Comments on the "Application for inclusion of Ketoconazole in the WHO Model List of Essential Medicines (EML) (April 2023)", submitted by Mark E. Molitch et al.

The technical unit does not support the application ""Application for inclusion of Ketoconazole in the WHO Model List of Essential Medicines (EML) (April 2023)", submitted by Mark E. Molitch et al. The application was not developed in consultation with this WHO department.

The application is not based on a thorough search of the available literature on the topic, no search strategy is described and no flow diagram provided to better estimate the body of evidence on medical treatment of Cushing's disease. For example, there are more systematic reviews on the topic which could have been included and critically appraised (1-3). Therefore, data on ketoconazole treatment appear somewhat selective.

With regard to the review of benefits the old studies (4, 5) based on bias-prone case series of 34 and 8 patients. The same holds true for the cited newer study (6) which had a retrospective observational design including 200 patients. The cited meta-analysis included both randomised-controlled trials (RCT) and cohort studies (35 studies with 1520 patients). In order to minimise risk of bias only data from RCTs should be described in the application. Of note, authors of this systematic review described that patients using medication monotherapy showed a lower percentage of cortisol normalisation compared to use of multiple medical agents (49.4% versus 65.7%). Furthermore, no direct comparisons between various medical therapies for Cushing's disease seem to be available.

With regard to applicants' review of harms and toxicity their list of adverse events of ketoconazole treatment appears to be limited (7 – 9). Even if only liver toxicity has to be monitored applicants should discuss difficulties in low- and middle-income countries to monitor liver enzymes frequently as well as availability of endocrinologists to monitor the treatment effect.

With regard to costs no adequate cost-utility/benefit analysis seems to be available. However, any estimation has to include costs to frequently measure urinary free cortisol level as well as monitoring liver enzymes and other possible adverse events.

Noncommunicable Diseases Management-Screening, Diagnosis and Treatment (MND)
NCD Department, World Health Organization

References

1. Gadelha MR, Neto LV (2014). Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol (Oxf) 80(1): 1-12
2. Galendi JSC et al. (2021). Effectiveness of Medical Treatment of Cushing's Disease: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 12: 732240
3. Pivonello R et al. (2020). Medical Treatment of Cushing's Disease: An Overview of the Current and Recent Clinical Trials. Front Endocrinol (Lausanne) 11: 648
4. Sonino N, Boscaro M, Paoletta A, Mantero F, Ziliotto D. Ketoconazole treatment in Cushing's syndrome; experience in 34 patients. Clin Endocrinol 1991;35:347-352. doi: 10.1111/j.1365-2265.1991.tb03547.x
5. Tabarin A, Navarranne A, Guérin J, Corcuff JB, Parneix M, Roger P. Use of ketoconazole in the treatment of Cushing's disease and ectopic ACTH syndrome. Clin Endocrinol 1991;34:63-69. doi: 10.1210/jcem-63-6-1365
6. Castinetti F, Guignat L, Giraud P, Muller M, Kamenicky P, Drui D, et al. Ketoconazole in Cushing's disease: is it worth a try? J. Clin. Endocrinol. Metab. 2014;99:1623-1630. doi
7. Fleseriu M, Castinetti F (2016). Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Pituitary 19(6): 643-653
8. Castinetti F et al. (2021). Approach to the Patient Treated with Steroidogenesis Inhibitors. J Clin Endocrinol Metab 106(7): 2114-2123.
9. Gilis-Januszewska A, et al. (2022). Individualized medical treatment options in Cushing disease. Front Endocrinol (Lausanne) 13: 1060884.