Cabergoline

Essential medicine status

Section: 18. Medicines for endocrine disorders > 18.8. Medicines for disorders of the pituitary hormone system

ATC codes: G02CB03

Indication	Other specified benign neoplasm of endocrine glands ICD11 code: 2F37.Y
INN	Cabergoline
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid > tablet: 0.5 mg ; 1 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	bromocriptine (ATC codes: G02CB01)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Cabergoline
DrugBank	Cabergoline

Expert Committee recommendation

The Expert Committee noted that prolactinomas were relatively rare, but were associated with important clinical sequelae from both hyperprolactinaemia (e.g. infertility) and physical mass effects of the tumour itself (e.g. headache, hypopituitarism and visual field defects). The Committee also noted that prolactinomas may be treated medically or surgically but recognized that the availability of specialized neurosurgeons was limited or even non-existent in some low- and middle-income settings. The Committee noted that dopamine agonist therapy was a preferred first-line intervention for medical management of hyperprolactinaemia and prolactinomas and may be the only option in settings where specialist neurosurgery is not available, or in patients for whom surgery is not feasible. The limitations of the application notwithstanding, the Committee considered that overall, the available evidence suggested that medical therapy with dopamine agonists could achieve prolactin normalization in most patients, while treatment was continued. Analyses suggest that cabergoline may be moderately more effective and have fewer adverse effects than bromocriptine but overall both have a favourable risk–benefit balance. The Expert Committee therefore recommended the inclusion of cabergoline on the core list of the EML for the medical management of hyperprolactinaemia associated with prolactinomas as the representative dopamine agonist for this indication based on a more favourable risk–benefit balance, albeit at a potentially higher cost. Listing was recommended with bromocriptine as therapeutic alternative under a square box listing.

Background

Bromocriptine, cabergoline and other oral dopamine agonists were evaluated in 2015 for inclusion on the EML for use in the treatment of Parkinson disease. At that time, the Expert Committee did not recommend inclusion due to insufficient evidence for clinically relevant efficacy or safety advantages of oral dopamine agonists over the existing medicines already included in the EML for treatment of Parkinson disease (5). Oral dopamine agonists have not previously been evaluated for addition to the EML for treatment of hyperprolactinaemia/prolactinoma. Currently, the Model Lists do not include any medicines for use in this indication.

Public health relevance

Prolactinomas (also called lactotroph adenomas) are pituitary adenomas that secrete prolactin and are the most common cause of pathological hyperprolactinaemia. Hyperprolactinaemia can cause amenorrhoea in women, erectile dysfunction in men and loss of libido, galactorrhoea and infertility in both sexes. Hyperprolactinaemia occurs in 5% to 17% of women with secondary amenorrhoea, which is an important cause of infertility (6–8). The prevalence of prolactinomas ranges from 25 to 63 per 100 000. The prevalence of symptomatic microprolactinomas and macroprolactinomas is about 40 per 100 000 and 10 per 100 000, respectively. The annual incidence of prolactinomas ranges from 2 to 5 new cases per 100 000, and the value is three times higher in women than in men (9). About 10% of unselected pituitaries examined at autopsy contain pituitary adenomas and magnetic resonance imaging scans of normal volunteers show a similar proportion of the tumours. Immunohistochemical staining shows that about 50% are prolactinomas (10). Patients may be symptomatic either from the effects of the hyperprolactinaemia or from the mass effect of the tumour (headache, hypopituitarism, visual field defects) and these symptomatic patients require treatment. An alternative to pharmacological treatment with dopamine agonists is trans-sphenoidal surgery performed by pituitary neurosurgeons. A survey in low- and middle-income countries published in 2018 showed that individuals living in 11 countries (of 68 countries with complete responses) did not have access to any neurosurgical care (11). Radiation therapy is usually reserved for patients not responding to pharmacological and/or surgical treatment or with invasive tumours and is also unavailable in many settings.

Benefits

Medical therapy with bromocriptine and trans-sphenoidal surgical removal of prolactinomas have been in clinical use since the 1970s, and with cabergoline since the 1980s. Dopamine agonists versus no treatment A 2012 systematic review and meta-analysis compared the efficacy and adverse effects of different treatment modalities (medications, surgery and radiotherapy) for hyperprolactinaemia (not specifically prolactinomas) (3). Three observational studies and one randomized controlled trial that compared dopamine agonists to no treatment were identified. Aggregated results showed that dopamine agonists significantly reduced prolactin levels (weighted mean difference (WMD), –45 ng/mL, 95% confidence interval (CI) –77 to –11 ng/mL) and the risk of persistent hyperprolactinaemia (risk ratio (RR) 0.90, 95% CI 0.81 to 0.99). No significant effect on clinical outcomes was demonstrated in this meta-analysis, however, the number of assessable patients was small for each outcome. Cabergoline versus bromocriptine A 2011 systematic review and meta-analysis of four randomized controlled trials (743 participants) compared cabergoline with bromocriptine for the treatment of patients with idiopathic hyperprolactinaemia and prolactinomas (2). Cabergoline was superior to bromocriptine for normalization of serum prolactin levels (RR 0.67, 95% CI 0.57 to 0.80), and normalization of menstruation with return of ovulatory cycles (RR 0.74, 95% CI 0.67 to 0.83). Dopamine agonists versus trans-sphenoidal surgery A 2021 systematic review and meta-analysis compared the outcomes of patients treated with dopamine agonists and patients treated with surgery as initial therapy for microprolactinomas (12). Overall, 16 case series and 2 retrospective cohort studies published between 1999 and 2018 (661 participants) were identified. At ≥ 12 months of follow-up, the medical treatment group achieved higher remission rates of hyperprolactinaemia (96% versus 86%, P = 0.02; absolute numbers not provided) but surgery showed a higher remission rate after treatment withdrawal of dopamine agonists (78% versus 44%, P = 0.003). No data comparing bromocriptine with cabergoline were provided. Given the non-randomized nature of these studies, the results need to be interpreted with caution. In a 2006 review of 50 surgical series (years not reported) including 2137 patients with microadenomas and 2226 with macroadenomas, normalization of prolactin levels was achieved in 74.7% (1596/2137) of those with microadenomas and 33.9% (755/2226) of those with macroadenomas by 1–12 weeks after surgery (13).

Harms

Commonly reported adverse effects of dopamine agonists include nausea, vomiting, headache, nasal stuffiness, orthostatic dizziness and Reynaud phenomenon. In studies comparing cabergoline and bromocriptine, adverse effects were reported less frequently and were less severe with cabergoline than bromocriptine (2,3). A 2011 systematic review and meta-analysis of four randomized controlled trials comparing cabergoline and bromocriptine in patients with idiopathic hyperprolactinaemia and prolactinomas found that the bromocriptine group experienced a significantly higher number of adverse effects compared with the cabergoline group (RR 1.43, 95% CI 1.03 to 1.98). Patients receiving cabergoline had significantly fewer occurrences of nausea (RR 1.66, 95% CI 1.33 to 2.06) and vomiting (RR 2.02, 95% CI 1.13 to 3.59). However, no notable differences were seen between the

treatment groups for constipation, headache, dizziness, vertigo, abdominal pain, dyspepsia, gastritis, fatigue, mastalgia, depression, hot flashes, somnolence or postural hypotension (2). Impulse control disorders have been found to be common in patients treated with dopamine agonists when used in high doses for the treatment of Parkinson disease. The mechanism of action behind impulse control disorders 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 behaviour, pleasure and addiction (14). Clinical experience and studies show that impulse control disorders also occur in patients with prolactinomas and are, in part, dose related. A cross-sectional multicentre study of 308 patients with prolactinomas (289 treated with cabergoline, 19 treated with bromocriptine) followed in 11 referral centres in Türkiye found that 16.6% (51 patients) developed an impulse control disorder (hypersexuality alone in 6.5% (20 patients), pathological gambling alone in 0.6% (2 patients), compulsive eating alone in 2.9% (9 patients), compulsive shopping alone in 1.0% (3 patients), and more than one impulse control disorder in 5.5% (17 patients); hypersexuality was more common in men and compulsive eating more common in women (15). Cardiac valve abnormalities, usually valvular insufficiency, have been reported with dopamine agonists used for treatment of Parkinson disease, and led to market removal of pergolide for the treatment of Parkinson disease in the United States in 2007 (16). Doses of dopamine agonists for the treatment of hyperprolactinaemia are lower than those used for the treatment of Parkinson disease (3–5 mg per day). Only 15–20% of patients treated with cabergoline for hyperprolactinaemia require doses higher than 2 mg/week and very few patients require doses approaching 1–2 mg/day. A 2018 meta-analysis of 13 case-–control studies (836 cases and 1388 controls) published between 2008 and 2013 assessed the association between the use of cabergoline for the treatment of hyperprolactinaemia and clinically significant cardiac valvulopathy (17). Significantly more cases of mild tricuspid regurgitation without clinical relevance were found in patients treated with cabergoline for more than 1 year (20% versus 11%; odds ratio (OR) 1.91, 95% CI 1.28 to 2.87). Clinically significant tricuspid regurgitation (reported as moderate or severe) was also more common in patients using cabergoline (5% versus 1%; OR 3.74, 95% CI 1.79 to 7.80) but the overall frequency was low (33 moderate and no severe instances among 693 cases with available data) and strongly influenced by a single study that contributed 27 instances of moderate tricuspid regurgitation alone (54% versus 18%) (18). A subsequent prospective study by the group reporting the 27 instances of moderate tricuspid regurgitation did not show an increased risk of significant cardiac valve regurgitation in 40 patients with newly diagnosed hyperprolactinaemia treated with cabergoline and followed up for 60 months (19). The mechanism for the valve abnormalities described with high-dose cabergoline is thought to be the action of the cabergoline at serotonin 5-HT2B receptors, which are present in human cardiac valves and are necessary for normal cardiac development. Excess stimulation of these receptors is thought to result in activation of mitogenic pathways with the development of a plaque-like process that extends along leaflet surfaces and encases the chordae tendinae (20). Bromocriptine does not seem to be associated with an increased risk of valvulopathy as evidenced in a nationwide Danish registry study including 3035 female bromocriptine users and 15 175 controls matched on age, sex and year of inclusion (21). Because the valve abnormalities are seen relatively commonly in people with Parkinson disease treated with 3–5 mg/day of cabergoline and not in cabergoline-treated patients in whom the dose is usually less than 2 mg/week, it is uncertain at what dose level these valve effects may occur if doses of cabergoline greater than 2 mg/week are needed to control prolactin levels and tumour growth. Therefore, it has been recommended that all patients receiving cabergoline doses greater than 2 mg/week have an annual echocardiogram. In 30–50% of patients who develop abnormities, reversal of abnormalities can occur if cabergoline is discontinued (22).

Additional evidence

The evidence provided by the applicants was incomplete and was supplemented by the reviewers and Secretariat.

Cost / cost effectiveness

Representative costs for 1 month of treatment with bromocriptine 5 mg/day and cabergoline 1 mg/week from different countries, as reported in the application, are shown in Table 25 (refer TRS 1049). A 2016 cost–effectiveness study compared medical therapy with either bromocriptine or cabergoline to trans-sphenoidal surgery (either microsurgical or endoscopic) (23). The analysis was conducted from the perspective of the United States third-party health care payer. In the base-case scenario, using a 5-year time horizon (medical therapy continued for 5 years or surgery followed for 5 years), the incremental cost–effectiveness ratios of microscopic trans-sphenoidal surgery and endoscopic trans-sphenoidal surgery were US$ 2797 per quality-adjusted life year (QALY) gained and US$ 3151 per QALY, respectively, compared with US$ 4380 per QALY for cabergoline and US$ 3901 per QALY for bromocriptine. Using a 10-year time horizon, the respective incremental cost–effectiveness ratios were US$ 1530 per QALY for microscopic surgery, US$ 1683 per QALY for endoscopic surgery, US$ 2876 per QALY for bromocriptine and US$ 3514 per

QALY for cabergoline. The authors concluded that surgery was more cost-effective than therapy with bromocriptine or cabergoline at 10 years, assuming a "cure" rate of 90% and a complication rate of < 1% with surgery. Under these assumptions surgery was dominant compared with treatment with dopamine agonists. However, the application highlighted that the study did not account for the fact that a 90% cure rate is achievable only for microprolactinomas in highly specialized surgical settings and that hyperprolactinaemia recurs after surgery in 10–20% of cases which then require treatment with dopamine agonists. A 2017 cost–effectiveness analysis compared surgery to treatment with dopamine agonists in the United States (24). The study used a third-party payer perspective and was based on data from 108 patients with prolactinomas seen by neurosurgeons at a single centre in the United States between 2010 and 2015. The base case assumed an 80% response to dopamine agonists and a 60% response to surgical treatment. For patients diagnosed with prolactinoma at 40 years of age, the analysis suggested that surgery had the lowest lifetime cost (US$ 40 473), followed by bromocriptine (US$ 41 601) and cabergoline (US$ 70 696). The analysis also suggested that surgery generated more QALYs. The authors concluded that surgery was a more cost-effective treatment than dopamine agonists for prolactinomas across a range of ages, medical/surgical costs and medical/surgical response rates if surgical cure rates are > 30%. A 2017 study used retrospective data from 126 patients with prolactinoma treated in a single centre in China between 2008 and 2009 to compare the cost–effectiveness of medical therapy with bromocriptine and trans-sphenoidal surgery. For microadenoma, the estimated costs of bromocriptine and surgical treatment were ¥20 555 and ¥22 527, respectively. For macroadenoma, the costs of bromocriptine therapy were ¥31 461 and ¥27 178 in males and females, respectively, while the costs of surgery were ¥42357 and ¥44 094 in males and females, respectively (25).

WHO guidelines

WHO is currently developing guidelines on the prevention, diagnosis and treatment of infertility. The guidelines will compare the effectiveness of cabergoline and bromocriptine for the management of infertility due to ovulatory dysfunction secondary to hyperprolactinaemia. The guidelines are expected to be published in late 2023 or early 2024.

Availability

Bromocriptine and cabergoline are available in most countries in branded and generic forms.

Other considerations

The Contraception and Fertility Care unit within the Department of Sexual and Reproductive Health and Research reviewed the application. The technical unit supported the inclusion of bromocriptine and cabergoline on the EML, highlighting that these medicines are important for the management of hyperprolactinaemia, a condition with consequences that affect a wide variety of people globally. Evidence suggests that compared to no treatment, oral bromocriptine is effective in normalizing prolactin levels in people with hyperprolactinaemia (1–3), may have some effect on return of ovulatory cycles (2,3) and may have a limited effect on live births in women with idiopathic hyperprolactinaemia (4). Evidence suggests that cabergoline is effective in normalizing prolactin levels (1,2). In addition, based on a de novo systematic search of data from randomized controlled trials published between 1990 and June 2019 by the sexual and reproductive Health department, there was low-quality evidence showing that cabergoline may increase pregnancy assessed at 6–7 weeks of gestation compared with bromocriptine. Data on live births are not available from these randomized controlled trials (unpublished data).

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