4 Concept paper on the development of Medicinal
5 products for the treatment of Autism Spectrum
6 Disorder

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Agreed by CNS Working Party	February 2013
Adopted by CHMP for release for consultation	21 March 2013
Start of public consultation	4 April 2013
End of consultation (deadline for comments)	4 July 2013

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Keywords	Autism, Paediatric population, Asperger's Disorder, Rett's disorder, Childhood disintegrative disorder and Pervasive Developmental Disorder – not otherwise specified

1. Introduction

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disabilities with symptoms typically presenting before the age of 3 years and persisting into adulthood. They are described as "spectrum disorders" because they affect each person in a variety of different ways and can range from very mild to severe. Delay in language development, impairment of social interaction, and restrictive, stereotyped behaviour patterns are characteristic features. The functioning of the affected individual varies substantially depending on language abilities, level of intelligence, co-morbidity, composition of symptoms and access to services. Cognitive functioning, learning, attention, and sensory processing are usually impaired and typically cause significant social, communication and behavioural challenges (1).

Current classifications differentiate Autistic disorder (also called "classic" autism), Asperger's Disorder (which lacks impairment of cognitive development and language), Rett's disorder, Childhood disintegrative disorder and Pervasive Developmental Disorder – not otherwise specified (PDD-NOS; also called atypical autism) (2). In the forthcoming DSM-5 these terms would be comprised under the umbrella term of "Autistic Spectrum Disorder (3).

Because of the lack of reliable biological marker, the diagnosis is essentially clinical. The prevalence of autism is difficult to assess due to variations in awareness of the condition and in diagnostic methods (4).

Management of ASD relies heavily on behavioural therapies and social and educational programmes. Although various therapies and interventions are available, few are supported by scientific studies. Pharmacotherapies approved to date for the management of autism have been non-specific for the condition (e.g. atypical antipsychotics for control of behavioural disturbance).

2. Problem statement

New treatments are currently under development for the treatment of autism.

No guideline is available for the development of medicines for the treatment of ASDs. Guidance is needed especially with regard to diagnostic criteria, definition of target treatment populations, efficacy criteria, specific age-category problems (childhood versus adulthood), and the need for comparative studies. Also because ASDs are life long conditions, new treatments need in principle to be evaluated in all age groups and there is a need for long-term safety data.

3. Discussion (on the problem statement)

In the guideline, guidance should be given on:

- Definition of target populations
    - diagnostic criteria (DSM-IV-TR, DSM-5) and diagnostic scales
    - inclusion of patients with diagnosis of Asperger's syndrome and PDD-NOS (or other dissociative disorders) and control of homogeneity of the study population
    - definition of subgroups according to severity of symptoms
    - presence of co-morbidities (e.g. depression, anxiety, ADHD, epilepsy)
    - concomitant medication
    - other inclusion and exclusion criteria
- The different age cohorts to be studied (infants, pre-school, pre- and post pubertal, adulthood)
- Justification for potential extrapolation (among age groups with the same disorder and between different autistic disorders)
- Study design and choice of comparator
- Standard of care (behavioural, social, educational etc)
- Duration of short-term efficacy trials, maintenance of effect trials
- Strategies for dose-finding
- Choice of endpoints
    - symptom rating scales (including validation)
    - acceptability of specific symptom domains as efficacy endpoints (e.g. specific maladaptive behaviours, insomnia, agitation)
    - observer or subject ratings
    - age related endpoints
    - need for cognition endpoints
    - need for functioning endpoints (communication, social, educational, occupational, family)
- Long-term safety data (including effects on growth, development and cognition)
- Applicability of non-EU (e.g. US) data to EU populations

4. Recommendation

The CNS working party recommends drafting of a specific guideline for the development of medicinal products for the treatment of Autism Spectrum Disorders (ASDs).

5. Proposed timetable

It is anticipated that the draft guideline will be published in 2014. The draft guideline will be available for 6-month consultation before its finalisation.

6. Resource requirements for preparation

The preparation of this Guideline will involve the Central Nervous System Working Party (CNSWP), Biostatistics Working Party (BSWP) and the PDCO.

7. Impact assessment (anticipated)

It is anticipated that the "Note for Guidance on the development of new products for the treatment of Autistic Spectrum Disorders (ASD)" will be helpful in ensuring the quality and comparability of submitted studies by pharmaceutical industries and to achieve more consensus in the evaluation of such products by regulatory authorities.

8. Interested parties

The interested parties in the guidance document include learned societies and academia, the pharmaceutical industry and other regulatory agencies.

9. References to literature, guidelines, etc.

1. Baird G. Diagnosis of autism. BMJ. 2003; 327:488-493.

2. American Psychiatric Association (2000). "Diagnostic criteria for 299.00 Autistic disorder". Diagnostic and statistical manual of mental disorders: DSM-IV (4th ed.) Washington, DC: American Psychiatric association

3. http://www.dsm5.org/Documents/12-03%20Autism%20Spectrum%20Disorders%20-%20DSM5.pdf

4. http://ec.europa.eu/health/archive/ph_information/dissemination/diseases/autism_1.pdf

Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)