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2 EMA/CHMP/318360/2015
3 Committee for Medicinal products for Human Use (CHMP)

4 Concept paper on the need for revision of the note for 5 guidance on clinical investigation of medicinal products 6 for the treatment and prevention of bipolar disorder

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Start of public consultation	28 July 2016
End of consultation (deadline for comments)	31 October 2016

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9 The proposed guideline will replace 'Note for guidance on clinical investigation of medicinal products for
10 the treatment and prevention of bipolar disorder' (CPMP/EWP/567/98).

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Comments should be provided using this template. The completed comments form should be sent to CNSWPSecretariat@ema.europa.eu.

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Keywords	Bipolar, Bipolar disorder

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1. Introduction

Bipolar Disorder (BD) I and II have long been well known psychiatric diseases that can be controlled with psychopharmacological and behavioural treatment. Over the past decades its prevalence remained stable (BD I 0.6% and BD II 0.4%, worldwide). Aetiology and pathophysiology of BD remain still largely unknown, however, recent research effort, especially genetic research using Genome Wide Association Studies (GWAS) and Copy Number Variations (CNVs) methodologies in extremely large samples, has shed some light into the neurobiology (1). Bipolar Disorder is now considered a bridging disease belonging to both the psychotic and the mood spectrum, with different dimension differentially involved in individual patients (2).

With the transition of DSM-IV into DSM 5, bipolar and related disorders have been separated from depressive disorders, and BD II is no longer considered a milder form of BD I. More important, Cluster A symptoms for BD I have changed and specifiers been added (e.g. anxious distress) with subsequent implications for identifying patients both in clinical and research settings.

Although BD primarily affects adults, evidence gathered has shown that it frequently begins in adolescence and diagnostic accuracy is moving towards early detection, and a younger patient population (3).

Drug development has mainly been focussed on Bipolar Disorder I, but slow progressions have also been made in both types of the disorder. The Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment and Prevention of Bipolar Disorder dates October 2001. Since then, only few new products have been registered for this indication, the latest being asenapine (2010) and aripiprazole for children >13 years of age (2012/2013). In addition, loxapine has been registered for mild- to moderate agitation in 2012 (4). The latter demonstrates that a shift also takes place in the treatment of specific symptoms within the disorder that is also foreseen with the added specifiers in the DSM 5. This strategy, embodied in the Research Domain Criteria project (RDoC) initiated by the National Institute of Mental Health in 2009 (5), is intended to identify psychopathology and treatment targets based upon basic functional mechanisms and their implementing neural systems that cut across traditional diagnostic categories. Together with the paradigm shift in psychiatry that certain domains, e.g. cognition, are paramount across CNS disorders and warrant a similar or distinct approach, this will challenge new drug development in the coming years.

Several products are currently under investigation either based on new concepts of mood stabilization, e.g. riluzole, taurine, omega-3 fatty acids, modafinil, or elaborating on existing insights, or targeting specific dysfunctional domains such as cognition (6, 7).

Altogether, the apparent changes in the conceptual framework of psychiatric diseases expressed in DSM 5, the shift towards early treatment, and the recognition of treatment targets across disorders, needs consideration of new strategies in clinical trial design, patient populations, endpoints and outcome and bridging with related guidelines, i.e. schizophrenia (8) and depression (9).

2. Problem statement

The transition from DSM-IV to DSM 5 brings about the opportunity to develop drugs for patient populations that have not been defined before (10). Second, although the current guideline includes studies in adolescents, identifying high-risk populations, if possible, warrants discussion on the need for prevention trials or early intervention and its inherent primary endpoints and outcome(11). In addition, whether specific (diagnostic) biomarkers can be identified and used is inherent to such

approach and anticipates on new insights in e.g. genetic- and neuroimaging research (12). Beyond targeting potential new patient populations that fit in the new DSM 5 criteria, targeting cognitive dysfunction as a treatment goal is seen in several CNS disorders (schizophrenia, depression, MS etc.). Characterizing whether distinctly different or specific for BD needs further research as well as the acceptance of the diagnostic and assessment tools available (7).

Despite the fact that DSM 5 adheres to the categorical classification of psychiatric disorders, dimensional approaches are not uncommon, and often reflect current clinical practice. Bipolar disorder shares symptoms with both Schizophrenia and Major Depression (13). Subsequently, scientific and regulatory discussion is needed when a population with specific psychopathological characteristics is targeted (e.g. mixed features); where can be extrapolated and where complementary data are needed distinct for the different disorders. This also anticipates on current initiatives to describe psychotropic drugs according to their mode of action and the underlying psychopathology that CNS disorders share. The trade off, however, is the potential need for specific safety studies, thereby shifting the field towards a more tailored approach of drug development.

3. Discussion (on the problem statement)

Because of important changes in DSM 5, new insights into the neurobiology of BD, the diagnostic accuracy moving towards early detection, and the recognition of additional domains that can be targeted to optimize treatment of Bipolar patients in general, revision of the currents guideline is warranted with the focus on 2 main topics:

1. Overall reconsideration of treatment targets and subsequent patient populations, trial design, endpoints and outcome with specific attention towards

    a. potential early diagnosis and the treatment of children and adolescents

    b. targeting specific domains that are either new specifiers in the DSM 5 or at the core of adjoining disorders, e.g. cognition

2. Harmonisation and bridging with the guidelines for schizophrenia and depression

4. Recommendation

The anticipated changes are considered substantial enough to recommend a public consultation to

a. explore the timing and validity of early treatment, patient need, and relevant outcome measures, and

b. the evidence needed for targeting specific symptom clusters or dimensions within the bipolar spectrum.

5. Proposed timetable

It is planned to release for consultation a draft CHMP guidance document not later than May 2017.

6. Resource requirements for preparation

The preparation of this guideline will involve the CNSWP. Drafts of the document will be discussed with SAWP and other relevant WPs and committees. Further consultation with PDCO and stakeholders from

academia, patient representatives and industry may be needed to discuss the issues mentioned in this CP.

7. Impact assessment (anticipated)

It is expected that the revised Guideline will be helpful in designing state of the art clinical trials in Bipolar Disorder, enhancing drug development in this field. It is expected that harmonizing guidelines of the major psychiatric disorders and complement them with new options for treatment, and tools that, with current innovative measures, will improve the use of relevant outcome measures, tailored to the patient's needs.

8. References to literature, guidelines, etc.

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