmatory trials should be double-blind, randomised, parallel group trials.

The study protocol should provide a justification of the choice of the active comparator – this would normally be an active comparator with proven efficacy and, if from a similar class, a similar clinical pharmacological profile to the test product. If the product is the first in its class an appropriate active comparator would be a product licensed in the target indication and population or, if there is no suitable licensed product, a medicinal product recognised as the "gold standard" for the target indication and population in clinical practice should be chosen as a suitable active comparator.

If the aim of the study is to demonstrate non-inferiority to an active comparator, then a three-arm study of placebo, test product and active comparator is recommended (see also section 4.4.3.7.). Superiority to placebo should be demonstrated in order to ensure assay sensitivity of the study.

Alternatively, a two-arm study of test and active comparator would be acceptable provided superiority of the test product over an appropriately justified active comparator was demonstrated.

4.4.3.2. Study population

Patients should be diagnosed and classified according to the criteria of DSM IV or ICD 10, and subsequently classified according to the longitudinal course of their disease (e.g. exacerbation, remission, inter-episode residual symptoms, or chronically ill). The diagnosis should be made by a qualified psychiatrist and confirmed with the use of a structured assessment tool e.g. the SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders). Further descriptive parameters (co-morbidity, substance abuse), demographic characteristics and a detailed disease history (duration of disease, duration and number of exacerbations, naïve or exposed status, and previous treatment outcome) should be documented.

In contrast to proof of concept studies, for pivotal efficacy studies it is important to maximise external validity and broad applicability to the intended patient population, without unduly compromising internal validity. This may require exclusion of patient groups that may introduce confounding by e.g. co-morbidities or concomitant medication. Exclusion criteria should be clearly justified.

Patients in an acute phase (with florid positive symptoms) may generally show a much larger response to pharmacological treatment compared to patients in a chronic phase. Therefore, if patients in different phases of the disease are included in the same clinical study, stratified randomisation is recommended to ensure that the different types of patients are evenly represented throughout treatment arms. It is recommended to include at least 20% of patients with a disease history of less than 5 years. The inclusion criteria should define the patient population in terms of severity of symptoms. Cut-off scores can be based on efficacy measurement scales (e.g. PANSS).

4.4.3.3. Study duration

The preferred design for demonstrating short term efficacy is a 6 week clinical trial. This is because so far for first- and second generation antipsychotics, a reasonable stability of effect has been observed as well as some effect on negative symptoms, often only after 6 weeks of treatment. Shorter study duration (e.g. 4 weeks) could also be considered, especially for drugs with a similar profile to existing antipsychotic drugs. This carries the risk of negative results if maximal therapeutic effect is not obtained at 4 weeks and the shorter duration is disadvantageous in terms of the ability to demonstrate stability of effect. For new compounds with novel mechanism of action (different from the currently available antipsychotics) and/or targeting other domains such as negative symptoms or cognition, the study duration might need to be adapted accordingly (see section 4.5).

4.4.3.4. Co-medication

Co-medications, for example benzodiazepines, may be permitted to the extent that they do not compromise detecting signals of safety and efficacy of the drug candidate. In the interest of generalizability of the data to the intended patient population, a rationale for excluding concomitant medications should be provided. It may be appropriate for the sponsor to place limits on the amount of use of benzodiazepines within a study or to specify that patients should be on a stable dose regimen for some time before starting the trial.

Treatments that may augment the test treatment should be excluded, despite the consequences of these exclusions for generalizability of the trial results. Therefore other antipsychotic drugs should be discontinued, except in the case of augmentation studies (see also section 4.5.4.).

Standardised psychotherapy, psycho-education, support or counselling may be offered as supplementary treatment, but their use should be prospectively defined in the protocol and documented in the trial report. The effects on treatment should be discussed in the dossier.

4.4.3.5. Screening and run-in periods

Following screening, qualitative and quantitative baseline assessments should be conducted in a short run-in period. Prior antipsychotic medication should be washed out, normally tapered in a single blind placebo run-in period of sufficient duration aiming at elimination of prior treatment without substantial worsening of symptoms. Typically a few days will be appropriate for run-in, but this period may vary according to the targeted patient population (e.g. chronically ill or acute exacerbation). Placebo responders should not be excluded from randomisation, except in the case of exploratory studies. In some instances screening, baseline assessments, randomisation and start of study medication may be performed in a single day, especially if patients are severely ill.

4.4.3.6. Efficacy parameters

Primary efficacy measure(s) should be presented as the numerical change in schizophrenia symptom score from baseline to study endpoint (final measurement). The results should be discussed not only in terms of statistical significance but also in terms of clinical relevance. Presentation of the proportion of patients with a pre-specified degree of improvement on the symptom score is valuable. For this purpose, responder analyses should be presented. Also the proportion of patients deteriorating during treatment should be documented.

In short term trials in patients with acute/exacerbated symptoms at least a 30% reduction on the total PANSS score compared to baseline is generally considered to be clinically relevant and can be accepted as a definition of responder. This figure may need adjustment in case of inclusion of more chronically ill patients, therefore a flexible approach can be taken. For sensitivity analyses the presentation of additional responder analyses using alternative criteria for response rates is recommended, e.g. the proportions of patients with minimal and with substantial improvement.

4.4.3.7. Statistical considerations

For more complete guidance on statistical principles for clinical trials, please refer to ICH E9 statistical principles for clinical trials.

The standard randomized placebo and active-controlled, parallel group trial design is intended to show superiority of the drug candidate to placebo and to quantify the efficacy of the drug candidate in comparison with a drug of known efficacy for the treatment of schizophrenia. Analysis populations should include the full analysis set (FAS) and the per protocol (PP) population.

A particular problem with both short and longer term trials in schizophrenia relates to patient withdrawals and consequent missing data. All reasonable steps should be taken to minimise their occurrence and to follow patients regardless of adherence to protocolled treatment to better understand the impact of missing data. Reasons for drop outs should be documented (especially to distinguish between lack of efficacy and undesirable effects). In this respect, special attention should be drawn to the issue of compliance, which is a problem in patients with schizophrenia. Assessment of compliance should be ensured during clinical studies by e.g. measurement of drug plasma levels, tablet counting.

Some of the commonly used analysis techniques, such as LOCF and BOCF approaches, have the potential to introduce bias. While easy to implement, these methods have a number of limitations, including over-estimation or under-estimation of treatment effects (and the associated variance) and inconsistency with the course of disease. Sensitivity analyses that evaluate missingness assumptions should be performed to assess the robustness of findings. All of the aforementioned analyses should be prespecified in the protocol. Since the statistical findings might be uninterpretable in the presence of high dropout rates, the dropout rates in a trial need to be considered when interpreting the efficacy findings

Reference is made to the CHMP guideline on missing data in confirmatory clinical trials and the advice therein to consider the problem of missing data in advance of the trial, and provide detailed discussion of the missing data pattern observed and potential biases introduced once the trial has been completed.

4.4.4. Study design for long term trials

Due to the chronic course of schizophrenia (with exacerbations) and the need for lifelong treatment, long term data are necessary in order to demonstrate that the treatment effect found in the acute

phase is maintained over time and that there is a continued need for treatment. Several approaches to study design are possible.

The objective of demonstrating a continued need for treatment with superiority to placebo in the long term is best achieved by means of a randomised withdrawal study. In this design patients are treated open label for a period of at least 12 weeks, whereas patients who show a stable favourable clinical response after that time are randomised to either the test product or placebo. The primary efficacy variable is the occurrence of symptom relapse rated on a symptom scale. Patients who relapse become study completers and can be re-started on open label treatment without delay. The randomised treatment period should be of sufficient duration to achieve sufficient events rates (i.e. relapses) to ensure the necessary statistical power. This will depend on the nature of the test treatment and the patient population; periods of up to 6 months are typical. A randomised withdrawal study is also useful for the evaluation of withdrawal phenomena.

A stand alone active comparator parallel trial is an alternative possibility. When the trial objective is to demonstrate non-inferiority, the active comparator should be a product with a well documented maintenance of treatment effect in schizophrenia. Due to the natural course of the disease, the duration of such a trial should be 12 months.

The main issue with parallel design schizophrenia trials such as these, with active comparator but no placebo, is substantiation of the assay sensitivity of the trial. If this cannot be assured then equivalence or non-inferiority to the active comparator cannot reliably be concluded.

Traditional open label single arm extensions studies can provide little or no evidence of long term efficacy. Apart from the obvious sources of bias, there is normally a steady withdrawal of patients who do not respond sufficiently to treatment so that analyses in the remaining patients provide an overestimate of overall long term efficacy.

Extension of short term studies can however provide evidence of maintenance of effect if there is an active comparator control group and the double blind is maintained. Sponsors are encouraged to adopt such designs instead of open label single arm extensions studies. Unbalanced randomisation so that the majority of patients receive the test drug is satisfactory provided the study has sufficient statistical power for its objectives. The design of the study should be such that the comparison between test and active comparator treatments in the long term phase remains a comparison between truly random groups. For example selecting responders to short-term treatment with the test product and re-randomising them to receive long term test or active comparator treatments would be unsatisfactory.

Neither a randomised withdrawal trial nor a parallel group active comparator trial is ideal on its own for showing long term efficacy for treatment of schizophrenia. The former generally does not allow for a clear estimation of the magnitude of the treatment effect while the latter has issues with assay sensitivity and does not reliably demonstrate continuing benefit from treatment. A hybrid design in which a randomised withdrawal period of 6 months is incorporated into a long term parallel group active comparator trial (after at least 12 months of treatment) could be an optimal approach as it could include the desired aspects from both of the basic designs. Demonstration of superiority of both active treatments to placebo in the randomised withdrawal period could confirm assay sensitivity of the parallel group trial and provide statistically robust evidence that patients continue to benefit from treatment in the long term.

4.4.4.1. Efficacy parameters in long term studies

The primary efficacy variables to measure maintenance of effect would depend on the design of the clinical study, indication and patient population.

In parallel design studies, the primary efficacy should be measured as the difference between baseline and endpoint on the symptom score, as in the short term studies. As in short-term efficacy studies, a proportional responder analysis would be supportive of the long-term treatment need. Drop out rates, which are indicative of treatment failure, and the proportion of patients meeting pre-specified criteria for relapse should be analysed at pre-specified time points as key secondary endpoints. In a randomised withdrawal design, the primary efficacy measure would be proportion of patients with relapse rated on a symptom scale at certain time intervals (e.g. at 1, 3, and 6 months) using pre-specified criteria. Patients with exacerbations must be clearly distinguished from withdrawals due to other reasons.

4.5. Specific claims

4.5.1. Efficacy on negative symptoms

If an effect on negative symptoms is claimed, specially designed studies in patients with predominant negative symptoms should be conducted. The duration of negative symptoms and onset of the current stable episode of schizophrenia should be documented (e.g. 6-12 weeks). To ensure that patients with true negative symptoms of schizophrenia are studied, and not those whose symptoms are related to depressive symptoms or extra-pyramidal symptoms (EPS), the inclusion criteria should encompass:

a) Predominant and persistent negative symptoms.

b) Flat affect, poverty of speech, and avolition being present as representative of core negative symptoms

c) Stable condition of schizophrenic illness for longer than 6 months, especially of the negative symptoms.

Exclusion criteria should include:

d) Major depression; low depression scores are preferable.

e) Subjects with substantially confounding extra-pyramidal symptoms.

f) Substantial non-compliance or substance abuse.

Improvement on negative symptoms should be demonstrated through validated scales (e.g. PANSS negative subscale, SANS or other), and presented as the difference between baseline and endpoint. Responder rates should be provided and demonstration of functional improvement, e.g. improvement in functional capacity, as key secondary outcome measure is recommended. The design can be either in an add-on or monotherapy setting (see 4.5.3 and 4.5.4.).

A study duration of at least 6 months on a stable dose is recommended. For design options, refer to section 4.5.4.

4.5.2 Efficacy on cognitive deficits

To support a separate claim for efficacy on cognitive aspects in patients with schizophrenia, specific studies should be performed. The patient population should be clearly defined in terms of a range of relevant measures of cognitive functioning. For this purpose, the cognitive test battery as proposed and defined by MATRICS is acceptable but other, comparable, test batteries may also be used provided their validity is demonstrated. A relatively younger patient population might be more appropriate for testing effect on cognition in schizophrenia, since with disease progression response to treatment of cognitive impairment may decline.

The effect of treatment on cognitive functioning should be demonstrated as the difference between baseline and endpoint on the cognitive functioning test score. Whichever tool is used, mere reduction on specific items of a larger test battery is not acceptable. In addition a functional outcome measure of clear clinical relevance to patients' functioning should be reported. Preservation or improvement of functioning as proposed for efficacy in treatment of negative symptoms would be acceptable, but the development of functional assessment instruments tailored to the assessment of treatment effects on cognitive functioning in schizophrenia is encouraged.

A study duration of at least 6 months on stable dose is recommended. Although an improvement of cognitive function might be observed after a shorter duration of treatment (e.g. 8-12 weeks), it will be necessary to demonstrate that the treatment effect is maintained over time. For this purpose, a maintenance of effect study of at least 6-12 months would suffice. Functional outcome assessed at the end of the long-term treatment period will be a particularly important secondary efficacy measure. For further considerations on design, refer to section 4.5.4.

4.5.3 Trials to study monotherapy in treatment resistant/refractory patients

Monotherapy in patients with treatment resistant schizophrenia could be a separate but additional claim for compounds with an adequately substantiated general schizophrenia indication. It is not approvable as the sole indication and should not be confused with an indication restricted to second or third line use because of safety issues. At least one additional trial should be performed to support extension of the indication to treatment resistant patients. Subgroup analyses among treatment resistant patients in trials conducted in a general schizophrenia population are generally not sufficient to obtain the extended indication, except when clearly pre-specified as a main objective of a broader trial including sufficient representation of treatment resistant patients. In such a case multiplicity of statistical testing should be adequately addressed if efficacy in the treatment resistant population is not the sole primary endpoint. The design of studies and endpoint in therapy resistant patients is essentially the same as described for other trials (see section 4.4.3.). The key differences are the choice of control and the definition of the patient population.

Treatment resistance in schizophrenia is defined as lack of satisfactory improvement despite the use of adequate doses of at least two different antipsychotic agents, including a second generation (atypical) antipsychotic agent, prescribed for adequate duration with adequate confirmation of treatment adherence and abstinence from CNS-active illicit drugs. It is essential to demonstrate clearly that the patients included in the trial are truly treatment resistant according to these criteria and treatment failure or insufficient response clearly documented in the dossier. It is in principle acceptable for one of these treatment failures to be retrospective assessed, but the second one needs to be demonstrated prospectively. Efficacy of the test drug in trials in treatment resistant schizophrenia needs to be demonstrated against an active comparator, the choice of which should be clearly justified. There are two possible approaches for demonstrating efficacy to support the treatment resistant indication:

1. Primary trial objective to demonstrate superiority to the active comparator, which should be a medicinal product with which treatment failure has been documented prospectively.
2. Primary trial objective to demonstrate non-inferiority to a medicinal product that is approved in the EU for the indication treatment resistant schizophrenia. At present the only such drug is clozapine.

In schizophrenia, superiority trials are generally preferred to non-inferiority trials because of the difficulties in assuring assay sensitivity. A three way trial in which the primary objective is to show superiority to a previously failed atypical antipsychotic, with clozapine mono therapy as a third arm to

provide a context for the magnitude of the treatment effect, might be preferable to a two way design. If short term efficacy in this schizophrenia treatment resistant patient population has been demonstrated, long term studies would not be required, since maintenance of effect could be extrapolated from the studies performed for the general schizophrenia indication.

4.5.4. Trials to study augmentation/add-on or combination treatment

Augmentation strategies may be useful where there is insufficient response to antipsychotic monotherapy. Compounds with mechanisms of action that are substantially different from typical and atypical antipsychotics are currently being developed for augmentation strategies. The use of such compound to augment the activity of another product (antipsychotic) is worth a specific claim leading to a separate indication statement. The patient population might include insufficient response to one or more antipsychotics, and the insufficient response might refer mainly to specific symptom domains, such as positive symptoms, negative symptoms, or cognitive symptoms. Therefore the patient population to be included in the studies should be clearly defined in terms of number and degree of treatment failures and domains with insufficient response.

Patients who are completely refractory to treatment with an antipsychotic agent (i.e. show no change from baseline as result of treatment) are generally considered not to be suitable for inclusion in augmentation trials. A switch to an alternative monotherapy (and ultimately perhaps to clozapine) is likely to be a more appropriate treatment option. In the recommended standard short term parallel group trial design for an augmentation indication, patients are randomised to receive active augmentation treatment or placebo in addition to open label standard medication. A list of appropriate baseline standard medications should be defined in the trial protocol. Both short term and maintenance data are required. A trial duration of 4-6 weeks is likely to suffice for demonstration of short term efficacy although substantially longer durations might be necessary according to the nature of the test treatment, patient population and symptom domains targeted.

A comparison with an established treatment is generally valuable in schizophrenia trials in order to estimate the clinical value of the test treatment. However there are currently no products approved for an augmentation indication and therefore a third treatment arm with an active comparator cannot be recommended at the present time for augmentation trials.

Maintenance of effect of long term augmentation treatment can be demonstrated in a randomised withdrawal design. In this case, responders to a combination treatment of a known antipsychotic and the new compound are randomised after an extended period of open label treatment to one of the following three treatments: combination therapy, monotherapy antipsychotic, and monotherapy new compound (if appropriate).

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

4.6. Special populations

4.6.1. Paediatric population

There are a number of significant differences in the typical clinical presentation, severity and natural course of schizophrenia in adolescents compared to adults. Because of the difficulties in diagnosis and low prevalence in younger children, it is not considered necessary to perform clinical studies in children under the age of 13 years.

Despite differences in typical clinical presentation, for the adolescent patient population, similar diagnostic criteria (DSM IV) apply. Compared with adults there is a high degree of co-morbidity (e.g.

autism) and overlap with symptoms of other psychiatric conditions. Because misdiagnosis at young age is a problem, a thorough and critical assessment including psychiatric, psychological and physical examination should be performed by clinical experts. In general the diagnosis of schizophrenia can only be established if all criteria are met and alternative psychiatric, neurological or other medical causes of symptoms have been excluded.

Studies in adolescents should include sufficient patients in each age range and the age distribution should reflect the target patient population. Stratification of patients by age, e.g. 13-15 years versus 16-18 years, or by sexual development stage is recommended since the clinical features and incidence of schizophrenia may differ between strata. Separate studies in subgroups are not required.

Early treatment of prodromal symptoms or prevention of progression to full schizophrenia is not sufficiently investigated to be applicable at this moment (see earlier).

The design of the studies and measurement tools are in general similar to the adult studies. It may be preferable to amend the rating scale tailoring it to the requirements of the adolescent population, and such amendments should be well justified and discussed.

Efficacy in acute treatment should be demonstrated in at least one short term trial of 4-6 weeks' duration. Provided pharmacokinetic data for the different age groups are assessed and short-term efficacy is similar to adults, data on maintenance of effect for antipsychotic drugs may be extrapolated from adults to adolescents as of the age of 15 years. Alternatively, pre- or post-marketing long term safety studies (see section 4.7.2) in children and adolescents could be structured to include also efficacy endpoints to support extrapolation of long-term efficacy from 13 years onwards.

4.6.2. Elderly

For the general indication “treatment of schizophrenia” no specifically designed trials in elderly (>65 years of age) patients are necessary. However, information for this group concerning dose recommendations and safety is necessary. Therefore the number of elderly patients included in the studies should suffice to generate this data.

4.7. 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, time to recovery/resolution time, age, and other relevant variables. If using adverse event scales, these should be standardised for use in studies with psychotropic drugs (e.g. UKU scale). Clinical observations should be supplemented by appropriate laboratory tests and other appropriate investigations (e.g. ECG). AE rates should be presented for the test treatment, placebo and active comparators.

As mean treatment durations including the long term open label trials will generally be longer for the test treatment 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 AEs that are characteristic 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, serotoninergic and a-adrenergic, and to glutamatergic or anti-GABAergic AEs, if relevant.

Paediatric population

Special attention should be given to possible adverse effects on sexual maturation, cognition, endocrine function and other aspects of development. Undesirable effects relating to changes in prolactin levels should be actively studied (see section 4.7.1). With regard to timing of the studies, reference is made to the requirements of the Paediatric Investigation Plans (PIPs). For long term safety evaluation, refer to section 4.7.2.

Elderly population

Safety data should be analysed separately with special attention to safety concerns relevant to this age group e.g. (cardio-) vascular and stroke events, as well as diabetes and CNS effects (see section 4.7.1).

4.7.1. Specific adverse events to be monitored

Extrapyramidal symptoms (EPS)

For dopaminergic products 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. Rates of restlessness should be described.

Any claims concerning a lower incidence of EPS as compared to alternative treatments should be substantiated by robust comparisons with at least one active control with consideration of both clinical and statistical significance.

Tardive dyskinesia occurs late in treatment and is reported for both atypical and typical antipsychotics. The possibility that a test drug might cause tardive dyskinesia cannot be excluded in the typical clinical development programme and therefore the possibility should be mentioned in the SPC even if there are no reported cases.

Withdrawal and dependence

The assessment of withdrawal symptoms should be a standard procedure in the longer term studies. Likewise, an estimate of the dependence potential of the new compound should be part of the dossier.

Psychiatric adverse events

Psychiatric adverse events typically represent a large proportion of the AEs reported in trials in schizophrenia patients. These events may be related to the disorder itself as well as to 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.

As part of the adverse event data, undesirable psychiatric effects including depression and anxiety should be measured using validated rating scales.

Adverse effects on cognitive functioning

The possibility of a detrimental effect on cognition and reaction time, whether via sedation or some other mechanism, should be monitored using validated rating scales, (e.g. part of the standard PANSS assessment). 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.

Suicide

The potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured in all clinical exploratory and confirmatory studies using validated rating scales (e.g. InterSePT Scale for Suicidal Thinking, Columbia Classification Algorithm for Suicide Assessment Columbia Suicide severity rating scale [C-SSRS]). Rates of suicidal events (from suicidal ideation to completed suicide) should be presented and narrative summaries of cases of suicidal behaviour or ideation (based on patient statements or behaviours) should be provided.

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).

Neuroleptic malignant syndrome (NMS)

Neuroleptic malignant syndrome (NMS) has been reported for all dopaminergic antipsychotics. Therefore possible cases should be thoroughly investigated and reported. The possibility that a test drug might cause NMS cannot be excluded in a typical clinical development programme. Therefore the possibility should be mentioned in the SmPC for dopaminergic drugs for drugs of this class even if there are no reported cases.

Haematological adverse events

Special attention should be paid to incidence of neutropenia, agranulocytosis and aplastic anaemia. If known, the time of appearance of any hematologic abnormalities should be described.

Endocrinological adverse events

Special attention should be paid to effects on sexual functioning, menstrual problems in females, galactorrhoea, and gynaecomastia. 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.

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.

4.7.2. Long term safety

The total clinical experience should include data on exposure of a large and representative group of patients in line with the guideline on population exposure (ICH E1).

Paediatric population

Long term safety data (2 years) should be generated, with a requirement of 12 months safety data before licensing, and the other part finalized post-licensing, e.g. through observational studies and registries.

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APPENDIX

Methodology of clinical trials concerning the development of depot preparations of approved medicinal products in schizophrenia

1. Introduction

One of the problems in treating schizophrenic patients is lack of compliance due to inability of the patient in recognising he or she is ill. Depot preparations are meant for maintenance treatment, once a patient is stabilised satisfactorily on an oral preparation. There are many antipsychotic agents on the market. All of them are effective in schizophrenia, but not all of them are effective or suitable for a specific patient. Therefore a patient usually will continue on the product that has been shown to be effective for him. It would be very rare to start a patient on a depot preparation, as e.g. dose titration is not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn. However, in some specific cases, exceptions are possible.

This annex is addressing the methodology of clinical trials for developing depot preparations. For long-acting parenteral formulations that are strictly speaking not depot preparations, this guidance should be considered as far as relevant.

2. Purpose of the development plan

Depot preparations of antipsychotic products will usually be given after the patient is stabilised on the oral form. For the latter, efficacy and safety will have been shown in agreement with the existing guidance. This implies that not only the effect in short-term trials is known (see section 4.4.3), but that also is shown that the effect of the product is maintained over time (see section 4.4.4).

The purpose of the development is:

- to establish the full pharmacokinetics of the novel formulation including the relevant release properties and thus to show that the formulation is a depot
- to compare bioavailability of the active ingredient from the depot versus the oral formulation, to assess the duration of an acceptable level of the active ingredient,
- to compare the efficacy versus the oral formulation in stabilised patients
- to address switching from oral to the depot formulation.
- to assess safety issues specific to the depot formulation For this the relation between PK and effect should be known.

In principle,, clinical studies to compare efficacy of the oral and depot preparation and to justify the dose interval are deemed necessary, unless a clear pharmacokinetic/pharmacodynamic relationship is demonstrated for the oral formulation.

3. Pharmacokinetics

Switching from oral to parenteral administration may also influence the interaction profile of the drug, due to pre systemic metabolism. If dose adjustment is required of the drug in consideration or with respect to co-administered drugs, these dose adjustments should be reconsidered with the new route of administration. Data on release rate over time, residues in the injection site and accumulation may be estimated by using adequate pharmacokinetic modelling with the use of pharmacokinetic data after oral administration and data after single dose with the depot preparation. It should be taken into consideration to calibrate a model on the different doses used, as well as in the oral treatment as used in the parenteral treatment.

4. Efficacy

As indicated, the efficacy and safety of the compound are known and it is not necessary to show this in itself for the depot formulation, provided no new claims are made.
However, it is of importance to know whether the new formulation affects efficacy or safety in comparison to the oral formulation. The bridging program should address and support the issues mentioned in section 2.
The indication is related to the patient population included in the bridging program. If the depot is aimed at more than one disorder, clinical trials will have to be conducted in each disorder, unless extrapolation of the data from one population to another can be justified.
In the treatment of schizophrenia usually a dose range is available and the correct dose is titrated individually. Various doses of the depot formulation might be developed to take care of this variation in individual doses.
The development plan should address the appropriateness of the doses chosen and the efficacy and safety of these doses.

4.1. Design features

The purpose of the study is to show non-inferiority of the depot formulation versus the oral formulation. This can be done in various ways, e.g., by showing that the situation at baseline is maintained or improved to the same extent, or by using relapse/deterioration as endpoint.

The results should demonstrate non-inferiority. The non-inferiority margin should be defined in advance and justified, taking into account among others, the available efficacy data and the patient population, the duration of the trial and the endpoint (see ICH E10).

As in all active controlled trials, assay sensitivity needs to be addressed. One way to address this could be to include a placebo arm. Alternatively the trial could include various dose arms.

In case a two-arm trial is chosen, including depot and oral formulation, assay sensitivity might be increased by e.g., a longer trial duration.

4.2. Trial population

A suitable patient population would be patients with schizophrenia who have responded adequately to the oral formulation after an acute episode and who maintained that response before being randomised. The adequate response should be defined and justified in the protocol. Sensitivity to change should be taken into account when choosing the actual patient population.

4.3. Comparator

The comparator of choice is the oral formulation in appropriate dose(s). The dose(s) should be justified in the protocol. In addition another antipsychotic agent, given as depot, could be considered. It would validate the patient population and help interpretation of the data. Placebo, as an additional arm would ensure assay sensitivity, but might be less feasible in this setting.

4.4. Endpoint

Efficacy should be scored by using appropriate scales, the choice of which should be justified. Maintenance of effect can be assessed by comparing scores at baseline and end of the trial. Relapse/deterioration, expressed as number of patients relapsing and/or time to relapse is another option and might be more sensitive. Relapse should be defined in the protocol; usually it includes the re-appearance of positive symptoms as scored during one or more visits on an appropriate scale.

4.5. Duration

Duration of 3 months of the double blind maintenance period will be acceptable, depending on the inter-injection interval, but a longer duration (e.g. 6 months) might increase the assurance that the study indeed has sufficient assay sensitivity.

5. Switching

As in clinical practice patients will be stabilised initially on the oral formulation, switching from the oral formulation to the depot formulation is an important issue. It should be specifically addressed in the clinical program and the recommendation in the SPC should be justified by pharmacokinetic and clinical data.

Two issues are of importance:

- The oral dose and its corresponding depot dose
- Whether the oral dose can be stopped immediately when the depot is given or should be phased out.

6. Safety

Product-related and dose-related adverse effects are known from the oral formulation, but the database of the depot formulation should be checked for comparability and unexpected adverse effects. In addition local adverse effects should be assessed specifically. Timing of scoring of adverse effects should be justified, especially in case the plasma levels from each injection should exceed the corresponding levels from oral administration for a substantial part of the inter-injection interval.

Depending on the type of formulation the possibility of a sudden increase in absorption and subsequently in side effects should be addressed. Data over a 6-month period will usually be sufficient, but this might depend on the length of the inter-injection interval.