1. **Title page**

Application for inclusion of Bromocriptine and Cabergoline In the WHO Model Lists of Essential Medicines (2023) for Adults and Children

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

This proposal requests inclusion of bromocriptine and cabergoline for the management of patients with hyperprolactinemia (ICD-10 code E22.1), with its clinical consequences of hypogonadism and infertility, and the management of prolactin-secreting pituitary adenomas (prolactinomas) (ICD-10 code D35.2) with respect to control of prolactin hypersecretion and tumor size. The listing is being sought for the core list for EML.

Bromocriptine has been evaluated by the Expert Committee on the Selection and Use of Essential Medicines in 2015. The application focused on the potential role and use of bromocriptine in Parkinson disease. The Expert Committee concluded that the most effective treatment for Parkinson disease is levodopa, deciding that there was insufficient evidence to show that dopamine agonists offered any clinically relevant efficacy or safety advantages over the existing medicines included in the EML (see TRS 994, P 285: The selection and use of essential medicines: report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children).

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.

Hyperprolactinemia

Hyperprolactinemia is due to the excessive secretion of the hormone, prolactin, from the pituitary (1-5). Physiologic hyperprolactinemia can occur during pregnancy and acutely with stress. The most common pathologic cause of hyperprolactinemia is a prolactin-secreting pituitary adenoma (prolactinoma). Other causes of hyperprolactinemia arise due to altered hypothalamic regulation of prolactin secretion. Prolactin secretion is tonically inhibited by hypothalamic dopamine which reaches the pituitary via the pituitary stalk (infundibulum). Medications that block dopamine receptors on the pituitary or decrease hypothalamic dopamine secretion, such as antipsychotics and anti-emetics, commonly cause hyperprolactinemia. Other non-pituitary conditions that can cause hyperprolactinemia include chronic kidney disease and hypothyroidism (3-5). Idiopathic hyperprolactinemia is the designation given to the small proportion of patients (<5%) in whom no identifiable cause can be found.

Prolactinomas comprise 40-50% of clinically identified pituitary adenomas (1-5). Over 90% of prolactinomas are < 10 mm in maximum diameter (microadenomas); malignant prolactinomas are very rare (1-5). Clinically nonfunctioning adenomas comprise about 35% of clinically identified pituitary adenomas (1) and they and other hypothalamic/pituitary lesions can cause hyperprolactinemia because they can alter hypothalamic-pituitary stalk function, thereby disrupting the transmission of hypothalamic dopamine to the pituitary.

Hyperprolactinemia causes hypogonadism and infertility primarily by inhibiting the pulsatile secretion of gonadotropin-releasing hormone and, therefore, gonadotropins (3-5). It also causes an inappropriate secretion of breast milk, referred to as galactorrhea, primarily in women. Because of the hypogonadism,

untreated hyperprolactinemia can cause osteoporosis. The approximately 10% of prolactinomas that are greater than 10 mm in diameter (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.

The preferred short- and long-term management of hyperprolactinemia and prolactinomas is the use of the oral dopamine agonists, bromocriptine and cabergoline, because of their high efficacy (3-5). Correction of secondary causes, of course, is also done. In patients with prolactinomas, normalization of prolactin levels can be achieved in 60 – 90% of patients treated with bromocriptine and cabergoline. Control of tumor size can be achieved in over 60% of those treated with bromocriptine and over 80% of those treated with cabergoline (3-5). Of patients who do not normalize prolactin levels with bromocriptine, about 50% can achieve prolactin level normalization if switched to cabergoline (3-5). Adverse effects of bromocriptine include nausea and vomiting, which can be controlled by slow titration and taking medication with food, and impulse control disorders. The same adverse effects can occur with cabergoline but in lower frequencies. Overall, cabergoline is better tolerated and some studies show that it is more efficacious than bromocriptine.

Transsphenoidal surgery is another treatment option. In experienced, expert neurosurgical hands, about 70-80% of patients with microadenomas and 25-30% with macroadenomas can have their prolactin levels normalized by transsphenoidal surgery (5). However, there is about a 20% recurrence rate of hyperprolactinemia, bringing the ultimate cure rate as low as 50-60% for microadenomas and 10-20% for macroadenomas (5). Some patients may choose surgery rather than medical therapy as an initial treatment, based on personal choice. Radiotherapy is reserved for the very small number of patients whose prolactin levels and tumors are not controlled by medical therapy and surgery (3-5).

A special consideration is those women who wish to become pregnant. Normalization of prolactin levels is necessary to permit ovulation and fertility. When bromocriptine and cabergoline are stopped once menses have been missed and a pregnancy test is positive, no adverse outcomes have been reported for mother or baby with either drug (6), although one report from France found that dopamine agonist exposure was associated with an increased risk of preterm birth and early pregnancy loss and an insignificant increase in fetal malformations (7). The risk of prolactinoma growth during pregnancy once the dopamine agonist has been stopped is 2.5% for those with microadenomas and 18% for those with macroadenomas (6).

Children with prolactinomas tend to have a disproportionately larger number of macroadenomas, for unclear reasons (8,9). However, they respond to dopamine agonists in a similar fashion to adults without any undue adverse effects and dopamine agonists are the preferred therapy for this age group as well (8,9).

3. Consultation with WHO

WHO Sexual and Reproductive Health and Research (SRH) was consulted and supports this application. The focal point was Dr Gitau Mburu.

4. Other 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. Besançon from Mali). This application is led by Global Pediatric Endocrinology and Diabetes (GPED) and the International Society of Endocrinology (ISE).

This application is supported by several key organizations and stakeholders (see letters of support).
International Society of Endocrinology (ISE)
Endocrine Society
Pituitary Society
International Consortium of Pediatric Endocrinology (ICPE)

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 hyperprolactinemia.

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 prolactinomas.

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 medicines

International Nonproprietary Name (INN).

INN: Bromocriptine
INN: Cabergoline

Anatomical Therapeutic Chemical (ATC) code of the medicine

Bromocriptine ATC: G02CB01
Cabergoline ATC: G02CB03

Dosage form(s) and strengths of the proposed medicine(s)

Bromocriptine is available as 2.5 mg tablets and 5 and 10 mg capsules. The availability of 10 mg capsules varies from country to country. It is not available as a liquid preparation
Cabergoline is available as 0.5, 1 and 2 mg tablets. The availability of 1 and 2 mg tablets varies from country to country. It is not available as a liquid preparation.

Suggested wording

Bromocriptin and cabergolin are indicated for the management of prolactinoma. The medical management is performed by endocrinologists, gynecologists and primary care providers and as such is appropriate for the core list of the EML. Our group is submitting 2 additional applications relevant to tumors of the endocrine system (octreotide/lanreotide and ketoconazole). These medicines could conceivably be included in Section 18 (18. MEDICINES FOR ENDOCRINE DISORDERS) or 8 (8. IMMUNOMODULATORS AND ANTINEOPLASTICS

Bromocriptin	Tablets: 2.5 mg tablets; capsules: 5 mg Prolactinoma
Cabergoline	Tablets: 0.5 and 1 mg tablets Prolactinoma

6. Proposal for an individual medicine or as representative of a pharmacological class/therapeutic group.

This application concerns bromocriptine and cabergoline as individual medicines. The other medicine of this pharmacological class that is used in this indication is quinagolide, which has efficacy and adverse effects similar to those of bromocriptine.

7. Information supporting the public health relevance.

Pituitary adenomas are common. Ten per cent of unselected pituitaries examined at autopsy contain pituitary adenomas and MRI scans of normal volunteers show a similar proportion (1). Of the tumors found at autopsy, immunohistochemical staining shows that about 40% are prolactinomas. Clearly, not all such tumors become clinically manifest. Clinical case-finding studies have shown an overall prevalence of pituitary adenoma of 1/1420 persons with 49% of these being prolactinomas (1). The great majority of patients are symptomatic from either the effects of the hyperprolactinemia or tumor size (see above) and these symptomatic patients are the target population for treatment with dopamine agonists (3-5). The proportions of patients treated with bromocriptine vs. cabergoline is highly variable from country-to-country, largely due to availability and cost. As noted above, normalization of prolactin levels can be achieved in 60 – 90% of patients treated with bromocriptine and cabergoline. Control of tumor size can be achieved in over 60% of those treated with bromocriptine and over 80% of those treated with cabergoline (3-5). Of patients who do not normalize prolactin levels with bromocriptine, about 50% can achieve prolactin level normalization if switched to cabergoline (3-5). About 25% of patients treated with bromocriptine and 40% of those treated with cabergoline may be successfully withdrawn from the medication after 2 years and the remainder must stay on (10). Women entering menopause are often able to stop their dopamine agonist because the effects of hyperprolactinemia on estrogen production become nil; some of these women may need to continue their dopamine agonist to control tumor size.

The alternative to medical therapy is transsphenoidal surgery. A cost-benefit analysis, taking into consideration the surgical cure/relapse rates and the ability of about one-third of patients to eventually come off dopamine agonists, showed that medical therapy with dopamine agonists is far less costly that transsphenoidal surgery (11). Furthermore, a very important point is that the numbers given above for control of prolactinoma prolactin-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 (12). In such circumstances, medical treatment with dopamine agonists may be the only effective treatment.

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

<u>Diagnosis</u>

A number of conditions and medications can cause hyperprolactinemia and most of these can be ruled out on the basis of a careful history and physical examination and routine chemistry and thyroid blood tests (3-5). Pregnancy must always be excluded. When there is no obvious cause of the hyperprolactinemia from the routine screening, a radiologic evaluation of the hypothalamic-pituitary area is mandatory to exclude a mass lesion (3-5). Magnetic resonance imaging (MRI) provides considerably more anatomic detail than computed tomography (CT). It is very important to distinguish between a large nonsecreting tumor causing modest prolactin elevations (usually < 250 ng/ml) from a

prolactin secreting macroadenoma (prolactin levels usually >250 ng/ml), as the therapy is quite different (3,4).

Dosage Regimen

Bromocriptine. A low dose of 1.25 – 2.5 mg daily with a snack at bedtime is usually the initial dose in order to minimize side effects. The dose is gradually increased over several weeks to 2.5 mg two times daily and prolactin levels checked 1 month later; if prolactin levels are not normal then the dose is gradually increased further. Most patients respond within 1 - 2 months, if they are going to respond (3-5). Doses higher than 7.5 mg per day of bromocriptine are usually not necessary, except in some patients with very large tumors. Patients who do not respond to bromocriptine are usually switched to cabergoline, which is effective in about half of such patients.

Cabergoline. A dose of 0.25 mg (1/2 tablet) once or twice weekly is usually the initial dose in order to minimize side effects. The dose is gradually increased over several weeks to 0.5 mg twice weekly and prolactin levels checked 1 month later; if prolactin levels are not normal then the dose is gradually increased further. Most patients respond within 1-2 months, if they are going to respond (3-5). 15-20% of patients who have large tumors have partial responses at a dose of 2.0 mg per week but then may require larger doses to normalize prolactin levels. Complete failure to respond to cabergoline is very uncommon, occurring in < 5% of cases. Those not responding to cabergoline may be candidates for surgery.

Treatment Duration

Patients can be continued on bromocriptine or cabergoline indefinitely. However, after 1-2 years of treatment, clinicians may try to taper the dose of the drug and if prolactin levels are maintained in the normal range at 2.5 mg daily of bromocriptine or 0.5 mg weekly of cabergoline, drug withdrawal may be tried. A meta-analysis showed that after two years of treatment, about one-quarter of patients treated with bromocriptine and about 40% of those treated with cabergoline can be successfully withdrawn (10). Longer duration of treatment and substantial tumor size reduction are factors that increase the success rates of withdrawal (10).

Current Guidelines

WHO guidelines for the management of hyperprolactinemia are not currently available.

Two guidelines from international organizations have been published, one by the Pituitary Society (3) and the other by the Endocrine Society (4). The discussions above about choice of initial therapy (medical vs. surgical and bromocriptine vs. cabergoline) are discussed in both guidelines and their recommendations coincide with what is recommended here. In general, cabergoline is recommended over bromocriptine because of efficacy and fewer adverse effects but bromocriptine may be recommended if cost is an issue, as it has lower cost than cabergoline.

Requirements and Monitoring

Doses are adjusted based upon periodic monitoring of prolactin levels (EDL 3 ncludes prolactin determination), initially every 1-2 months and then every 3-6 months for the first 1-2 years. Once prolactin levels have normalized, they need to be checked only every 6 – 12 months. Escape from the suppressive effect of dopamine agonists is very rare (3-5). If patients have microadenomas and they respond appropriately to dopamine agonists, care can be provided by primary healthcare providers, including gynecologists. For those with macroadenomas and those not responding well to medication,

referral to an endocrinologist is appropriate. Patients with "giant" (> 4cm in diameter) adenomas and/or macroadenomas invading the cavernous sinus or causing visual field defects should be referred to an endocrinologist experienced in the care of such patients. Patients should be referred for neurosurgery only after consultation with an experienced endocrinologist. If surgery eventually 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.

Core vs. Complementary List

We request inclusion of bromocriptine and cabergoline in the core list of essential medicines, as many who prescribe these medications can be primary care providers, including gynecologists. In general, cabergoline is recommended over bromocriptine because of efficacy and fewer adverse effects but bromocriptine is also recommended as a core medication because cabergoline is not available in some countries.

9. Review of benefits: summary of evidence of comparative effectiveness

Medical therapy with bromocriptine and transsphenoidal surgical removal of prolactinomas have been done routinely for over 40 years and therapy with cabergoline for over 30 years. Many reviews have been done over this period. In summaries of the literature, Gillam et al found that in 19 series of patients treated with bromocriptine (13) and 16 series of patients treated with cabergoline (5), the latter was found to be moderately more efficacious and had fewer adverse effects than the former. More recent meta-analyses by Santos Nunes et al (14) and Wang et al (15) found similar results. In 50 surgical series comprising 2137 patients with microadenomas and 2226 with macroadenomas, Gillam et al noted that normalization of prolactin levels was achieved in 74.7% of those with microadenomas and 33.9% of those with macroadenomas (5). In 2021, Lu et al performed a meta-analysis comparing surgery to medical therapy for patients with microprolactinomas, with their final sample of 16 case series and 2 retrospective cohort studies totaling 661 patients (16). They found that at 12 months, the medical treatment group achieved higher remission rates of hyperprolactinemia (96% vs. 86%) but they did not compare bromocriptine to cabergoline (16).

Overall, case series, general reviews and systematic reviews show that dopamine agonist therapy achieves a higher rate of prolactin normalization and is more cost effective than surgery; in fact, the larger the prolactinoma the greater the difference. Analyses also show that cabergoline is moderately more effective and has fewer adverse effects than bromocriptine but both are quite efficacious and well-tolerated.

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

Overall, the prevalence of prolactin-secreting tumors ranges from 25 per 100,000 to 63 per 100,000. The prevalences of symptomatic microprolactinomas and macroprolactinomas are approximately 40 and 10 per 100,000, respectively (17). The annual incidence rate of prolactinomas ranges from 2 to 5 new cases/100,000, and the value is 3-times higher in women than in men (17). There are no precise estimates of the relative proportions of patients treated medically vs. surgically and this may vary considerably between countries. It is likely that over 90% are treated medically in most countries. Because of its somewhat better efficacy/adverse effects ratio, cabergoline is also generally preferred but cost and availability considerations will impact the use of these medications in many countries.

Adverse effects of dopamine agonists include nausea, vomiting, headache, nasal stuffiness, orthostatic dizziness, and Reynaud's phenomenon, with cabergoline having less of such symptoms compared to bromocriptine (14,15).

Two additional adverse effects of these drugs became apparent after many years of use and deserve additional comment. Impulse control disorders (ICD) had long been found to be common in patients treated with these drugs when used in high doses for the treatment of Parkinson's disease. The mechanism of action behind ICDs seems to be an interaction between the dopamine agonists and the D3 receptors in the mesolimbic system, known to be responsible for the processes governing behavior, pleasure, and addiction (18). Clinical experience and then detailed studies showed that ICDs also occur in patients with prolactinomas and are, in part, dose-related (18). A cross-sectional multicenter study in Turkey of 308 patients with prolactinomas (289 treated with cabergoline, 19 treated with bromocriptine) found that 17% developed an ICD (hypersexuality alone in 6.5%, pathologic gambling alone in 0.6%, compulsive eating alone in 2.9%, compulsive shopping alone in 1%, and more than one ICD in 5.5%); hypersexuality was more common in men and compulsive eating more common in women (19).

The second adverse effect is the development of cardiac valve abnormalities, usually valvular insufficiency, with cabergoline. Such valve abnormalities had been found when cabergoline was used in high doses (3-5 mg per day) to treat patients with Parkinson's disease (20). As mentioned above, 15-20% of patients treated with cabergoline require doses higher than 2 mg/week and rare patients require doses approaching 1 – 2 mg per day. A meta-analysis by Stiles et al (21) reviewed 13 studies comprising totals of 836 patients with prolactinomas who were treated with cabergoline and 1388 controls. There were significantly more cases of mild tricuspid regurgitation in patients treated for $\geq$ 1 year (20% vs. 11%; OR 1.91; 95% CI 1.28-2.87; p=0.002) (21). Mild tricuspid regurgitation is not considered clinically relevant (21). Clinically significant tricuspid regurgitation (reported as moderate or severe) was increased in those using cabergoline ((5.0% vs. 1%; OR 3.74; 95% CI 1.79-7.8, p<0.001) (21) but the frequencies were very low and strongly influenced by a single study (54% vs. 18%) (22) with the other studies having such data showing no such increase (21). A subsequent report from the group reporting this increased risk of clinically significant tricuspid regurgitation did not show such an increase (23). The mechanism for the valve abnormalities is thought to be action of the cabergoline at serotonin (5-HT) 2B receptors, which are present in human cardiac valves and are necessary for normal cardiac development. Excess stimulation of these receptors results in activation of mitogenic pathways with the development of a plaque-like process that extends along leaflet surfaces and encases the chordae tendinae (24). Bromocriptine does not cause this problem. Because the valve abnormalities are seen relatively commonly in Parkinson's disease patients treated with 3-5 mg per *day* and not in cabergoline treated patients in whom the dose is usually $\leq$ 2mg per *week*, it is uncertain at what dose level these valve effects become significant if doses of cabergoline greater than 2 mg per week are needed for control of prolactin levels and tumor growth. Therefore, it has been recommended that all patient receiving >2 mg/week be assessed with an echocardiogram on a yearly basis. Because trivial valve changes are found commonly in the normal population [21], it is reasonable to perform the first echocardiogram at the time of initiation of a dose >2 mg/week, so that future echocardiograms can then be used to evaluate for changes. Should clinically significant valve changes then be noted, consideration would then be given to switching to bromocriptine or surgery. Reversal of abnormalities can occur in over 50% of patients who develop abnormities if the cabergoline is discontinued (25).

In summary, cabergoline appears to be somewhat more efficacious with fewer of the common adverse effects than bromocriptine and only needs to be taken 1-2 times a week. Impulse control disorders may

be seen with both drugs and are, in part, dose-related. Tricuspid valve regurgitation is limited to cabergoline, but in only the small proportion of patients who require substantially greater than usual doses. Echocardiographic monitoring can discern early valvular changes in such patients, allowing switching to alternative modes of therapy and reversal of early lesions.

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

In the U.S. and most countries around the world, both bromocriptine and cabergoline are generic. In the U.S., the retail cost for bromocriptine is $6 per 2.5 mg tablet and for a typical dose of 5 mg per day for 30 days this comes to 60 tablets = $360 (Source: Epocrates 11/6/21). The retail cost in the U.S. for cabergoline is $49 per 0.5 mg tablet and for a typical dose of 1 mg per week for 30 days this comes to 8 tablets = $392 (Source: Epocrates 11/6/21). Some representative costs from LMIC are as follows for bromocriptine 5 mg/day and cabergoline 1 mg/week for one month:

- Brazil $46 and $18;
- India $12 and $6;
- Bolivia $17 for cabergoline and bromocriptine is not available;
- Argentina: $ 24 for cabergoline and bromocriptine is not available
- Mexico: $ 20.1 and $ 39.6

No cost-effectiveness studies have been carried out comparing these two drugs. However, one cost-effectiveness study has been carried out comparing medical therapy to transsphenoidal surgery, showing that surgery has better cost-effectiveness at 10 years assuming a “cure” rate of 90% and a complication rate of < 1% (24). Surgery provided an incremental cost-effectiveness ratio of $80,235 per quality-adjusted life years at 5 years and $40,737 per quality-adjusted life years at 10 years (24). However, this study did not account for the fact that a 90% “cure” rate is achievable only for microprolactinomas in highly expert neurosurgical hands and does not account for the 10-20% recurrence rate of hyperprolactinemia, when dopamine agonists would be used again. As noted above, another such analysis that took into account these recurrence rates and ability of about one-third of patients to discontinue dopamine agonists showed that medical therapy was less costly than surgery (11).

The above medication costs need to be balanced against the much greater costs of various interventions to improve fertility in hyperprolactinemic patients. In hypogonadal patients who do not have macroadenomas and who are not interested in fertility, replacement with estrogen/progestin (oral contraceptives) in women and testosterone in men is certainly more cost-effective and has been recommended (3,4). For macroadenomas, dopamine agonists are far more effective in controlling tumor size than surgery. However, cost-effectiveness studies have not been performed for prolactin-secreting macroadenomas.

12. Summary of regulatory status, market availability and pharmacopoieal standards

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

Bromocriptine 2.5 mg tablets and 5 mg capsules and Cabergoline 0.5 mg tablets are on the Approved Drug Product List – Orange Book,
Accessed November 6, 2021

European Medicines Agency (EMA):

Bromocriptine 2.5 mg, 5 mg, and 10 mg and Cabergoline 0.5 mg, 1 mg and 2 mg are on the List of Nationally Approved Medicinal Products.

Accessed November 6, 2021

Australian Government, Department of Health, Therapeutic Good Administration:

Bromocriptine 2.5 mg tablets and 10 mg capsules and Cabergoline 0.5 mg, 1 mg and 2 mg tablets are on the Australian Register of Therapeutic Goods (ARTG) List.

Accessed November 6, 2021

Health Canada:

Bromocriptine 2.5 mg tablets and Cabergoline 0.5 mg tablets are on their Drug Product List of approved medications.

Accessed November 6, 2021

Japanese Pharmaceuticals and Medical Devices Agency:

Bromocriptine and Cabergoline are include in the approved medicines list published by the Pharmaceuticals and Medical Devices Agency

Update and safety review statements accesses December 2021 and November 2022

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

	International Pharmacopoeia	United States Pharmacopoeia	European Pharmacopoeia	British Pharmacopoeia	Japanese Pharmacopoeia
Bromocriptine tablets	No	Yes	No	Yes	Yes
Cabergoline	No	Yes	No	Yes	Yes

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