A.7	Bromocriptine and cabergoline – hyperprolactinaemia – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: The reviewer supports the request for inclusion in the core list for EML of bromocriptine and cabergoline for the management of patients with hyperprolactinemia, with its clinical consequences of hypogonadism and infertility, and the management of prolactin-secreting pituitary adenomas (prolactinomas) with respect to control of prolactin hypersecretion and tumour size.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Pituitary adenomas are common. Furthermore, clinical case-finding studies have shown an overall prevalence of pituitary adenoma of 1/1420 persons with 49% of these being prolactinomas. Normalization of prolactin levels can be achieved in 60 – 90% of patients treated with bromocriptine and cabergoline. Control of tumour size can be achieved in over 60% of those treated with bromocriptine and over 80% of those treated with cabergoline
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: 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. Normalization of prolactin levels can be achieved in 60 – 90% of patients treated with bromocriptine and cabergoline. Control of tumour size can be achieved in over 60% of those treated with bromocriptine and over 80% of those treated with cabergoline Analyses also show that cabergoline is moderately more effective and has fewer adverse effects than bromocriptine but both are quite efficacious and well-tolerated. In one recent meta-analysis (Lu et al, 2021) comparing surgery to medical therapy for patients with microprolactinomas, with their final sample of 16 case series and 2 retrospective cohort studies totalling 661 patients it was 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.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: 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
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Two adverse effects of these drugs became apparent after many years of use: 1. Impulse control disorders (ICD) had long been found to be common in patients treated with Bromocriptine and cabergoline when used in high doses for the treatment of Parkinson's disease. 2. 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. It has been recommended that all patients receiving >2 mg/week be assessed with an echocardiogram on a yearly basis. Because trivial valve changes are found commonly in the normal population, 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
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: For diagnosis of the causes of hyperprolactinemia, it is necessary to rule out several conditions (i.e., pregnancy) and medication that can cause hyperprolactinemia. 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. Magnetic resonance imaging (MRI) provides considerably more anatomic detail than computed tomography (CT). The clinical management can be performed by endocrinologists, gynaecologists and primary care providers and as such is appropriate for the core list of the EML. Doses should be adjusted based upon periodic monitoring of prolactin levels (EDL 3 includes 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.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: 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. Both medications are widely available and are affordable. Bromocriptine and cabergoline are the most cost-effective approach for the management of prolactinoma. Normalization of prolactin levels can be achieved in 60 – 90% of patients treated with bromocriptine and cabergoline. Control of tumour size can be achieved in over 60% of those treated with bromocriptine and over 80% of those treated with cabergoline 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 (as an alternative to medical therapy) finding 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). 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
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Both bromocriptine and cabergoline are widely registered internationally in both, brand, and generic versions
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: WHO guidelines for the management of hyperprolactinemia are not currently available, however, two guidelines from international organizations have been published, one by the Pituitary Society (3) and the other by the Endocrine Society. Bromocriptine and cabergoline are the first line therapy for prolactinoma in several guidelines. 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.