1. **Title page**

Application for inclusion of Ketoconazole in the WHO Model List of Essential Medicines (EML) (April 2023)

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2. Summary statement of the proposal for inclusion, change or deletion

This proposal requests inclusion of oral ketoconazole tablets for the management of patients with Cushing syndrome. The listing is being sought for the complementary list for EML.

Ketoconazole offers a safe and affordable first line of treatment in countries where surgery or radiotherapy are not available. This submission is particularly relevant to medical care in low- and middle-income countries where neurosurgery, the first line treatment for pituitary disease, may not be available or may not have the same positive outcomes compared to centers where a high number of surgeries is performed (see below).

Ketoconazole had been included as an antifungal therapy in the EML in 1988 (TRS770). It was removed in 2000 (TRS895) and replaced by fluconazole which is more cost-effective and is associated with fewer adverse effects.

Context

- *Non-communicable diseases*

Endocrinology is a subspecialty of medicine that focuses on the diagnosis and treatment of patients with diseases of the endocrine system. These conditions are part of the non-communicable diseases (NCD) group.

Cushing Syndrome

Cushing syndrome is due to the excessive secretion of the hormone, cortisol, from the adrenal glands (1-7). About 80% of cases arise from the excessive secretion of adrenocorticotropic hormone (ACTH) from pituitary adenomas (referred to as Cushing Disease [CD]) or nonpituitary cancers (ectopic ACTH secretion) which then stimulates the adrenals to secrete cortisol and adrenal androgens. About 20% of cases arise due to autonomous secretion of cortisol and other steroids from adrenal adenomas, nodular hyperplasia and carcinomas (1-3,6,7). Cushing syndrome can also be due to the administration of hydrocortisone or other synthetic glucocorticosteroids and treatment therefore is the reduction or cessation of such medications. This application is for ketoconazole for the treatment of endogenous Cushing syndrome by reducing the production of cortisol.

ACTH-secreting tumors have an annual incidence of new diagnoses of about 2-3 per million (1-2). They comprise about 5% of clinically identified pituitary adenomas. About 90% of ACTH secreting pituitary adenomas are < 10 mm in maximum diameter and 10% are > 10 mm; malignant ACTH-secreting tumors are very rare (1-7).

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 (3-7). In children, weight gain with decreased growth velocity is often the presenting feature (4,6). Mortality is also increased 2 – 5 fold over the general population (8-11). Morbidity and mortality are related to the amount of cortisol as well as the duration of disease and can be greatly ameliorated by early diagnosis and treatment that normalizes cortisol levels (4-7). The approximately 10% of pituitary tumors that are

macroadenomas can continue to grow and cause mass effects, such as visual field defects due to optic chiasm compression, hypopituitarism, cranial nerve palsies, and headaches. Adrenal lesions also usually present with symptoms and signs related to excessive cortisol and androgen secretion (3-7). Some adrenal adenomas present as incidental findings on imaging studies carried out for other reasons and about 14% of those are functional, secreting excess amounts of steroid hormones but < 1% progress to overt Cushing syndrome (12).

Cushing syndrome is diagnosed biochemically, with the finding of elevated 8AM serum cortisol levels (included in the 3rd EDL) which cannot be suppressed by the administration of dexamethasone (included in Section 2.3 of the EML) the previous evening, by the finding elevated late night salivary cortisol levels, or by elevated 24-hour urinary free cortisol levels (3,5-7,13). The distinction between pituitary and adrenal causes is determined by finding elevated ACTH levels in the case of pituitary/ectopic ACTH causes or suppressed ACTH levels in the case of autonomous adrenal lesions. Ectopic ACTH secretion is distinguished from pituitary ACTH secretion by measuring ACTH levels in the venous effluent from the pituitary into the petrosal sinus using inserted catheters, with elevated levels in the petrosal sinus being found with pituitary adenomas but not ectopic sources. Following the biochemical confirmation, an MRI or CT scan is done to delineate the size and invasiveness of the tumor (3,5-7).

The goals of treatment are (1) elimination of effects due to the mass of the tumor (hypopituitarism, visual field defects, etc.); (2) reduction of elevated ACTH levels and cortisol levels to normal; (3) amelioration of the end-organ effects of the elevated cortisol levels; (4) avoidance of damage to remaining normal hypothalamic or pituitary function if a pituitary adenoma was treated; (5) minimizing other potential adverse effects of therapy (1-7).

Three therapeutic options are available. It is important to keep in mind that the guidelines for the management of Cushing syndrome caused by a pituitary adenoma, the most common form, assume that all 3 options are available and can be implemented safely (See Figure 1). This is not always the case in many resource-limited countries where some therapeutic options may simply not be available (i.e. radiation) or may not have the desirable outcomes (i.e. complications following neurosurgery in centers where neurosurgeons have limited expertise) (see below).

Where available, transsphenoidal surgery is considered the treatment of choice for pituitary Cushing as it offers the patient a chance for cure in the cases with pituitary adenomas (Figure 1). Even when "cure" is not achieved, surgery may effect a significant reduction in ACTH and cortisol levels and considerable amelioration of clinical symptoms. As would be expected, the smaller the tumor and the lower the basal ACTH levels, the better the surgical result. Using the criteria of postoperative hypocortisolism with cortisol levels <2 µg/dL (due to suppression of the normal pituitary corticotroph cells) to define cure, cure rates of 80% to 90% can be expected for microadenomas and 25% to 50% for larger tumors when the operation is performed by experienced neurosurgeons (4-7). In those “cured” by surgery, there is a 10% recurrence rate by 10 years (4-7). With microadenomas, the risks of surgery are very small in centers with a large experience and with surgeons who perform many surgeries every year; the mortality from surgery approaches that of anesthesia alone. The complication rate is higher for larger tumors, with risks for CSF leak, meningitis, and permanent DI reaching 2% each. Loss of one or more anterior pituitary hormones occurs in 5 - 10% of patients. Rarely, patients with very large tumors may need craniotomy and a subfrontal lobe approach (4-7).

For Cushing caused by primary adrenal disease, almost all patients with adrenal adenomas can be cured by unilateral adrenalectomy. Surgery for adrenal carcinomas is less successful with rates dependent upon initial size and whether distant metastases are present (6).

Following successful surgery, patients require hydrocortisone replacement for several weeks to months while awaiting recovery of their hypothalamic-pituitary-adrenal axes (4).

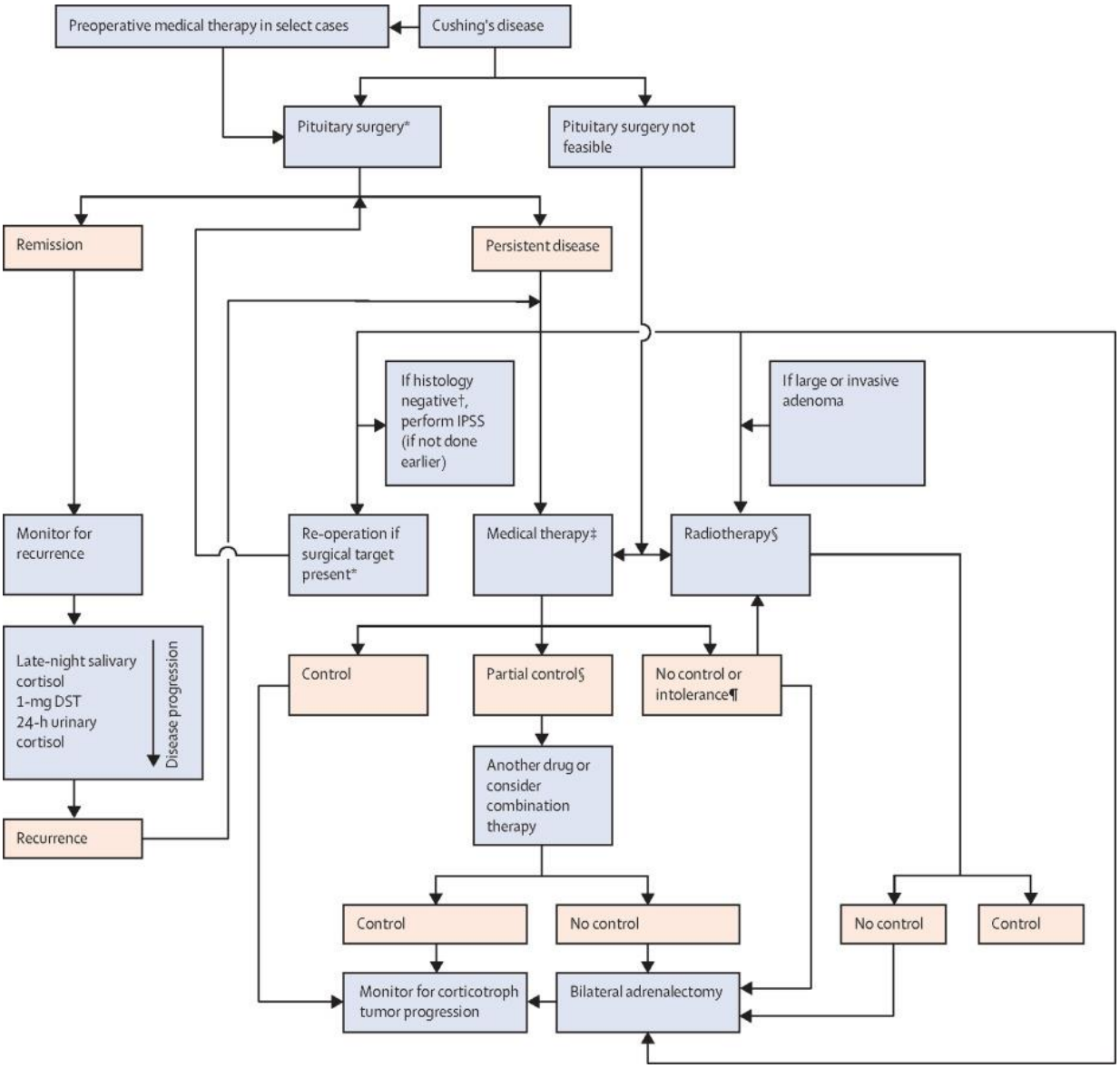

Figure 1. Management of Cushing disease (pituitary) (7)

In the patient is not cured by surgery, options include repeat surgery by an experienced pituitary surgeon (4,7,14,15), irradiation (usually stereotactic) (4,15,16), or medical therapy (13, 16, 17). If irradiation is chosen, it takes years for this to be effective (15). Medical therapy is generally reserved for patients who fail to achieve normal cortisol levels with surgery (4-7,15,17,18). Given the surgical control rates noted above, medical therapy is generally needed in 10-20% for those with microadenomas and

50-75% of those with macroadenomas. Medical therapy may be used alone or may be given following irradiation while awaiting the effects of the irradiation. Rarely, patients may also be considered for primary medical therapy if they are medically unable to undergo surgery. Another approach is to perform a bilateral adrenalectomy in patients with pituitary dependent ACTH hypersecretion but this approach carries a 50% risk of later pituitary tumor enlargement (Nelson's syndrome) as well as making the patient absolutely dependent upon exogenous glucocorticoid and mineralocorticoid replacement(4-7,15).

Drug therapy has been directed at the pituitary to decrease ACTH secretion by corticotroph tumors, at the adrenal to block multiple steps involved in cortisol synthesis, and at the cortisol receptor to block cortisol action. It should be noted that adrenal-directed therapy does not treat any underlying pituitary or ectopic ACTH-secreting tumor. Pituitary-directed drugs include cabergoline and pasireotide; neither has a high rate of efficacy (4-7,17,18). Adrenal steroidogenesis inhibitors include ketoconazole, metyrapone, osilodrostat, levoketoconazole and mitotane (4-7,17-20). The last is adrenolytic but has a high rate of adverse effects and its use is generally limited to patients with adrenal carcinoma. Ketoconazole is an imidazole derivative that has been the mainstay of medical treatment for Cushing's syndrome for many years. It blocks several steps in cortisol synthesis, including side chain cleavage, 17-hydroxylase, 17,20 lyase, 11β-hydroxylase, and aldosterone synthase (4,7,17-20**).** Metyrapone blocks the 11β-hydroxylase step and is fairly effective and but has many adverse effects (17-20). Osilodrostat blocks 11β-hydroxylase step and also the aldosterone synthase step; it is much more effective than metyrapone but also has a much higher cost (7,17-20). Mifepristone is the only cortisol receptor blocker currently available and is very costly (7,21).

3. Name of the WHO technical department and focal point supporting the application

To our knowledge, there is no specific department at WHO that focuses on Cushing syndrome specifically or in pituitary diseases in general.

4. Name of organization(s) consulted and/or supporting the application.

This submission is part of a larger project by a group of endocrinologists with worldwide representation who met regularly for 12 months (2020-2021) with the goal of performing an in-depth review of the essential medicines included in Section 18. of the EML and the EMLc ("Medicines for endocrines disorders"). The group included both adult and pediatric endocrinologists: Drs. Chanoine (Canada) and Molitch (USA) (co-Chairs) and Drs. von Oettingen (Canada), Villarroel (Bolivia), Kalra (India), Paulose (India), Abodo (Ivory Coast), Ramaiya (Tanzania), Donaghue (Australia), Junfen Fu (China) and de Beaufort (Luxembourg). In addition, we worked with economists (Drs. Ewen and Beran from Switzerland), pharmacists (Drs. Kavanagh and Gray from UK and Karekezi from Kenya) and a dietitian (Dr. Besancon from Mali).

This application is supported by the International Society for Endocrinology (applicant MM is a member), the International Consortium for Pediatric Endocrinology and Diabetes (ICPE) (co-applicant JPC is a member), the Endocrine Society and by the Pituitary Society (applicant MM is a member) (see letters of support).

The **International Society of Endocrinology (ISE)** represents the global endocrine community through its members and partners; national and regional organizations of clinicians, researchers, academics, nurses, dietitians and other allied health professionals active in the field of endocrinology. It collaborates with

over 80 national and regional societies, comprising more than 50.000 health professionals globally. ISE promotes the dissemination of the latest scientific discoveries and clinical translations of such discoveries through a biennial international meeting and other meetings all over the world. The ISE has developed new diverse training and education opportunities for the community of endocrinologists around the world, including a continue medical education program which aims to help foster the globalization and inter-regional development of existing national meetings by offering ISE supported Symposia and travel fellowships to member societies all over the world and an online portal – the ISE Global Education Hub that gathers and blends educational content from ISE's own and supported meetings. The portal serves as a year-round virtual community and single-entry point for online educational resources in endocrinology

The **Endocrine Society** is an international organization of over 18,000 endocrinologists that includes clinicians and basic scientists. It promotes breakthroughs in scientific discovery and medical care through publishing in its peer-reviewed journals, hosting an annual scientific meeting, creating resources and educational materials to help clinicians and investigators accelerate the pace of scientific discovery and translation of the latest science into clinical care, advocating for appropriate support and policies that benefit healthcare providers and patients, and educating the public about hormones and the roles that endocrine scientists and clinicians play in achieving optimal public health. The Endocrine Society publishes Clinical Guidelines for clinical care, including one on the management of patients with Cushing's Syndrome.

The **Pituitary Society** is an international organization of endocrinologists, neurosurgeons and others interested in pituitary disease and includes clinicians and basic scientists. The Society is dedicated to furthering the understanding of diseases of the pituitary gland. The Society sponsors educational conferences highlighting new advances in research and clinical care of pituitary diseases, provides information to the public about pituitary diseases, publishes a peer-reviewed journal that focuses on pituitary disease, and publishes Clinical Guidelines for clinical care, including one on the management of patients with Cushing's disease.

The **International Consortium for Pediatric Endocrinology and Diabetes (ICPE**) was founded in September 2015 with the goal of increasing collaborations at all levels between Pediatric Endocrinologists across the five continents. It regroups all major regional Pediatric Endocrine Societies, as well as the International Society for Pediatric and Adolescent Diabetes (ISPAD) and Global Pediatric Endocrinology and Diabetes (GPED): the Arab Society for Paediatric Endocrinology and Diabetes (ASPED); the Asian-Pacific Pediatric Endocrine Society (APPES); the African Society for Paediatric and Adolescent Endocrinology (ASPAE); the Chinese Society for Pediatric Endocrinology and Metabolism (CSPEM); the European Society for Paediatric Endocrinology (ESPE); the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE); the Japanese Society of Pediatric Endocrinology (JSPE); the Pediatric Endocrine Society (PES), the Latin American Society for Pediatric Endocrinology (SLEP) and the Russian Paediatric Endocrinology Group. ICPE, through their regional societies, represents more than 5,000 pediatric endocrinologists across the 5 continents.

5. Key information for the proposed medicine

INN: Ketoconazole

ATC: H02CA03, J02AB02

Indications (ICD 10):
E24 Cushing syndrome
E24.0 Pituitary-dependent Cushing disease, Overproduction of pituitary ACTH, Pituitary-dependent hyperadrenocorticism
E24.3 Ectopic ACTH syndrome
E24.9 Cushing syndrome, unspecified

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Ketoconazole is available in 200 mg tablets.

This application is restricted to ketoconazole.

7. Information supporting the public health relevance

About 80% of cases with Cushing syndrome are due to ACTH-secreting pituitary tumors and the remaining 20% are due to cortisol-producing adrenal adenomas and carcinomas. ACTH-secreting tumors comprise about 5% of clinically identified pituitary adenomas (1-2). The annual incidence of new diagnoses of about 2-3 per million. About 90% of ACTH secreting pituitary adenomas are < 10 mm in maximum diameter and 10% are > 10 mm; malignant ACTH-secreting tumors are very rare (1-7).
The great majority of patients are symptomatic from either the effects of the hypercortisolism (see above) and these symptomatic patients are the target population for treatment with ketoconazole if they are not controlled by surgery (4-7,15,17-21). As noted above, about 90% of patients have microadenomas and 10-20% of those are not controlled by surgery and the 10% with macroadenomas have even lower control rates, with 50 – 75% not being controlled by surgery. Almost all patients with Cushing syndrome due to benign adrenal adenomas or bilateral nodular hyperplasia are cured by adrenalectomy (6). Those not controlled by surgery are treated medically, with ketoconazole being an appropriate choice of medical therapy with hormonal control being achieved in 40-50% of patients.

A very important point is that the numbers given above for control of pituitary tumor ACTH-secretion by neurosurgery are those of expert pituitary neurosurgeons. In fact, in many low-income countries the availability of such surgeons is quite limited, with one 2018 survey showing that 16% of such countries have no practicing neurosurgeon at all (22). In such circumstances, medical treatment with ketoconazole may be the only effective treatment and would be considered primary treatment rather than secondary treatment.

8. Treatment details (requirements for diagnosis, treatment and monitoring)

Diagnosis

Cushing syndrome is diagnosed biochemically, with the finding of elevated 8AM serum cortisol levels (included in the 3rd EDL) which cannot be suppressed by the administration of dexamethasone (included in section 2.3 of the EML), by the finding elevated late night salivary cortisol levels, or by elevated 24 hour urinary free cortisol levels. (3-7). The distinction between pituitary and adrenal causes is determined by finding elevated ACTH levels in the case of pituitary/ectopic ACTH causes or suppressed ACTH levels in the case of autonomous adrenal lesions. Ectopic ACTH secretion is distinguished from

pituitary ACTH secretion by measuring ACTH levels in the venous effluent from the pituitary into the petrosal sinus using inserted catheters, with elevated levels in the petrosal sinus being found with pituitary adenomas but not ectopic sources. Magnetic resonance imaging (MRI) and computed tomography (CT) are used to determine tumor size, invasiveness of adjacent structures, and suitability for surgical removal (3-7).

Dosage Regimen

Standard ketoconazole dosing is 200 – 1200 mg per day, with most requiring 600 – 800 mg per day in divided doses (4-7, 17-21).

Treatment Duration

Patients can be continued on ketoconazole indefinitely.

Current Guidelines

We are unaware of any WHO guidelines for the treatment of Cushing syndrome.

Guidelines from international organizations have been published by the Endocrine Society (3,4), by the American Academy of Clinical Endocrinologists (AACE) (5) and the Pituitary Society (7). Professor M Molitch, lead author of this submission, is a co-author on the Guidelines of the last one. The discussions above about choice of initial therapy (medical vs. surgical and the various medical treatments) are discussed in all three guidelines and their recommendations coincide with what is recommended here.

Requirements and Monitoring

Doses are adjusted based upon periodic monitoring of urinary free cortisol (UFC) levels, initially every 2-4 weeks and then every 3-6 months (17-20). Escape from the suppressive effect of ketoconazole is uncommon. Because of the multiple organ systems involved in patients with Cushing syndrome, the medical management of most patients is done by endocrinologists. Patients should be referred for surgery only after consultation with an experienced endocrinologist. If pituitary surgery is performed, it should be carried out only by a neurosurgeon with expertise in pituitary surgery and who carries out a high volume of such surgeries to insure effectiveness and low adverse effects. Postoperative follow-up is carried out by experienced endocrinologists.

Core vs. Complementary List

We request inclusion of ketoconazole in the complementary list of essential medicines, as it is the most efficacious in controlling the hypercortisolism of Cushing syndrome and improving the long-term morbidity and mortality of Cushing syndrome. It will be used primarily by specialists in tertiary care centers.

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

Early studies using ketoconazole to treat Cushing syndrome suggested a normalization rate of UFC of over 90% (23,24). A more recent series reported data on 200 patients with Cushing disease (78% females, 106 microadenomas, 36 macroadenomas, 58 with no tumor visible) treated with ketoconazole in doses ranging from 200 – 1200 mg/d, most receiving 600 and 800 mg/d (25). Of 39 patients treated prior to surgery for 4 months, 19 pts (48.7%) achieved a normal UFC. In 158 patients treated postoperatively or primarily (surgery contraindicated), 78 (49.3%) achieved normal UFC, 37 (23.4%) had a >50% decrease in UFC and 43 (27.2%) had an unchanged UFC. The drug was stopped in 26.8% due to lack of efficacy and in 25.6% due to adverse effects (25).

Individual prospective, randomized studies showed normalization of cortisol levels in 28% of patients treated with cabergoline (26), 43% of patients treated with metyrapone (27), 20% of those treated with pasireotide LAR (28), 66% of those treated with osilodrostat (29), and 31% of those treated with levoketoconazole (30). 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. In the SEISMIC study, 88% of subjects treated with mifepristone were judged to have progressive clinical improvement (21,31). A meta-analysis done in 2018 that did not include osilodrostat or mifepristone came up with the following proportions of Cushing syndrome patients brought under control with various agents (Cushing's disease alone, all-cause Cushing syndrome including adrenocortical carcinoma): Mitotane (n=173) 81.8%, 79.8%; Pasireotide (n-132) 41.1%, 41.1%; Cabergoline (n=70) 35.7%, 35.7%; Ketoconazole (n=220) 49.0%, 71.1%, Metyrapone (N=10) 60.0%, 75.9% (32). The authors concluded that: "This meta-analysis shows that medication induces cortisol normalization effectively in a large percentage of patients. Medical treatment for Cushing's disease patients is thus a reasonable option in case of a contraindication for surgery, a recurrence, or in patients choosing not to have surgery" (32).

Another imidazole derivative is fluconazole, which is used primarily as an antifungal agent but has been reported in a several case reports to be effective in Cushing's syndrome (33-36). However, there are no large series reporting the efficacy and safety of fluconazole so it cannot be adequately compared to these other more well-established medications.

10. Review of harms and toxicity: summary of evidence of safety

The major adverse effect of ketoconazole is liver toxicity. In the large report of 200 patients treated with ketoconazole for Cushing syndrome (25), liver enzyme elevations were found as follows: <5x increase in 30 (15.8%), a 5-10x increase in 4 and a 40x increase in 1. These increases occurred within 4 weeks of starting or with dose increments and all increases returned to normal with drug withdrawal. Other side effects of ketoconazole include rash, gastrointestinal symptoms and hypogonadism in men. Ketoconazole is a strong CYP3A4 inhibitor (substrates include amiodarone, carbamazepine, amitriptyline, SSRIs, benzodiazepines, calcium channel blockers, statins, colchicine) and therefore may affect dosing of these and other drugs.

In 2013, the U.S. Food and Drug Administration (FDA) specified a "black box warning" regarding liver toxicity with ketoconazole use; ketoconazole had never had U.S. FDA approval for use in Cushing's syndrome (37). The European Medicines Agency (EMA) recommended against prescribing ketoconazole in 2013 as well, because of liver toxicity (38). Nonetheless, both drugs remain on the approved drugs lists of the FDA and EMA, although ketoconazole is approved only for the treatment of fungal conditions by the FDA (see below). Given its clinical benefits, the ability to monitor for liver toxicity by early and

frequent monitoring of liver enzymes, and its relatively low cost compared to other medications, it remains in clinical use in the U.S. and Europe and most other countries around the world.

11. Summary of available data on comparative cost and cost-effectiveness of the medicines.

Burton et al compared costs for 877 patients with Cushing Disease (CD) (pituitary tumor) compared to 2631 matched controls using an insurance administrative claims database covering 12.9 million persons from 7/1/06 – 6/30/12 in the US, finding that the mean number of health care visits (ambulatory, emergency department, inpatient) was two to four times higher for CD patients than CD-free controls (39). Total mean all-cause health care costs were also higher for CD patients than CD-free controls, driven primarily by medical costs, which accounted for 87 and 79 % of total costs for CD patients and CD-free controls, respectively. On average, medical costs were nearly seven times higher for CD patients than CD-free controls (33). Truong et al compared annual costs (in 2013 US$) of various medications used to treat CD, finding the following: Pasireotide $144,280, Mifepristone $207,562, Ketoconazole $25,475, Cabergoline $32,179, and Mitotane $40,893 (40).

In the US, the cost for ketoconazole is $1.43 per 200 mg tablet (January, 2022). For a 30 day course of 800 mg/day, therefore, the cost would be $172. Costs for a 30 day course at the same time period in representative LMIC are (in US$) $36 in Argentina, $6 in Bolivia, $36 in Brazil, and $6-22 in India, and $25 in Mexico. Costs for the other drugs in $US for a 30 day course are shown in Table 2. Therefore, based on the efficacy shown in Table 1 and these costs shown in Table 2, ketoconazole is the most cost-effective treatment.

Table 2. 30 Day Costs ($US) for Medications Used to Treat Cushing Syndrome

Medication	Cost per Dose*	Average Effective Dose	Cost for 30 days	Ref
Ketoconazole	$1.43/200 mg	800 mg/day	$172	25
Cabergoline	$46/0.5 mg	3.6 mg/week	$1,325	26
Metyrapone	$32/250 mg	1375 mg/day	$5,280	27
Pasireotide	$15,255/30 mg	30 mg/30 day	$15,255	28
Osilodrostat	$553/10 mg	10 mg/day	$16,590	29
Mifepristone	$603/300 mg	734 mg/day	$44,260	21
Levoketoconazole	$313/150 mg	563 mg/day	$35,244	30

*Retail costs in $US as of 1/28/22

12. Summary of regulatory status and market availability of the medicines

U.S. Food and Drug Administration (FDA):

Ketoconazole is on the Approved Drug Product List for the treatment of fungal conditions. A Black Box warning for Liver Toxicity is appended (Accessed January 17, 2022)

European Medicines Agency (EMA):

Ketoconazole is on the List of Nationally Approved Medicinal Products for the treatment of Cushing syndrome (Accessed January 17, 2022)

Australian Government, Department of Health, Therapeutic Good Administration:

Ketoconazole is on the Australian Register of Therapeutic Goods (ARTG) List for the treatment of Cushing syndrome (Accessed January 17, 2022)

Health Canada:

Ketoconazole is on their Drug Product List of approved medications for the treatment of fungal Conditions (Accessed January 17, 2022)

Japanese Pharmaceuticals and Medical Devices Agency:

Ketoconazole is included in the Japanese approved medicines list.

Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

	International Pharmacopoeia	United States Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia
Ketoconazole	Yes	Yes	Yes	Yes

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