A.21	Ketoconazole – Cushing syndrome – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Ketoconazole plays an important role in the management of Cushing syndrome in every setting (HIC and LMICs) Additionally it may be the only available option for many patients (see below)
Does the proposed medicine address a relevant public health need?	☐ Yes ☐ No ☐ Not applicable Comments: Cushing syndrome due to ACTH secreting adenomas (Cushing disease) is responsible for about 80% of the cases. Reported incidence is 1.2 to 2.4 million per year in Europe (1) and 6.2 to 7.6 million per year in the United States (2). No information is available about incidence in other regions. The recommended treatment for this condition is neurosurgery, removing the adenoma. Access to experienced neurosurgeons in low and middle- income countries is quite limited (3). Additionally, Cushing disease and other causes of Cushing syndrome may require medical management with ketoconazole if surgery fails to resolve the problem or if the patient is not a surgical candidate. These patients may continue to require treatment indefinitely. Ketoconazole is also used to control of hypercortisolism in preparation for surgery, in patients who have undergone radiation therapy (while waiting for the clinical effect) and in patients where the source of excessive cortisol is unknown/ unclear, such as occult or metastatic ectopic ACTH syndrome (4).
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Cohort studies have shown a significant proportion of patients with good response to ketoconazole (including normalization of urine free cortisol). A systematic review published in 2018 (35 trials, N=1520) showed 49% of efficacy (defined as cortisol normalization) in Cushing disease and 49.3% in Cushing syndrome (all etiologies). It is important to highlight that some of the other drugs evaluated were associated with better outcomes (5).

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Ketoconazole has been in the market for a long time. Potential adverse events have been clearly described in the management of Cushing syndrome and as an antifungal drug.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: • Hepatotoxicity is a potential severe side effect. Due to this, ALT must be motored frequently during treatment. Damage is reversible. • Ketoconazole has multiple drug interactions. • It is a teratogenic drug. • Can prolong the QT interval. • Ketoconazole decreases estradiol and testosterone production. This may lead to gynecomastia, decreased libido, and impotence in me. In women, the effects are not clinically apparent because of the oligomenorrhea, or amenorrhea associated with Cushing's syndrome (6)
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: • Patient with Cushing syndrome should be managed by an endocrinologist. • Urinary free cortisol must be monitored frequently to adjust dosing. • Liver enzymes must be monitored prior to starting treatment. It is contraindicated in patients with liver disease whose ALT values are ≥3 times the upper normal range.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Cost-effectiveness analyses are not available. Treating patient with Cushing disease decreases their health care visits and their medicals costs. The drug is affordable in multiple countries. Additionally, ketoconazole is much cheaper that other therapeutic options.

Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: In the United States, Canada it is an off-label use for the treatment of Cushing's syndrome. It is approved by EMA, Australian agency for the treatment of Cushing syndrome
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Ketoconazole for the treatment of Cushing syndrome is not included in any of the WHO guidelines. It is recommended in guidelines developed by other institutions: • Endocrine society • American Academy of clinical endocrinologists • Pituitary society

1. Lindholm J, Juul S, Jørgensen JO, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab 2001; 86:117. (Not included in the application)
2. Broder MS, Neary MP, Chang E, et al. Incidence of Cushing's syndrome and Cushing's disease in commercially insured patients <65 years old in the United States. Pituitary 2015; 18:283. (Not included in the application)
3. Punchak M, Mukhopadhyay S, Sachdev S et al. Neurosurgical care: availability and Access in low-income and middle-income countries. World Neurosurg 2018;112:e240-e254. doi: 10.1016/j.wneu.2018.01.029
4. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100:2807.
5. Broersen LHA, Jha M, Biermasz NR, Pereira AM. Effectiveness of medical treatment for Cushing's syndrome: a systematic review and meta-analysis. Pituitary 2018;21(6):631-641. doi: 10.1007/s11102-018-0897-z
6. Gal M, Orly J, Barr I, et al. Low dose ketoconazole attenuates serum androgen levels in patients with polycystic ovary syndrome and inhibits ovarian steroidogenesis in vitro. Fertil Steril 1994; 61:823. (Not included in the application)