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COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR REVISION OF NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF DEPRESSION WITH REGARD TO TREATMENT RESISTANT DEPRESSION

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Comments should be provided using this template to EWPSecretariat@emea.europa.eu

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1. INTRODUCTION

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders, which is the fourth leading cause of global disease burden and affects about 15 % of the general population. As outlined in the guidance document MDD is not a benign disorder and risk of suicide is considerable. Although a broad therapeutic armamentarium for treatment of major depressive episodes (MDE) is available, still about one-third of patients treated for the condition do not respond satisfactorily to the first antidepressant described [1,2,4]. Incomplete treatment response or treatment resistance have been described commonly in up to 30 % of the treated patient population, and may even as high as 60 % if treatment resistant depression (TRD) is defined as absence of remission [3-11].

However, whereas the clinical picture of TRD is common in everyday practice, the conceptual elaboration and definition of clear criteria for incomplete response and TRD has been limited[9,11,12]. In a clinical pragmatic view a patient is considered suffering from TRD when consecutive treatment with two products of different pharmacological classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect [5, 9-11]. As no specific treatments have been approved for this condition and scientific data base is limited, TRD is mentioned in the guideline on treatment of depression, however, no specific guidance has been given (CPMP/EWP/518/97 rev.1).

Recently new diagnostic criteria for TRD including operationalizing severity of resistance have been suggested [6, 13-15] and in scientific advice procedures possible study designs have been proposed.

2. PROBLEM STATEMENT

Despite the many treatment options currently available for MDD, a relevant proportion of patients up to one third does not adequately respond to treatment and up to 20% are considered non-responders, even if there is good compliance and the treatment has been taken long enough with an adequate dosage. So there is a clear unmet medical need for patients, in whom even “state of the art”-antidepressant therapy fails to elicit a sufficient treatment response.

In clinical practice treatment algorithms have been established for TRD including reevaluation of the initial diagnosis and, when no correctable cause for TRD is found, optimization of the initial regimen using switching to other antidepressants, augmentation strategies (e.g. combination therapy, lithium and other mood stabilizers, thyroid hormones, antipsychotics, etc.) or even monotherapy with second generation antipsychotics has been considered within the psychopharmacologic options [3, 5, 13, 16, 17]. In many clinical treatment guidelines electroconvulsive therapy is a further and sometimes firstline option for patients suffering from severe TRD[18-19] and new modalities like deep brain stimulation[20] or vagus nerve stimulation[21] are under study.

Unfortunately there is remarkable degree of variation in TRD definition. The most used one, and cited in our guidance paper for treatment of MDD as well, is the common idea that a patient has clinically relevant TRD if a current episode of MDE has not benefited from at least 2 adequate trials of antidepressant compounds of different mechanism of action. This approach assumes, that non-response to two compounds with distinct mechanism of action (e.g. one tricyclic and one SSRI) is more difficult to treat than non-response to two compounds with the same mechanism of action (e.g. two SSRI’s). Moreover it assumes that switching treatment within a given class is less effective than switching to a different pharmacologic class. However, this has not been verified by data from publications and has been recently questioned by the results of the STAR*D program sponsored by the NIMH [22-23].

There is still an ongoing discussion whether TRD is a specific subtype of MDD or a continuum within MDD ranging from partial response to complete treatment resistance. Several groups of clinical researchers have proposed now strict criteria for the purpose of clinical trials in patients with TRD to reduce heterogeneity of the study populations and to avoid overlap to terms like difficult-to-treat-depression, partial respondent depression, chronic depression and refractory depression. In addition proposals for staging of TRD have been published. However, data on validity and reliability of the proposals and optional thresholds is still limited [9,10,14,15].

As CHMP and its working parties are now confronted with new approaches to address TRD in clinical trials new developments should be taken into consideration and implemented into an updated guidance document for treatment of depression. Major points for clarification are inclusion and exclusion criteria to define an appropriate and homogeneous patient population with TRD, the adequate study

design for a follow-up program in addition to a development for MDD or for an stand-alone application in TRD without established efficacy in MDD as outlined in the following section.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

In the proposed update of the guidance document guidance should be specified to:

- target population with TRD (diagnostic criteria, threshold for severity, inclusion and exclusion criteria)
- TRD: indication as follow-up to established efficacy in MDD or stand-alone indication without established efficacy in MDD
- Inclusion of an active comparator in clinical trials, is there a gold standard acceptable as active control
- study duration (short-term efficacy, maintenance of effect)
- choice of endpoints
- validity of diagnostic criteria, measurement tools (self-ratings, observer-ratings)
- long-term safety
- special populations (childhood and adolescence, geriatric population)
- presence and acceptance of co-morbidity

4. RECOMMENDATION

There are new proposals with operationalized criteria for TRD available allowing definition of a patient population, which suffers from clinically relevant impairment and requires alternative treatment options including augmentation with add-on strategies or monotherapy options. Therefore CHMP recommends to update the guideline on the treatment of depression with regard to these issues of TRD.

5. PROPOSED TIMETABLE

It is planned to circulate the updated draft CHMP guidance document 6 months after adoption of the concept paper by CHMP.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this guideline will involve the EWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is aimed that the updated “Note for guidance on the development of medicinal products for the treatment of depression” with regard to treatment resistant depression (TRD) will be helpful to achieve consensus in the evaluation of such products by regulatory authorities in the European Community. Furthermore, it is expected, that such guidance document would improve quality and comparability of development programs for this specific indication by pharmaceutical companies.

8. INTERESTED PARTIES

European College of Neuropsychopharmacology

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