



November 22, 2023

Submitted electronically to publiccomments@icer.org

RE: Institute for Clinical and Economic Review (ICER) Draft Scoping Document on 3,4-Methylenedioxymethamphetamine-Assisted Therapy (MDMA-AT) For Post-Traumatic Stress Disorder (PTSD)

Otsuka America Pharmaceutical, Inc. (Otsuka) appreciates the opportunity to submit comments on ICER’s draft scoping document on MDMA-AT For PTSD (Draft Scoping Document).ⁱ Relying on that document, ICER seeks to “evaluate the health and economic outcomes of MDMA-AT for PTSD.”ⁱⁱ

Otsuka and its affiliates oversee research and development and commercialization activities for innovative products in North America. At Otsuka, our driving philosophy is to defy limitation, so others can too. We seek to serve those with unmet medical needs in three important treatment areas: nephrology, central nervous system, and digital therapeutics. Otsuka is proud to be at the forefront of the research and development of new therapies designed to help patients with Alzheimer’s disease, mental illness, and chronic kidney disease. We respect the value within every mind—whether it’s a grand idea that changes the world, a simple human connection that changes someone’s life, or something in between.

Otsuka offers comments on various elements of the Draft Scoping Document below, including the clinical evidence review, the comparative value analysis, and other benefits and context.

A. Scope of Clinical Evidence Review

Population Focus. ICER identifies the population of focus for its review as “adults with a diagnosis of moderate-to-severe PTSD.”ⁱⁱⁱ Otsuka encourages ICER to adopt a clear definition of what it means to have “moderate-to-severe PTSD.” Clinical impressions of patients and the nature or severity of their PTSD can vary and experts in the field routinely identify concerns with accurately identifying these patients.^{iv}

In addition, ICER has also indicated, data permitting, that it will evaluate the evidence related to MDMA-AT for PTSD for different subpopulations. Otsuka encourages ICER to consider the following with respect to these proposals:

- Otsuka agrees that it will be critical to identify PTSD patients by subtypes and encourages ICER to define those subtypes.
- In addition to selective serotonin reuptake inhibitors (SSRI) use, ICER should collect and consider information on whether patients used psychotherapy or pharmacotherapy for management of PTSD symptoms.
- Finally, ICER should evaluate patient demographic information, including age and subpopulations with distinct PTSD characteristics (such as civilians and non-civilians).

Considering this information will help ensure that ICER’s findings are appropriately applied.

Comparators. ICER has indicated that it will compare “MDMA added to [Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation (MAPS PBC)]-specific manualized psychotherapy to psychotherapy alone as estimated by the placebo arm in clinical trials.”^v Otsuka asks ICER to consider the following comments on this approach:

- Including additional pharmaceutical comparators that might help evaluate MDMA-AT as compared to treatments for PTSD, given the significant heterogeneity in the PTSD population.^{vi} Such comparators could include certain SSRIs and serotonin and norepinephrine reuptake inhibitors, antidepressants, cognitive behavioral therapy, and prolonged exposure therapy, which are recommended by PTSD guidelines.^{vii} In addition, ICER should consider neuromodulation and neurofeedback as comparators, to the extent data exists, as these therapies have shown some promise in treating PTSD.
- Describing how ICER will identify the costs for psychotherapy, and any other treatment modalities, in the comparator arm, given the variety of codes used for some treatments.

Outcomes. Otsuka appreciates ICER’s carefully chosen list of patient-important outcomes of interest.^{viii} However, Otsuka encourages ICER to add the following to its list of outcomes:

- Clinician-reported outcomes (e.g., the Clinician Administered PTSD scale (CAPS)-5).
- Patient reported outcomes (e.g., the PTSD Checklist for DSM-5 (PCL-5)).
- Impact on occupational and social functioning (such as family and other relationships), to help provide more holistic insight into the effects of treatment.
- Family spillover effects, including secondary stress, anxiety/depression, and substance abuse.
- Physical health, including hypertension, metabolic disease, gastrointestinal, hormonal conditions, sleep quality, heart rate variability, and other digital biomarkers.

In addition, Otsuka encourages ICER to clarify what “loss of diagnosis” means as an outcome.

Additional comments. Otsuka also encourages ICER to consider the following in its review:

- Real-world evidence, in addition to randomized controlled trials and systematic reviews, as the former could offer a more practical perspective on the effectiveness and applicability of MDMA-AT in diverse clinical settings.

- Explicitly including Veterans Affairs providers among the relevant settings in its review.

B. Scope of Comparative Value Analyses

In addition to the above clinical evidence review, ICER “will develop an economic model to assess the lifetime cost effectiveness of [MDMA-AT] in patients with moderate to severe [PTSD].”^{ix} Otsuka supports this approach and, in addition, encourages ICER to:

- Complete a detailed analysis of its cost assumptions for both direct and indirect costs of PTSD treatment. This analysis should include all health care resource utilization direct costs, including any hospital stays and treatment provided by a psychiatrist and nurse. This analysis is also critical for indirect costs, which frequently are of significant concern and magnitude with respect to PTSD.^x
- Consider psychotherapy alone as a comparator in addition to “usual care therapy,” which is typically a mix of psychotherapy and pharmacotherapy.
- Consider aligning comparators for the value analysis and clinical evidence review.
- Clearly define the health states that are to be used in the determination of overall health outcomes and costs. It is critical that these health states be defined objectively given the significant heterogeneity in the PTSD population and the diversity of symptoms. In addition, it is critical that the patient voice be included in the assessment of health state.

Given the impacts of PTSD beyond the patient’s health outcomes, Otsuka further encourages ICER to couple the cost-effectiveness analysis with a macroeconomic model, such as an input-output model or computable equilibrium model.

C. Potential Other Benefits and Contextual Considerations

In addition to the above comments, Otsuka encourages ICER to consider the following throughout its evaluation of MDMA-AT for PTSD.

- There is significant enthusiasm for MDMA-AT, but it may be difficult for many patients to access these therapies given the challenges to appropriately scaling this treatment, existing stigma, and policies against drug use.^{xi}
- ICER should further explore its concerns with respect to other impacts of MDMA-AT for PTSD, including the goal of reducing health inequities.^{xii}

* * * * *

Otsuka appreciates the opportunity to comment on the Draft Scoping Document. If you have any questions about these comments, please contact Heidi Waters.

Sincerely,

Kaan Tunceli, PhD
VP Global Value & Real World Evidence

ⁱ ICER, *MDMA-Assisted Therapy for Post-Traumatic Stress Disorder (PTSD): Draft Background and Scope* (Nov. 1, 2023) [hereinafter Draft Scoping Document].

ⁱⁱ *Id.* at 3.

ⁱⁱⁱ *Id.* at 3.

^v Draft Scoping Document at 4.

^{vi} American Psychological Association, *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults*, at ES-8(Feb. 24, 2017), available at <https://www.apa.org/ptsd-guideline/ptsd.pdf> [hereinafter Guidelines] (“Panel members agree however that examination of treatment effect heterogeneity with diverse samples should be prioritized for future research.”)

^{vii} Guidelines at ii, 69.

^{viii} Draft Scoping Document at 4.

^{ix} *Id.* at 5.

^{xi} Draft Scoping Document at 5.

^{xii} *Id.*