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Clinical Outcome Assessments Used/Recommended by the EMA and FDA for the Evaluation of Products to Treat Autism Spectrum Disorder

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Methodological Question Being Addressed: This abstract intends to address the methodological question of which clinical outcome assessments (COAs) to select and include in the evaluation of products for the treatment of autism spectrum disorder.

Introduction (Aims). Autism spectrum disorder (ASD) is a group of developmental disorders characterized by disturbance in language, perception and socialization. The objectives of this study were: 1) To review which guidance were published by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to help industry prepare marketing-authorization applications for medicinal products for ASD treatment; 2) To identify which products were approved specifically for ASD; and 3) To find out about the use of clinical outcome assessments (COAs) in the approval process.
Methods. This research was conducted through a review of ASD-specific EMA and FDA regulatory guidelines, product labeling and corresponding assessment reports or medical reviews. The PROLabels database was used for labeling claim identification. PROInsight was used for guidelines identification.
Results. The search of guidelines revealed that only the EMA has issued a draft guideline in 2016 (02/25/2016) with advice on the main efficacy measures to be used, e.g., symptomatic, functional and global scales. The EMA recommends that symptoms should be assessed with scales validated for the full age range of patients to be studied. The use of the same rating scale for inclusion, efficacy and responder definition is recommended wherever possible. Scales based on clinician ratings using information obtained from reliable informants are most appropriate as primary efficacy measures. Both raters (clinicians) and observers (parents, caretakers, teachers etc.) should be adequately trained, including recording of data in observer diaries or into a database. As for functional scales, the EMA acknowledges that no validated scale of functioning has yet been clearly identified that would be specific to ASD. Functional scales developed for other conditions (e.g. ADHD) might have questionable applicability to ASD and might lack sensitivity for detecting a treatment effect in ASD patients. The development of a functional scale validated for autism is therefore encouraged. The FDA has approved only two products with an indication of autistic disorders, i.e., risperidone and

aripiprazole; two atypical antipsychotics for control of behavioural sympatology. No products with this indication could be found on the EMA website. The main criterion of evaluation for the products approved by the FDA was changes in symptoms measured by COAs. Risperidone and aripiprazole used the Aberrant Behavior Checklist (ABC), a measure completed by caregivers to assess changes in irritability (primary endpoint). Secondary endpoints involved the use of ClinROs: the Clinical Global Impression - Change (CGI-C) scale (risperidone), and the Clinical Global Impression - Improvement (CGI-I) scale (aripiprazole) to measure changes in irritability.

Conclusion. The review revealed major discrepancies between the FDA and the EMA. COAs played a major role in the evaluation of medicinal products approved for ASD in the USA. With globalization of research, more harmonization is needed between both agencies.

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