Regulatory Perspective – CHMP

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AGENDA

- **Recent Issues with MDD**
- **Guidance Update for MDD**
  - Content
  - Changes / Challenges
- **Partial Response/Treatment Resistance**

Key Topics for the Update:

- target population with TRD or partial response (diagnostic criteria, DD bipolar disorder, 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
- 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

It took a long time ...

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/185423/2010 Rev. 2 previously (CPMP/EWP/518/97, Rev. 1)
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of depression

- First came into effect in 2002
- Revised draft for external consultation in Sept 2011
- Final/current version effective Dec 2013
  - Expanded guidance for partial response (augmentation therapy) and TRD (switch)

Study Designs in Major Depression

- **Three adequate and well controlled designs possible:**
  - **Placebo control** — **Superiority**
  - **Dose comparison** — **Superiority**
  - **Active control** — **Superiority or Equivalence/Non-Inferiority**

- **Non-Inferiority Design tested in most cases**
  - **New drug is not inferior by more than some predefined amount ➔ *Non-Inferiority Margin***
    - **To define this margin *„assay sensitivity“* has to be known**

Maintenance of Effect

- **Short-term effects should be maintained during the episode**
- **Randomized withdrawal study (relapse prevention study) is the preferred design**
- **Duration: 6 months**
- **Placebo-controlled extension study is not preferred**

Clinical Decision Making in TRD

- from: Papakostas GI, J Clin Psychiatry, 70 (Suppl. 6) 16-25, 2009

FOR CLINICAL USE

- Choose evidence-based treatment strategies for antidepressant-resistant depression such as raising the dose of the initial antidepressant, switching to a different antidepressant, and augmentation and combination therapies.
- Evaluate patients with treatment-resistant depression by confirming the diagnosis, ensuring the adequacy of and adherence to the first-line treatment trial, assessing for comorbid medical and psychiatric diagnoses, and differentiating between nonresponse to therapy and depressive relapse.
- Consider the tolerability of the first-line agent and the potential loss of partial benefit (if any) from the first-line antidepressant when choosing between switching and augmentation and combination strategies.

- **How to deal with it from a regulatory perspective ? Labeling?**

Treatment Resistance/Partial Response

- **High variability in definition of TRD**
- **Commonly used in practice:**
  - **Two products of**
    - **different pharmacological classes (?)**
    - **long enough (?)**
    - **high enough (?)**
- **Switch Approach not unanimously supported by STAR*D**
- **Standardized, operational criteria needed:**
  - **TRD / Partial Response / Response / Remission**
- **Absence of prospective data for validation of criteria**

Where did we come from?

- Effect Sizes of AD are small
- Safety issues
  - Suicidality issues
  - QT_c
  - Metabolic issues
- Polypharmacy in practice

Guideline Definition on TRD

- **In the regulatory setting TRD is considered, when treatment with at least two different antidepressant agents prescribed**
- **in adequate dosages**
- **for adequate duration**
- **and with adequate affirmation of treatment adherence**
- **showed lack of clinically meaningful improvement (nonresponse)**

Assessment of Treatment Failure

- **At least one treatment failure should be prospectively shown.**
- **Instruments used to assess adequacy of previous antidepressant treatment (retrospective data):**
  - **ATHF (Antidepressant Treatment History Form)**
  - **HATH (Harvard Antidepressant Treatment History)**
  - **Massachusetts General Hospital Antidepressant Treatment Response Questionnaire**

Guideline Update: Resistance

- Resistance = no meaningful effect after two antidepressants long enough high enough = nothing to augment
- at least one treatment failure should be shown prospectively
- **switch to other monotherapy**, which should be known as antidepressant (additional claim)
- separate study
- usual study design: short term

Guideline Update: Partial Response

- Partial response = insufficient effect after an antide-pressant long enough high enough = augmentation with add-on treatment
- classical **add-on to standard antidepressant** treat-ment
- experimental compound vs. placebo (and active comparator)
- separate studies
- usual study design: short term and maintenance

Defining the Right Patient Population

Section 4.4.2 Trials to study augmentation/add-on treatment

Patients with partial response to standard medication are randomised to receive active augmentation treatment or placebo in addition to standard medication, which should be blinded if feasible. ***It is of critical importance that the applicant can establish that the population recruited to the trial are true partial responders.*** A run-in period alone with assessment of response to standard intervention may not be sufficient since partial response may be driven by other factors than the actual pharmacological treatment in this population. Instead, an initial randomisation to standard medication or placebo would be the best way to characterise the proportion of the population that were partial responders for reasons other than the actual pharmacological treatment. In any case criteria for inclusion should be carefully defined to best identify "true" partial responders, and relevant data properly documented and critically appraised. Medical history and use of and response to non-pharmacological interventions may help identify the appropriate patient population.

Partial Response: Need for Maintenance Data

Section 4.4.2 Trials to study augmentation/add-on treatment

Depending on the mechanism of action and already established antidepressant efficacy maintenance studies will be necessary; in case maintenance data are needed, they should be obtained pre-licensing. (again scientific advice is recommended). ***A randomised withdrawal study is the design of choice to establish maintenance of effect of long term augmentation treatment within the episode.*** In this case responders to a combination treatment of a known antidepressant and the new compound are randomized to one of the following three treatments: combination therapy, monotherapy antidepressant, and monotherapy new compound (if appropriate).

An alternative might be a long term extension trial with parallel design including test product, placebo and active comparator added to a well established antidepressant. However, such a study would not answer the question whether long-term augmentation is really needed and therefore this is not the favoured option. If chosen, it needs justification and should be verified with scientific advice before starting the study (see 4.1.2.).

Summary

- a lot of criticism on the current approach in the guidance document
- Next month meetig at EMA with representatives from EFPIA
- Open for new approaches with better feasibility and practicalities for clinical trials
  - Approaches should be data driven