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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**APPENDIX TO THE NOTE FOR GUIDANCE ON THE CLINICAL
INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT
OF SCHIZOPHRENIA - METHODOLOGY OF CLINICAL TRIALS
CONCERNING THE DEVELOPMENT OF DEPOT PREPARATIONS OF
APPROVED MEDICINAL PRODUCTS IN SCHIZOPHRENIA**

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APPENDIX TO THE NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF SCHIZOPHRENIA - METHODOLOGY OF CLINICAL TRIALS CONCERNING THE DEVELOPMENT OF DEPOT PREPARATIONS OF APPROVED MEDICINAL PRODUCTS IN SCHIZOPHRENIA

This document is an appendix to the existing note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95); it will only address specific problems in developing depot preparations for approved medicinal products in schizophrenia. For general issues the note for guidance itself should be considered.

The document should be read in conjunction with current and future guidelines, especially:

- Note for guidance on modified release oral and transdermal dosage forms - (CPMP/EWP/280/96)
- Statistical principles in clinical trials (ICH E9)
- Choice of control in clinical trials (ICH E10)

I. INTRODUCTION

Schizophrenia is characterised by positive symptoms like delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms. It is a chronic disorder with a high suicide risk and lifelong treatment may be necessary.

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. Long-acting parenteral antipsychotic medications have several advantages over short-acting oral or intra-muscular agents when administered for the treatment of chronic schizophrenia. The major advantage is the assurance of compliance leading to fewer relapses and re-hospitalisations. Hence, for some of the older typical antipsychotic agents, depot preparations were developed. When injected intramuscular, these products are effective for 2 – 4 weeks.

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 these 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.

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.

II. PURPOSE OF THE DEVELOPMENT PLAN

As mentioned in the introduction, 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 6.4.1), but that also is shown that the effect of the product is maintained over time (see section 6.4.2).

As the efficacy and safety of the immediate formulation is accepted and in line with the modified release guideline, a bridging program should be performed to support the indication “Maintenance treatment of schizophrenia”.

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

It has been discussed whether these points could be addressed by pharmacokinetic studies and safety data alone. 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 dosing interval are deemed necessary, unless a clear pharmacokinetic/pharmacodynamic relationship is demonstrated for the oral formulation.

III. PHARMACOKINETICS

Pharmacokinetic data as detailed below are a necessary part of the dossier. The studies could be conducted in healthy subjects, but are often carried out in schizophrenic patients.

Of specific interest is the comparison of the concentration time curves after administration of the oral formulation and the depot formulation over the dosing range. This comparison should be used for an adequate dose and dose interval selection of the depot formulation.

For intra muscular or subcutaneous administration of depot formulations, attention should be paid to the place of administration. Degradation products at the injection site should be taken into consideration. These data might come from animal experiments.

Depending on the type of formulation, the influence of volume, amount and concentrations injected (dose proportionality), or other circumstances (like exercise), on the release characteristics should be discussed or investigated especially with respect to the possibility of dose dumping.

As the parenteral administration of a depot formulation will release the drug slowly compared to oral formulation, the time to achieve steady state concentration after switching from oral to parenteral treatment should be taken into consideration especially with respect to the efficacy. Pharmacokinetic justification is compulsory. Under normal circumstances single dose administration of the parenteral formulation compared with multiple dosing of the oral immediately release formulation will suffice. However, information on the residue in the injection site should be submitted for safety reasons and for an adequate extrapolation of single dose to multiple dose administration. This may especially be of importance if the release rate is dependent on the amount of active substance in the injection site. In that case a constant release rate may result in an underestimation of the residue.

Special attention should be paid to the first pass elimination of the active substance as this may be substantially different between the two routes of administration.

Switching from oral to parenteral administration may also influence the interaction profile of the drug, e.g. 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.

IV. EFFICACY

As indicated above, 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 specific 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 II .

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.

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.

Whatever method is chosen, assay sensitivity has to be addressed and either shown or justified by other data.

Trial population

A suitable patient population would be patients with schizophrenia (see guideline on 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.

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.

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 a 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.

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.

V. 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.

VI. 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.