



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the note for guidance on clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95)

Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 July 2010

The proposed guideline will replace NfG on clinical investigation of medicinal products in the treatment of schizophrenia (CPMP/EWP/559/95).

Comments should be provided using this [template](#). The completed comments form should be sent to EWPSecretariat@ema.europa.eu

Keywords	<i>Schizophrenia, Cognitive dysfunction, impaired working memory, Paediatrics, Psychosis</i>
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1. Introduction

Since the publication of the guideline for schizophrenia in 1998 and its appendix related to the depot preparations in 2001, scientific progress has been made towards identification of specific functional domains that may be potential targets for treatment beyond the traditional treatment of psychosis, i.e. positive and negative symptoms in schizophrenia. Furthermore, additional efforts have been made to optimize treatment through new treatment strategies and algorithms, and therefore target populations, in order to further reduce symptoms that remain present after conventional treatment^{1, 2}. Whether such treatment strategies refer to all patients or to a restricted population, needs to be discussed.

In addition to the psychotic symptoms in schizophrenia, cognitive impairment is recognised as a domain in schizophrenia related to central cholinergic activity. The ability of atypical antipsychotics such as clozapine, olanzapine, risperidone or ziprasidone to improve some of the aspects of cognitive dysfunction in schizophrenia may be attributed to increased acetylcholine release in the medial prefrontal cortex³.

The legislation with regard to the need and encouragement of the development of medication for children has brought the scientific community to re-evaluate the presence of psychosis and psychotic symptoms in the age group below 18 years of age^{4, 5, 6}.

Together with the prospect of the revision of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), e.g. possible changes in categorical approaches and introduction of new categories⁷, several additions and changes in this guideline are needed to review and express the current state of scientific knowledge.

2. Problem statement

The current guideline is not entirely up to date and should cover the latest scientific developments with regard to the options of targeting new functional domains, of using new treatment strategies, and defining what kind of data are needed in children and adolescents. Consequently, it will be discussed if the appendix on depot formulations is in line with the revised note for guidance.

3. Discussion (on the problem statement)

In the proposed update of the guidance document, the following issues will be discussed:

- Extrapolation of data to other psychotic conditions beyond schizophrenia.
- Revision of text about negative symptoms.
- Choice of comparator group (active comparator and/or placebo).
- Design of (long term) efficacy studies.
- Usefulness of combination therapy and corresponding study designs, add-on and augmentation.
- Generalisability of data with respect to different age groups.
- Generalisability of data with respect to potential cross cultural differences.
- Long term safety data.
- Acceptance of cognitive deficit as a domain in schizophrenia.
- Choice of outcome parameters and assessment tools to measure effects on cognition in patients with schizophrenia.
- The need of clinical development plan in the paediatric population, in particular diagnostic criteria, target population, study design, specific issues on safety.

4. Recommendation

To ensure uniformity of clinical studies and to set standards, the CHMP recommends revising the guidance on clinical investigation of medicinal products in the treatment of schizophrenia.

5. Proposed timetable

It is planned to publish a revised guideline within 6 months of the adoption of this concept paper by the CHMP. The draft guideline will be available for 6 month consultation before its finalisation.

6. Resource requirements for preparation

The preparation of the revised guideline will involve the EWP, PDCO, SAWP and SAG-CNS (if relevant).

7. Impact assessment (anticipated)

It is expected that the revised "Note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia" should provide guidance for pharmaceutical companies with respect to methodology, assessment tools, measurements, clinically relevant outcomes, etc. for clinical investigation in schizophrenia. Furthermore, the revised guidance should ensure uniformity and comparability of the performed clinical studies for the indication schizophrenia in the European Union.

8. Interested parties

European College of Neuropsychopharmacology.

1. References to literature, guidelines, etc.

¹ Wolff-Menzler C et al: Combination Therapy in the Treatment of Schizophrenia. Ppharmacopsychiatry 2010 (to be completed)

² Allen t., et al. Galantamine as an adjunctive therapy in the treatment of schizophrenia. Presented at 11th Congress of the International Psychogeriatric Association (IPA), Chicago, Ill., 2003, August 17-22.

³ Ichikawa, J. et al.: Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. *Neuropsychopharmacology 26 (2002): 325-339.*

⁴ J, Chavez A, Greenstein D, Addington A, Gogtay N. Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited , *J Am Acad Child Adolesc Psychiatry.* 2009 Jan; 48(1): pp 10-8.

⁵ Ulloa RE, et al., 'Psychosis in a pediatric mood and anxiety disorders clinic: Phenomenology and correlates.' *J Am Acad Child Adolesc Psychiatry,* 2000, 39(3), pp 337–345

⁶ Sosland MD, Edelson GA. Hallucinations in children and adolescents. *Curr Psychiatry Rep.* 2005 Jun;7(3): pp180-8.

⁷ www.dsm5.org