Ketoconazole

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

ATC codes: H02CA03

Indication	Cushing syndrome ICD11 code: 5A70.Z
INN	Ketoconazole
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 200 mg
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Ketoconazole
DrugBank	Ketoconazole

Expert Committee recommendation

The Expert Committee noted that ACTH-secreting pituitary tumours are responsible for 80% of cases of Cushing syndrome and are relatively rare, with a reported annual incidence of 2–3 cases per million people. The Committee noted that neurosurgery can cure most cases and is the recommended treatment intervention for this condition. Pharmacological treatment may be required in some patients who are not candidates for surgery, or in settings where experienced neurosurgeons and surgical facilities are not available. The Committee noted that the evidence presented in the application suggested that a significant proportion of patients had a good response to treatment with ketoconazole as measured by normalization of urinary-free cortisol levels, however, the certainty of evidence was low and drawn from retrospective observational studies and a single meta-analysis. Data from individual randomized studies of other medicines suggested alternative treatments were associated with better outcomes, however direct comparisons were not available. The Committee expressed grave concerns about the safety profile associated with systemic use of ketoconazole, including serious liver toxicity requiring monitoring with regular liver function tests, QT prolongation and the potential for numerous drug–drug interactions as a result of CYP3A4 inhibition by ketoconazole. Based on these considerations, the Committee did not recommend the inclusion of ketoconazole on the EML for use in the management of patients with Cushing syndrome.

Background

Ketoconazole was added to the EML in 1987 for the treatment of systemic fungal infections. A square box was added to the listing in 1989 to indicate that other azole antifungals could serve as suitable therapeutic

alternatives. In 1999, ketoconazole was replaced by fluconazole as the representative medicine on the basis of better cost–effectiveness and fewer adverse events. Ketoconazole remained a therapeutic alternative to fluconazole under the new square box listing until 2019, when the square box was removed from the listing for fluconazole, following the addition of the new azole antifungals itraconazole and voriconazole. Ketoconazole tablets have not previously been evaluated for inclusion on the Model Lists for use in Cushing syndrome.

Public health relevance

Cushing syndrome is caused by the excessive secretion of cortisol from the adrenal glands. About 80% of cases of Cushing syndrome are due to adrenocorticotropic hormone (ACTH)-secreting pituitary tumours and 20% are due to cortisol-producing adrenal adenomas and carcinomas. ACTH-secreting tumours represent about 5% of clinically identified pituitary adenomas. The annual incidence of ACTH-secreting tumours is about 2–3 per million. About 90% of ACTH-secreting pituitary adenomas are less than 10 mm in maximum diameter (microadenomas) and 10% are more than 10 mm (macroadenomas); malignant ACTH-secreting tumours are rare (4,5). Excess cortisol may cause considerable morbidity, including hypertension, diabetes, heart disease, muscle weakness, fatigue, depression, osteoporosis, weight gain, easy bruising, facial plethora and skin striae due to excessive cortisol levels and hirsutism due to excessive adrenal androgen levels (6–10). In children, weight gain with decreased growth velocity is often the presenting feature (7,9). Mortality in patients with Cushing syndrome is also two to five times higher than that of the general population (11–14). Macroadenomas can continue to grow and cause mass effects, such as visual field defects, hypopituitarism, cranial nerve palsies and headaches. Adrenal lesions also usually present with symptoms and signs related to excessive cortisol and androgen secretion (6–10). Almost all patients with Cushing syndrome due to benign adrenal adenomas or bilateral nodular hyperplasia can be cured surgically by adrenalectomy (9). Those not controlled by surgery are treated medically with the goal of achieving hormonal control. Medical treatment may be the only option in some settings where availability of neurosurgeons is limited.

Benefits

Early studies using ketoconazole to treat Cushing syndrome suggested a normalization rate of urinary-free cortisol levels of over 90% (15,16). A retrospective, multicentre study reviewed data on 200 patients with Cushing disease (78% females, 106 microadenomas, 36 macroadenomas, 58 with no visible tumour) treated with ketoconazole in doses ranging from 200 mg to 1200 mg a day, with most patients receiving 600 mg and 800 mg a day (17). Of 39 patients treated for 4 months before surgery, 19 (48.7%) achieved a normal urinary-free cortisol. In 158 patients treated postoperatively or primarily (when surgery was contraindicated), 78 (49.4%) achieved normal urinary-free cortisol, 37 (23.4%) had a > 50% decrease in urinary-free cortisol and 43 (27.2%) had unchanged urinary-free cortisol. Ketoconazole treatment was stopped in 26.8% of patients due to lack of efficacy and in 25.6% of patients due to adverse effects. Individual prospective, randomized studies of other medicines for management of Cushing syndrome showed normalization of cortisol levels in 28% of patients treated with cabergoline (18), 43% of patients treated with metyrapone (19), 20% of patients treated with pasireotide (20), 66% of patients treated with osilodrostat (21), and 31% of patients treated with levoketoconazole (22). In the SEISMIC study, 88% of patients treated with mifepristone were judged to have progressive clinical improvement (23,24). Because mifepristone blocks the cortisol receptor and does not interfere with cortisol synthesis, measurement of cortisol levels cannot be used as a measure of efficacy. A 2018 systematic review and meta-analysis of 35 randomized trials and cohort studies (1520 participants) evaluated the effectiveness of medical treatment for Cushing syndrome (25). The review reported the percentage of patients with pituitary Cushing disease who achieved normalization of cortisol levels as 81.8% (95% confidence interval (CI) 75.4% to 87.6%, four studies) for mitotane, 60.0% (95% CI 31.3% to 83.2%, one study) for metyrapone, 49.0% (95% CI 42.0% to 56.0%, three studies) for ketoconazole, 41.1% (95% CI 32.7% to 49.8%, two studies) for pasireotide and 35.7% (95% CI 24.6% to 47.6%, three studies) for cabergoline. The corresponding percentages for patients with all etiologies of Cushing syndrome, including adrenal carcinoma were 78.9% (95% CI 73.3% to 85.7%, four studies) for mitotane, 75.9% (95% CI 57.5% to 90.9%, two studies) for metyrapone, 71.1% (95% CI 51.6% to 87.5%, seven studies) for ketoconazole, 41.1% (95% CI 32.7% to 49.8%, two studies) for pasireotide and 35.7% (95% CI 24.6% to 47.6%, three studies) for cabergoline. The authors concluded that medication induces cortisol normalization in a large percentage of patients with Cushing disease and would

be a reasonable option for patients who chose not to have surgery or in whom surgery was contraindicated, and for patients with recurrence following surgery.

Harms

The main adverse effect of ketoconazole is liver toxicity. In a retrospective study of 200 patients treated with ketoconazole for Cushing syndrome, liver enzyme elevations of up to five-fold of normal were reported in 15.8% of patients, four patients experienced five- to 10-fold elevations and one patient experienced a 40-fold increase (17). These increases occurred within 4 weeks of starting treatment or with dose increments. All increases returned to normal after treatment withdrawal or dose reduction. Other reported adverse effects of ketoconazole were gastrointestinal symptoms (13.1%), adrenal insufficiency (5.4%) and pruritus (3.7%). Ketoconazole is a strong CYP3A4 inhibitor and therefore may affect dosing of other medicines that are substrates for this enzyme (e.g. amiodarone, carbamazepine, amitriptyline, selective serotonin reuptake inhibitors, benzodiazepines, calcium channel blockers, statins and colchicine). In 2013, the United States Food and Drug Administration issued a drug safety communication on ketoconazole use because of potentially fatal liver injury, risk of drug interactions and adrenal gland problems (26). In 2013, the European Medicines Agency's Committee on Medicinal Products for Human Use recommended marketing authorizations of oral ketoconazole be suspended throughout the European Union due to the risk of liver toxicity outweighing the benefits in the treatment of fungal infections. This recommendation was subsequently endorsed by the European Commission. However, it was noted by the European Medicines Agency that ketoconazole was used off-label for the treatment of patients with Cushing syndrome and indicated that national regulatory authorities may make ketoconazole available for these patients under controlled conditions (27).

Cost / cost effectiveness

A retrospective cohort study compared costs for treatment of 877 patients with Cushing syndrome compared with 2631 matched controls without this disease using a United States insurance administrative claims database to assess the economic burden of Cushing syndrome (28). The study found that the mean number of health care visits (ambulatory, emergency department and inpatient) was two-to-four times higher for patients with Cushing syndrome than for control patients. The total mean all-cause health care costs were also higher for patients with Cushing syndrome than for control patients, driven primarily by medical costs, which accounted for 87% and 79% of total costs for patients with Cushing syndrome and controls, respectively. On average, medical costs were nearly seven times higher for patients with Cushing syndrome than for control patients. The costs of treatment for Cushing syndrome (including drug cost, treatment, complications, adverse events, comorbidity and monitoring) were reported in a 2014 study that assessed the budget impact of pasireotide in the United States (29). The annual cost per patient for treatment with ketoconazole was US$ 25 475 (of which monthly drug costs were US$ 127). Corresponding figures for other medicines were US$ 144 280 (US$ 14 583) for pasireotide, US$ 207 562 (US$ 15 140) for mifepristone, US$ 32 179 (US$ 719) for cabergoline and US$ 40 893 (US$ 1364) for mitotane. Costs of treatment for Cushing syndrome using ketoconazole and other medicines reported in the application are shown in Table 24 (refer TRS 1049). Costs for a 30-day course of ketoconazole were reported in the application as US$ 36 in Argentina, US$ 6 in Bolivia (Plurinational State of), US$ 36 in Brazil, US$ 6–22 in India and US$ 25 in Mexico.

WHO guidelines

WHO guidelines for the management of Cushing syndrome are not currently available.

Availability

Ketoconazole (200 mg tablets) has regulatory approval from the European Medicines Agency for use in the treatment of adults and children aged 12 years and older with Cushing syndrome. Ketoconazole (200 mg tablets), produced by three manufacturers, has regulatory approval from the United States Food and Drug Administration for use in the treatment of fungal infections. The regulatory status of ketoconazole 200 mg tablets in Australia,

Canada and Japan, as presented in the application, was unable to be verified.

Other considerations

The technical team for Screening, Diagnosis and Treatment in the Department of Noncommunicable diseases reviewed and provided comments on the application. The technical team advised that it did not support the application, highlighting its views that the data included appeared to be selective, omitting systematic reviews on the topic that could have been included and critically appraised (1–3), and there was risk of bias in the included case series, and retrospective observational and cohort studies. The technical unit also noted that the application did not address difficulties in low- and middle-income countries in monitoring liver enzymes and the availability of endocrinologists to monitor treatment effects, nor did it provide any estimation of costs associated with measuring urinary free cortisol levels, monitoring liver enzymes and other possible adverse events.

1. Gadelha MR, Vieira Neto L. Efficacy of medical treatment in Cushing's disease: a systematic review. Clin Endocrinol (Oxf). 2014;80(1):1–12.
2. Simões Corrêa Galendi J, Correa Neto ANS, Demetres M, Boguszewski CL, Nogueira V. Effectiveness of medical treatment of Cushing's Disease: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2021;12:732240.
3. Pivonello R, Ferrigno R, De Martino MC, Simeoli C, Di Paola N, Pivonello C, et al. Medical treatment of Cushing's disease: an overview of the current and recent clinical trials. Front Endocrinol (Lausanne). 2020;11:648.
4. Molitch ME. Diagnosis and treatment of pituitary adenomas: a review. JAMA. 2017;317(5):516–24.
5. Melmed S. Pituitary-tumor endocrinopathies. N Engl J Med. 2020;382(10):937–50.
6. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40.
7. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2008;93(7):2454–62.
8. Hamrahian AH, Yuen KC, Hoffman AR. AACE/ACE disease state clinical review: medical management of Cushing disease. Endocr Pract. 2014;20(7):746–57.
9. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913–27.
10. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021;9(12):847–75.
11. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab. 2011;96(3):632–42.
12. Dekkers OM, Horvath-Puho E, Jorgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab. 2013;98(6):2277–84.
13. Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB. Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. J Clin Endocrinol Metab. 2013;98(3):1022–30.
14. Limumpornpetch P, Morgan AW, Tiganescu A, Baxter PD, Nyawira Nyaga V, Pujades-Rodriguez M, et al. The effect of endogenous Cushing syndrome on all-cause and cause-specific mortality. J Clin Endocrinol Metab. 2022;107(8):2377–88.
15. Sonino N, Boscaro M, Paoletta A, Mantero F, Ziliotto D. Ketoconazole treatment in Cushing's syndrome: experience in 34 patients. Clin Endocrinol (Oxf). 1991;35(4):347–52.
16. 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 (Oxf). 1991;34(1):63–9.
17. 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(5):1623–30.
18. Lila AR, Gopal RA, Acharya SV, George J, Sarathi V, Bandgar T, et al. Efficacy of cabergoline in uncured (persistent or recurrent) Cushing disease after pituitary surgical treatment with or without radiotherapy. Endocr Pract. 2010;16(6):968–76.
19. Daniel E, Aylwin S, Mustafa O, Ball S, Munir A, Boelaert K, et al. Effectiveness of metyrapone in treating Cushing's syndrome: a retrospective multicenter study in 195 patients. J Clin Endocrinol Metab. 2015;100(11):4146–54.
20. Lacroix A, Gu F, Gallardo W, Pivonello R, Yu Y, Witek P, et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. Lancet Diabetes Endocrinol. 2018;6(1):17–26.
21. Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. Lancet Diabetes Endocrinol. 2020;8(9):748–61.
22. Fleseriu M, Pivonello R, Elenkova A, Salvatori R, Auchus RJ, Feelders RA, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. Lancet Diabetes Endocrinol. 2019;7(11):855–65.
23. Fleseriu M, Molitch ME, Gross C, Schteingart DE, Vaughan TB, 3rd, Biller BM. A new therapeutic approach in the medical treatment of Cushing's syndrome: glucocorticoid receptor blockade with mifepristone. Endocr Pract. 2013;19(2):313–26.
24. Katznelson L, Loriaux DL, Feldman D, Braunstein GD, Schteingart DE, Gross C. Global clinical response in Cushing's syndrome patients treated with mifepristone. Clin Endocrinol (Oxf). 2014;80(4):562–9.
25. 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;21(6):631–41.
26. FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems [internet]. Silver Spring, MD: United States Foo

d and Drug Administration; 2013 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-limits-usage-nizoral-ketoconazole-oral-tablets-due-potentially, accessed 6 October 2023).
27. Ketoconazole-containing medicines. European Commission final decision [internet]. Amsterdam: European Medicines Agency; 2013 (https://www.ema.europa.eu/en/medicines/human/referrals/ketoconazole-containing-medicines, accessed 6 October 2023).
28. Burton T, Le Nestour E, Neary M, Ludlam WH. Algorithm development and the clinical and economic burden of Cushing's disease in a large US health plan database. Pituitary. 2016;19(2):167–74.
29. Truong HL, Nellesen D, Ludlam WH, Neary MP. Budget impact of pasireotide for the treatment of Cushing's disease, a rare endocrine disorder associated with considerable comorbidities. J Med Econ. 2014;17(4):288–95.

