

A.21	Ketoconazole – Cushing syndrome – EML
Draft recommendation	<input type="checkbox"/> Recommended <input checked="" type="checkbox"/> Not recommended Justification: The proposed medicine is not the primary treatment of the condition in many settings. The medicine is currently available in most countries although not specifically indicated for treatment of Cushing syndrome. Information related to the use of ketoconazole in Cushing syndrome is supported mainly by noncontrolled retrospective studies, which might have overestimated the efficacy and underestimated the safety of the drug.
Does the proposed medicine address a relevant public health need?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: The incident of the conditions needed the proposed medicine is very rare. The primary treatment is surgery, however, in many low-income countries the availability of expert pituitary neurosurgeons who could perform the surgery is quite limited. Hence medical treatment might become primary in such situation.
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)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: Has been recommended in multiple guidelines as medical therapies for Cushing syndrome. However, the recommendations are based on low level of evidences (case series and retrospective studies with small sample size), since the possibility to conduct RCT in this rare condition is also limited. The efficacy of the proposed medicine is also not the highest among all available medical therapies. ¹
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)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: AEs are considered balanced with the efficacy. However, data is from retrospective study involving 200 patients.

¹ Broersen LHA, Jha M, Biermasz NR, Pereira AM, Dekkers OM. Effectiveness of medical treatment for Cushing's syndrome: a systematic review and meta-analysis. Pituitary. 2018 Dec;21(6):631-641. doi: 10.1007/s11102-018-0897-z. PMID: 29855779; PMCID: PMC6244780.

Are there any adverse effects of concern, or that may require special monitoring?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: The major adverse effect of ketoconazole is liver toxicity, mostly transient, but regular liver function test monitoring required. There are several drug–drug interactions with ketoconazole; careful review of the patient's medication list for potentially problematic interactions is essential.. ²
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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: Doses are adjusted based upon periodic monitoring of urinary free cortisol (UFC) levels, initially every 2-4 weeks and then every 3-6 months The medical management of most patients is done by endocrinologists in the tertiary care center.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: Cost is the lowest among all available medical therapies. However it's not included the cost of periodic monitoring of UFC and liver function test monitoring.
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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: Currently approved as treatment for anti-fungal conditions by FDA and Health Canada; off label for Cushing syndrome. Approved for treatment of Cushing syndrome by EMA. Included in the EML of 90+ countries.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not applicable Comments: No current WHO guideline on Cushing syndrome

² Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 2021; 9: 847–75