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2 EMA/CHMP/183826/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Concept paper on the need for revision of the guideline**
5 **on clinical investigation of medicinal products in the**
6 **treatment of depression**

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Agreed by Central Nervous System Working Party	October 2016
Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	18 November 2016
End of consultation (deadline for comments)	28 February 2017

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10 The proposed guideline will replace 'Guideline on clinical investigation of medicinal products in the
11 treatment of depression' (CPMP/EWP/518/97, Rev. 2)

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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	Major Depression, Treatment Resistant Depression, Partial Response, Antidepressants, Augmentation Strategies, Cognitive Dysfunction
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16 **1. Introduction**

17 Major Depressive Disorder (MDD) is one of the most common psychiatric disorders, which is the fourth
18 leading cause of global disease burden and affects about 15 % of the general population. As outlined in
19 the guidance document MDD is not a benign disorder and risk of suicide is considerable.

20 Although a broad therapeutic armamentarium for treatment of major depressive episodes (MDE) is
21 available, still about one-third of patients treated for the condition do not respond satisfactorily to the
22 first antidepressant prescribed¹⁻⁴. Incomplete treatment response or treatment resistance have been
23 described commonly in up to 50 % of the treated patient population^{3,5,6}.

24 The current guideline distinguishes between requirements for trials to study monotherapy in treatment
25 resistant depression (TRD) and trials to study augmentation/add-on treatment in case of insufficient
26 response to monotherapy. However, in light of the most up to date evidence generated, the definition
27 and identification of partial responders needs to be revisited. In clinical practice, moreover,
28 augmentation and combination strategies in TRD appear valid approaches⁷. Several aspects for
29 different trial designs in these difficult patients (TRD and partial responders) therefore require
30 reconsideration⁸.

31 A paradigm shift is taking place in psychiatry where increasingly separate domains in the broader
32 context of a categorical disorder are studied separately⁹ and may become the target of drug
33 development if sufficient rationale exists in support. The treatment of specific symptoms within the
34 disorder is also reflected in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
35 (DSM 5). As e.g. cognitive disturbances are paramount across CNS disorders and may warrant a
36 distinct approach, this will challenge new drug development in the coming years¹⁰⁻¹². To support a
37 separate claim for efficacy on cognitive aspects in patients with MDD, specific studies should be
38 performed¹³. *It depends on the robustness of the results whether a separate indication can be pursued
39 or whether the data should rather be mentioned in section 5.1. For application of an indication on
40 cognitive aspects in patients with MDD a specific effect on cognitive function needs to be shown that
41 could clearly be disentangled from the overall depressive symptoms.* The current guidance lacks
42 recommendations with respect to cognitive function in MDD.

43 In addition, a number of methodological issues in the way clinical trials in depression are conducted
44 are now being discussed in the scientific community including the reasons for increasing placebo
45 response and the adequateness of the measures of outcome¹⁴⁻¹⁷. These issues, together with the need
46 to account for population differences in terms of gender and drug metabolism might need regulatory
47 guidance.

48 Altogether, the apparent changes in the conceptual framework of psychiatric diseases expressed in the
49 DSM 5, the unmet medical need in TRD and insufficient treatment responders, and the recognition of
50 specific treatment targets across disorders, warrant reconsideration of strategies in clinical trial design,
51 recruitment of patient populations and definitions of endpoints. Hence, several amendments of the
52 depression guideline as well a reconsideration/reconfirmation of existing principles need discussion.

53 **2. Problem statement**

54 The current guideline needs revision covering the latest developments with regard to requirements for
55 clinical trials in partial and non-responders with MDD and options of targeting new functional domains.
56 In addition, it may include requirements to increase depression clinical trials efficiency.

57 **3. Discussion (on the problem statement)**

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

- 59 • Definition of target population: general MDD population, treatment resistant depression and
60 partial responders:
 - 61 ○ Diagnostic criteria
 - 62 ○ Age and gender sensitivity
 - 63 ○ Presence of co-morbidities
 - 64 ○ Cross cultural differences, e.g. non-EU (e.g. US) data to EU populations
- 65 • Design strategies:
 - 66 ○ Choice of comparator
 - 67 ○ Appropriate endpoints
 - 68 ○ Usefulness of combination therapies and corresponding study designs, e.g. add-on and
69 augmentation
 - 70 ○ Placebo effect
- 71 • Cognitive deficit as a separate domain in depression:
 - 72 ○ Definition of cognitive disturbances in depression
 - 73 ○ Trial design strategies

74 **4. Recommendation**

75 In conclusion, it is recommended to update the current Guideline on clinical investigation of medicinal
76 products in the treatment of depression. Although some of the key issues of guidance have not
77 changed, more elaborate recommendations could be given to increase clinical trial efficiency
78 maintaining the validity of the conclusions. Updated recommendations are especially needed on the
79 conduct of trials in TRD and partial responders. New guidance on the requirements to support specific
80 separate claims, e.g. on cognition, should also be included.

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

82 To ensure uniformity of clinical studies and to set standards, the CNS Working Party (CNSWP)
83 recommends revising the guideline.

84 **5. Proposed timetable**

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

86 **6. Resource requirements for preparation**

87 The preparation of this guideline will involve the CNSWP. Drafts of the document will be discussed with
88 Biostatistics Working Party (BSWP), Scientific Advice Working Party (SAWP) and other relevant WPs
89 and committees.

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91 **7. Impact assessment (anticipated)**

92 It is expected that the update of the Guideline will be helpful to achieve consensus in the evaluation of
93 medicinal products for the treatment of MDD by regulatory authorities in the European Community.
94 Furthermore, it is expected, that such guideline will provide guidance with respect to methodology,
95 assessment tools and clinically relevant outcomes in

- 96 a) Major Depressive Disorder (MDD)
- 97 b) Partial responders with MDD
- 98 c) Treatment Resistant Depression (TRD)
- 99 d) Cognitive disturbances in depression

100 and thus would improve quality and comparability of development programs for these specific
101 indications by pharmaceutical companies.

102 **8. Interested parties**

103 The interested parties in the guidance document include learned societies and academia (e.g.
104 European College of Neuropsychopharmacology (ECNP) and others), pharmaceutical industry (e.g.
105 EFPIA and others) and other regulatory agencies.

106 **9. References to literature, guidelines, etc.**

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