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**NOTE FOR GUIDANCE ON
THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS
IN THE TREATMENT OF SCHIZOPHRENIA**

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THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF SCHIZOPHRENIA

These notes are intended to provide guidance for the evaluation of drugs in the treatment of schizophrenia. They should be read in conjunction with the Directive 75/318/EEC and 83/570/EEC and current and future guidelines, especially those on

- Clinical investigation of medicinal products in geriatrics
- The extent of population exposure to assess clinical safety for drugs intended for long-term treatment in non-life threatening conditions
- Biostatistical methodology in clinical trials in applications for marketing authorisations
- Pharmacokinetic studies in man

They are intended to assist applicants in the interpretation of specific problems presented by anti-schizophrenia products (especially section 2 of this document).

1. INTRODUCTION

Schizophrenia is often a chronic disease. Although in this diagnosis a heterogeneous group of patients is covered, 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 0.85 percent across diverse geographic, cultural, and socio-economic categories. The onset of the disorder occurs relatively early in life, and most patients have long-lasting impairment.

The development of effective approaches to the treatment of schizophrenia requires an accurate method of diagnosis. 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, Injuries and Causes of Death (ICD 10). These criteria are valid for the purpose of case identification.

In the past, products that demonstrated efficacy in schizophrenia, were generally called neuroleptics. Psychosis is a rather unspecific term, historically defined in various ways. Psychotic symptoms are also a part of syndromes such as Delusion disorder, or for example Substance-Related disorder and traditionally, products that demonstrated efficacy in schizophrenia have also been used to treat these disorders.

This guideline focuses mainly on antipsychotic products developed specifically for schizophrenia, although some comments are also made about the extension of the indication to related psychotic syndromes (see section 2.3).

Antipsychotics

Traditionally, antipsychotic agents have been used in three ways: in the acute phase to treat positive symptomatology, as maintenance therapy to control symptoms, and as long-term prophylactic treatment to prevent relapses/recurrence. At present products are also investigated for their possible effect on negative symptoms and there are some studies investigating the effect on cognitive symptoms and depressive symptoms seen in schizophrenia.

Initially the effect of anti-psychotic agents on positive symptoms (= delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour), demonstrated in

schizophrenic patients, was attributed to the anti-dopamine effect of these compounds (dopamine theory of Schizophrenia). Recently so-called atypical antipsychotic agents have been developed, which *in vitro* show more affinity for serotonergic receptors, though they also have an affinity for dopamine receptors.

2. SPECIFIC CONSIDERATIONS WHEN DEVELOPING PRODUCTS FOR THE TREATMENT OF SCHIZOPHRENIA

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

2.1 Use of placebo

There is debate about the use of placebo in clinical trials. On the one hand, a placebo-control is necessary to define the 'absolute' effects - therapeutic and adverse - of a product and as an internal validation of the trial. On the other hand, use of placebo raises ethical problems, especially if effective treatment is available and/or in case of a progressive disease, when changes are irreversible.

When developing a product these two issues have to be weighed in order to find the optimal way for generating data that will enable the competent authorities to come to a conclusion with regard to efficacy and safety of a product.

In schizophrenia new products are being developed, using modern trial methodology, whereas at the same time, the concept of the disorder, the diagnostic criteria and the efficacy criteria have changed. This implies that historical information of the efficacy of the older products may not be useful. In recent trials, using placebo and/or an active comparator as controls, it was found that the difference in efficacy between active comparator and placebo was small or in the same range. Also, the newer products may have a different effect on factors like negative symptoms or extra pyramidal side effects, which may confound the efficacy analysis.

Therefore in principle placebo-controlled trials will be required to show efficacy of a new product, but it is recognised that suitable alternative designs may be developed. In the latter case it is recommended to discuss this approach in the expert report and/or with the competent authorities.

2.2 Negative symptoms

In the literature many conflicts about negative symptoms arise because different authors use different definitions of negative symptoms. Another problem is that negative symptoms may be secondary to other causes, such as psychotic symptoms, the side effects of medicinal products, depression and under-stimulation (as a result of hospitalisation). For example, if the investigational product is more efficacious than the control treatment against psychotic symptoms, then the effect on social withdrawal arising from paranoid ideation could be erroneously interpreted as a superior effect of the investigational product on negative symptoms. Another error could be made if the investigational product has less extrapyramidal adverse reactions as compared to a control product and this is interpreted as less negative symptoms.

Claims concerning negative symptoms can only be made when negative symptoms are clearly defined and when it is shown that the effect is a direct effect on negative symptoms and not

secondary to other causes. Therefore it is not sufficient to simply record a favourable change on a negative symptom rating scale.

Sophisticated methods of statistical analysis on their own (path analysis, regression methods) cannot be relied upon to disentangle effects on positive and negative symptoms, even if pre-specified in the protocol. They may, however, provide supportive evidence.

In agreement with the literature when an effect on negative symptoms is claimed it is necessary to do specific trials with the following recommendations:

Patient selection:

- a) Predominant and persistent negative symptoms
- b) Stable condition of schizophrenic illness > 6 months, especially negative symptoms
- c) Flat affect and poverty of speech represent core negative symptoms, though the extent may differ between patients
- d) Major depression should be excluded; low depression scores are preferable.
- e) Accounting for effects on EPS (Extrapyramidal adverse reactions).

In addition the time since the start of the current stable episode of schizophrenia should be recorded together with the time since the start of negative symptoms so that an estimate can be made of the time of overlap.

For assessment of negative symptoms the use of specially designed rating scales are necessary. Older assessment scales for schizophrenia, such as the BPRS (Brief Psychiatric Rating Scale) give little emphasis to negative symptoms and should not be used anymore for the assessment of negative symptoms.

Satisfactory construct validity and inter-rater reliability have been demonstrated for PANSS (Positive and Negative Symptom Scale) and SANS (Scale for the Assessment of Negative Symptoms). Such scales should be used in the assessment of negative symptoms only if inter-rater reliability studies are performed in advance and during the studies and if the inter-rater reliability scores for the negative symptoms are satisfactory.

In addition to these scales the extent and severity of EPS and depression should be scored. It should be tried, when analysing the effect to distinguish between these sets of symptoms.

To demonstrate efficacy in patients with predominant and persistent negative symptoms a placebo-controlled design is necessary. It is anticipated that patients receiving the investigational product will show more improvement in negative symptomatology than those treated with placebo. There is currently no reference therapy ("gold standard") for negative symptoms.

However, changes in clinical symptomatology may occur due to a number of heterogeneous confounding factors such as withdrawal of pre-medication and/or worsening of coexisting positive symptoms.

Therefore, in order to avoid inconclusive results and interpretation problems, the inclusion of a third arm with a classic neuroleptic agent is highly recommended to validate the study model and to assure that the effect of the investigational product has been truly established in primary negative symptoms without simultaneous emergence of positive symptoms. The choice of the dose of both the investigational product and the neuroleptic agent, used as comparator, has to be justified.

It is expected that therapeutic effects on negative symptoms take more time to develop than effect on positive symptoms. Therefore, the duration of the trials should be at least 8 weeks, probably longer.

In an acute episode of schizophrenia it is difficult to distinguish negative symptoms from other phenomena as indicated above. Nevertheless also in these circumstances it may be of interest to the patient and doctor if these symptoms are diminished. Due to the confounding factors it would not be appropriate to mention an effect found in an acute phase in the Indication. However an effect could be mentioned in the Pharmacodynamic part of the SPC provided that it is supported by the results of studies specifically designed to test the hypothesis that the treatment had a beneficial effect on negative symptoms. A post hoc analysis would not be sufficient.

2.3 Extrapolation(s)

As stated in Section 1 psychotic symptoms may occur in other disorders. Diagnostic criteria can be found in DSM IV and ICD 10. As these various disorders include different patients and as the natural course of the disorders may differ, extrapolation of data from a specific disorder (e.g. Schizophrenia) to another disorders (e.g. Delusion disorder) is not possible. At least one specific prospective study is required to establish efficacy in another psychotic disorder, when efficacy has been established in schizophrenia.

This is especially true for schizo-affective disorders. Many recent trials have evaluated a population consisting of a mixture of schizophrenic and schizo-affective patients. However these studies generally have sufficient power for an overall analysis of all patients entered, and cannot be used to show reliably the similarity of the treatment effects in the two subgroups of patients. Therefore schizo-affective patients should be excluded from the trials in schizophrenia and specific trials in schizo-affective patients are needed, if a specific claim is made.

Patients in an acute exacerbation, in DSM IV terminology episode, (re-emergence of prominent positive symptoms) can not be compared to patients without an acute exacerbation. This means that extrapolation of results from patients with an acute exacerbation to patients without an acute exacerbation (and vice versa) is difficult.

Other (non-core) symptoms (e.g. depressive symptoms), may occur in schizophrenic patients. These symptoms may be partly or wholly secondary to schizophrenia or the result of treatment. When trying to determine whether a product affects these symptoms in a positive or negative way, it will be difficult to distinguish between a genuine effect and a 'secondary' effect. To support a claim, data should be gathered from studies prospectively designed to assess the effects in schizophrenic patients with the relevant symptoms (e.g. clinically prominent depressive symptoms). Post-hoc analysis will be acceptable as hypothesis generating, but it has to be tested in another study. The patient population that is studied, the comparator that is chosen and the usefulness (validity, relevance) of the scales for that situation should be justified.

2.4 Recurrence/episodic symptoms and relapse

Recurrence is defined as a re-emergence of prominent psychotic symptoms (= episodic symptoms) after a time without or nearly without symptoms.

Relapse is defined as an increase in symptomatology immediately or almost immediately after medication is stopped. It usually indicates that treatment duration was too short.

As schizophrenia covers a heterogeneous group of patients there is a large variance in symptoms but also in natural course. Recurrence of symptoms often occurs.

Relapse prevention studies may be used to show that the effect of medicinal products is maintained, but it is not an indication in itself (see section 6.4.2). Prevention of recurrence could be a useful claim, but there are insufficient data available to recommend a specific trial design. In case a claim is made concerning recurrence the design of the study should be justified taking into account the definition given above.

2.5 Study design in therapy resistant Schizophrenia patients

To demonstrate efficacy in therapy resistant patients, 'therapy resistance' has to be well defined, and it has to be shown that the patients included in the trial indeed are therapy resistant. Two well documented treatment periods, each of at least 6 weeks, using sufficiently dosed neuroleptics of two different pharmacological classes without adequate response are considered acceptable.

The design of studies in therapy resistant patients is the same as compared to other trials. The choice of the comparator has to be justified.

2.6 Special groups

For the indication Schizophrenia no specifically designed trials in geriatric patients are necessary. However information for this group concerning the effective and safe dose is necessary.

As schizophrenia is not a disorder of younger children, no specific studies are needed for this indication in this population. However efficacy and safety evaluation in young adolescents is highly desirable.

3. ASSESSMENT OF EFFICACY CRITERIA

Efficacy has to be demonstrated in short-term studies showing an effect in schizophrenia and in addition maintenance of efficacy has to be shown. For specific claims additional studies are necessary.

Results obtained should be discussed in terms of statistical significance and in relation to their clinical relevance. At present, response criteria are not well defined, neither is there agreement on the improvement needed to be considered as clinically relevant. However in advance of the studies, choice of endpoints and clinical relevance of expected effects (e.g. degree of symptom reduction experienced by responders) have to be discussed in the protocol with reference to other comparative data or publications available or between specialists in the treatment of schizophrenia.

3.1 Improvement in symptomatology

Improvement on treatment with an anti-schizophrenia compound should be documented as the difference between baseline and post-treatment score on the symptomatology and should also be assessed with respect to response criteria; for example the proportion of patients with a certain % of improvement, depending on the kind of patients included (e.g. 50% improvement in patients with an acute exacerbation).

Also the % patients deteriorating during treatment should be documented.

3.2 Relapse/recurrence prevention

Relapse and recurrence are two different things (see section 2.4) and therefore the objectives of trials in relapse and recurrence are different. However, for both, criteria for stabilisation, prodromal signs and relapse/recurrence have to be defined in advance and discussed in the protocol with reference to other comparative data or publications available or to consensus between specialists in the treatment of schizophrenia. Usually a relapse/recurrence includes the reappearance of positive symptoms, scored during one or more visits.

3.3 Negative symptomatology

Improvement on negative symptoms should be documented as the difference between baseline and post-treatment measurements of these symptoms and should also be assessed with respect to response criteria; for example the proportion of patients with 20% improvement on the negative subscale of the PANSS (see also section 2.2).

4. METHODS TO ASSESS EFFICACY

Efficacy can be assessed by means of rating scales. At any rate the choice of instruments (rating scales) should be justified from the test quality criteria (reliability, validity). For the assessment of improvement specific developed rating instruments are necessary. In addition, global assessment (item 2 of the CGI (Clinical Global Impression)) is needed as a secondary endpoint.

4.1 Improvement in symptomatology

The PANSS and BPRS are reliable and validated rating scales for assessing improvement in schizophrenia (see also section 2.2).

4.2 Relapse prevention (maintenance therapy)

The expected attrition rate should be taken into account for power calculation. Time to relapse could be analysed and there also should be a direct comparison between treatment arms in terms of proportion patients who relapsed.

4.3 Negative symptomatology

For the assessment of negative symptoms specially designed rating scales (see also section 2.2) are necessary, global assessment (item 2 of the CGI) could be added.

5. SELECTION OF PATIENTS

5.1 Study population

The disorder should be classified according to an internationally acknowledged classification system, preferable DSM IV or ICD 10, using the diagnostic criteria given herein. A rating score alone is insufficient and is not equivalent to a diagnosis. Patients should also be classified according the longitudinal course (e.g. acute exacerbation); a high score on a rating score \neq acute exacerbation. It can be expected that patients in an acute phase (with florid positive symptomatology) have in general a much better response to pharmacological treatment than patients that are in a chronic phase.

Further descriptive parameters (severity of the present episode) as well as a detailed history (duration of schizophrenia, duration of present episode, number of exacerbation's, residual symptoms between episodes or continuous schizophrenia, as well as previous treatment outcome) should be documented.

In addition cut-off scores, based on appropriate scales (e.g. PANSS), may be used as inclusion criteria.

It is highly desirable that the study population is homogeneous with respect to the indication for the dose finding and pivotal studies (see also section 2.3).

When the intention of a study is to demonstrate efficacy in negative symptomatology, specially designed studies in patients with "negative symptomatology" should be conducted (see also section 2.2).

5.2 Study design

While certain methodological requirements pertain to all studies performed in patients with schizophrenia, there are additional specific features for different fields of applications.

In principle, to assess the effect of medicinal products parallel, double blind, randomised placebo controlled trials are necessary (see also sections 6.4.2 and 2.1). In addition, comparison with a standard product in an adequate dosage is generally needed. The appropriateness of the dosage compared should be addressed. Preferably the treatment should be preceded by a placebo wash-out period in patients that are already treated with a given compound, because only then can (negative) schizophrenic symptomatology be optimally assessed and rated (and differentiated from e.g. EPS; see also section 2.2) and adverse effects of new compounds evaluated. The washout period should be sufficiently long to allow elimination of the compound, but not so long that it results in an increase of symptoms. Patients should preferably start the treatment on a more or less stable symptom baseline, and any reason to exclude placebo-responders should be discussed.

The sample size should be justified from biostatistical criteria. Statistical analysis should include per protocol as well as intention-to-treat analysis. In case of multicentre trials special attention has to be paid to dealing with possible sources of unrelated variation (for prerequisites and assumptions that have to be met see EC Note for Guidance "Biostatistical Methodology in Clinical Trials"). Furthermore in multicentre/multi-investigator studies inter-rater reliability scores (kappa) should be documented for each investigator in advance and during the study, both with regard to the diagnosis and to rating scales used for efficacy and/or where relevant safety, as this is a source of variation.

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

Dropouts are a significant problem in schizophrenia trials and all reasonable steps should be taken to minimise their occurrence. They should be documented in detail including the reasons for dropout. Patients should be followed up as completely as possible in line with the protocol even after they have stopped their trial treatment, and key measurements should also be made at the time of stopping treatment. These steps will allow alternative “intention to treat” strategies to be applied in the analysis.

Standardised psychotherapy, psycho-education, support or counselling may be given as supplementary treatment, though it may enhance the placebo effect, but should be prospectively defined in the protocol. It should be documented in detail and its effect on treatment effect should be analysed.

As compliance is a problem in these patients, assessment of compliance (e.g. plasma levels, tablet counting) and screenings (urine) for additional illicit psychotropic substances are recommended.

6. STRATEGY/DESIGN

6.1 Pharmacodynamics

A variety of tests can be performed but there is no specific model for schizophrenia. Studies in cognition, reaction time etceteras may be necessary depending on the side effect pattern of the product (see section 7.1.1.2).

6.2 Pharmacokinetics

No specific requirements for medicinal products in schizophrenia are necessary (see Guideline on Pharmacokinetic studies in man).

6.3 Interactions

Interaction with alcohol, other CNS active drugs and neuro-endocrinological parameters should be investigated.

6.4 Therapeutic studies

6.4.1 Short-term clinical trials

The purpose of these trials is to:

- identify patients who may benefit from the medicinal product
- obtain initial information on safety
- establish suitable therapeutic dose ranges and frequency of dosing
- to demonstrate the efficacy of the medicinal product

Dose ranging studies should be performed in a controlled, parallel fixed dose design, using at least 3 dosages, to establish the lower end of the clinical effective dose range as well as the optimal dose. Generally it is useful to add a placebo arm as well as an active comparator. Determination of plasma levels may be useful. Usually it takes about 6 weeks in patients with

an acute exacerbation to estimate the maximum effect on positive symptoms of a certain dose. For negative symptoms the duration is longer.

The dossier should include controlled, parallel group studies against placebo and active comparator (3-way studies) and depending on the results already available positive controlled trials (2-way studies) should be performed aiming at demonstrating at least a similar balance between benefit and risk of the product under investigation in comparison to an acknowledged standard anti-schizophrenia compound.

In schizophrenia with an acute exacerbation a double-blind treatment phase of at least 6 weeks is generally considered adequate for proof of efficacy, although it may be longer depending on the included patients.

6.4.2 Maintenance therapy

Due to the chronic character of schizophrenia (with relapses/recurrences), longer double-blind controlled studies are necessary to show that the effect found in the acute phase is maintained.

The usefulness of including more than one dose of the investigational product to investigate the optimal dose for long-term treatment should be considered.

Extension studies may be performed as long as they stay double-blind. A product with a well documented efficacy in the maintenance treatment of schizophrenia should be used as the active comparator. The duration of such a trial should be one year due to the natural course of the disorder and the assay sensitivity should be argued. Another possibility is a so-called relapse prevention study, in which responders to the acute treatment are included and randomised into a medication and a placebo group and for which rate of or time to relapse is used as criterion for efficacy. However, when this design is used, the duration of the acute therapy period probably needs to be longer than 6 weeks and it may be useful to stabilise the patients first during an open treatment period. A long-term placebo-controlled trial during 6 months also may be an option. If one of the latter two options is used, one needs to make sure that the protocol includes specific measures like close monitoring and the possibility to use rescue medication. Other designs also may be used, but the usefulness for the specific situation has to be shown or argued (see section 3.2).

7. SAFETY ASPECTS

Identified ADRs should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Adverse reaction scales should be standardised for use in studies with psychotropic drugs (e.g. UKU scale). Clinical observations should be supplemented by appropriate laboratory tests and cardiological recordings.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug reactions, dropouts and patients who died while on therapy. Specific attention should be paid to the possibility of suicides, Neuroleptic Malignant Syndrome and Sudden Death. Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided. Special efforts should be made to assess potential adverse effect reactions that are characteristics of the class of drugs being investigated depending on the action on various receptor sites. Particular attention should be paid to anti-dopaminergic, anti-cholinergic, anti-histaminergic, serotonergic and α -adrenergic side effects.

7.1.1 Neurological adverse events

Extrapyramidal adverse reactions should be followed with specifically designed rating-scales. During the washout phase, an attempt should be made to distinguish between acute and tardive EPS. Any claims should be substantiated by comparison with at least one active control. Preferably more than one dose of each product should be used. The choice of the comparator and the dose(s) should be justified.

In addition it may be useful to follow patients after treatment is stopped, as adverse reactions, especially EPS, may increase.

Tardive Dyskinesia (TD) is an adverse reaction that occurs late in the treatment. The possibility should be mentioned in the SPC (Summary of Product Characteristics). Specific claims have to be substantiated using the same conditions as for EPS. The duration of treatment has to be justified.

7.1.2 Psychiatric adverse events

Depending on the class and the interactions with various receptors effects on cognition, reaction time, and/or driving and the extent of sedation should be studied. Specific claims always have to be based on specific studies.

7.1.3 Haematological adverse events

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

7.1.4 Endocrinological adverse events.

Special attention should be paid to effects on sexual functioning, galactorrhea, gynaecomasty and weight gain.

Investigation of neuro-endocrinological parameters (e.g. prolactin) is necessary.

7.1.5 Cardiovascular events

Cardiovascular events like orthostatic hypotension and the effect of the medicinal product on the heart, e.g. QT-interval dispersion should be investigated.

7.2 Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see EC Guideline on population exposure).