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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the 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

Agreed by CNS Working Party	July 2011
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1. Introduction

Schizophrenia is a severe psychiatric disease with a heterogeneous course and symptom profile. It is a chronic disorder with a high suicidal risk and in most patients a life long treatment is necessary. One of the problems in treatment of these patients is the lack of compliance due to inability of the patient to recognise the existence and seriousness of his/her condition. Additionally, cognitive dysfunction are often present in these patients potentially interfering with antipsychotic oral maintenance treatment due to cognitive limitations, negative symptoms/lack of initiative and/or impaired working memory.

Depot preparations of medicinal products for treatment of schizophrenia are developed for maintenance treatment of patients who have been satisfactorily stabilised on an oral preparation of the product or for those individuals for whom the lack of adherence/poor compliance could increase the risk of relapses.

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2. Problem statement

The Guideline on clinical investigation of medicinal products in the treatment of schizophrenia is currently under revision (the end of public consultation period is 31 August 2011). Proposed revisions are mainly related to the study design for demonstration of short and long term efficacy, as well as the patient population (including paediatric patients), strategies for investigation of medicinal products for treatment of specific symptom domains (such as cognitive deficit or negative symptoms) and add-on strategies in subjects with insufficient treatment response to monotherapy. At this stage it is logical to consider whether the appendix related to depot preparations would need a revision as well.

The main issues which are discussed in the current version of the appendix for depot preparations are related to:

- Pharmacokinetic data for bridging from the oral to the depot preparation

- Study design of non-inferiority trials versus the oral preparation

- Patient population to be included in the trials

- The choice of active comparator

- The endpoints for measuring maintenance of effect

- The trial duration

- Data on switching

- Safety issues related to i.m. and/or s.c. administration

3. Discussion (on the problem statement)

The statements and guidance as given in the current version of the appendix are still valid and in accordance with the proposed revisions in the draft Guideline currently published for consultation.

Main issues under discussion both in the scientific and regulatory community are related to the switching from oral to depot preparation and the disadvantages of starting treatment with a depot preparation in a patient who has never received the oral formulation of the same antipsychotic. Starting directly with a depot antipsychotic could be justified in some exceptional clinical situations, but is not a standard practice since it does not allow dose titration and carries safety risks. Therefore no further development along this line is encouraged. Data on switching is considered essential. The recommendations in this respect have been explicitly made in the current appendix and are still valid.

Hence it is not considered necessary to revise the guidance for clinical investigation of depot preparations for the treatment of schizophrenia. It is logical to integrate the appendix to the revision of the guideline on clinical investigation of medicinal products in the treatment of schizophrenia before its finalisation with textual adjustments and harmonisation, as appropriate.

4. Recommendation

The CNS Working Party recommends no revision of the appendix concerning depot preparations of approved medicinal products in schizophrenia. It is proposed to integrate the appendix to the revision of the guideline on clinical investigation of medicinal products in the treatment of schizophrenia before its finalisation.

5. Proposed timetable

It is planned to integrate the appendix at the time of publication of the final revised guideline on clinical investigation of medicinal products in the treatment of schizophrenia.

6. Resource requirements for preparation

Not applicable

7. Impact assessment (anticipated)

Not applicable

8. Interested parties

European College of Neuropsychopharmacology