HISTORICALLY ACCEPTED USE

Tertiary and Quaternary Committee

Executive Summary

Date: May 2022

Medicine (INN): Cabergoline

Medicine (ATC): N04BC06

Indication (ICD10 code): Prolactinoma, refractory/intolerant to bromocriptine (D35.2)

Patient population: Patients with prolactinoma who are intolerant or refractory to bromocriptine therapy.

Prevalence of condition: Prevalence and incidence of prolactinomas are approximately 50 per 100,000 and 3–5 new cases/100,000/year.[1]

Level of Care: Tertiary and Quaternary

Prescriber Level: Specialist

Current standard of Care: Hospital level – Bromocriptine[2]

Referral criteria for those intolerant to bromocriptine

Efficacy estimates:

For those intolerant to bromocriptine:

- Twenty-seven patients with prolactin-pituitary tumours were included in a study evaluating response of cabergoline in patients intolerant or resistant to bromocriptine (intolerant n=11, resistant n = 16). In the intolerant group,the initial prolactin value (61.45 +/- 19.82) decreased by the third month to 4.94 +/- 1.79 ($p < 0.024$). In the resistant group (n= 16), basal prolactin values were 119.53 +/- 11.52, and in 15 of these patients, the prolactin value significantly decreased to 12.95 +/- 3.66 ng/ml ($p<0.005$) by the third month of treatment.[3] *[limitation: small study]*
- Ten patients with prolactinoma intolerant (n=7) or resistant (n=3) to bromocriptine were included in a study to assess the use of cabergoline in this cohort. For those intolerant, use of cabergoline had no adverse effects, 2 patients became pregnant, and 5 achieved normoprolactinaemia. For those resistant to bromocriptine, cabergoline was active and well tolerated in 2 out of the 3 patients (patient 1 achieved 3 pregnancies, patient 2 had normoprolactinaemia restored). One resistant patient discontinued cabergoline due to adverse effects and inefficacy.[4] *[limitation: small study]*

General efficacy compared to bromocriptine:

- A quantitative and systematic review evaluating cabergoline versus bromocriptine for the treatment of giant prolactinomas included 10 articles with 104 patients. Cabergoline was show to be significantly better than bromocriptine in normalizing prolactin levels (69.4% versus 31.7%, p = 0.01). There was no difference between the two agents in terms of tumour shrinkage, tumour response or visual field defect improvement ($p>0.05$).[5]

Cabergoline is recommended in international guidelines:

- Endocrine Society Clinical Practice Guidelines recommends cabergoline as the preferred agent for management of prolactinomas.[6]
- Clinical guidelines for the diagnosis and treatment of prolactinoma and hyperprolactinemia recommend cabergoline as first choice.[7]

Historically accepted use Criteria

	Criteria	Comment
1	The medicine is included in the WHO Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES: ; NO: X *Prolactinoma not listed as a condition. Bromocriptine is also not included. (Considered a rare disorder)*
2	The medicine is currently registered by SAHPRA for the indication.	YES: X; NO:
3	There is evidence of long-established (prior to 1996*) safe and effective use of the medicine for the recognised indication in the public health sector.	YES: X; NO: Comment: *1996 study evaluating use of cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine; found cabergoline to be an appropriate alternative in this group of patients.*[8]
4	New safety or efficacy concerns.	YES: ; NO: X Comment:
5	Is budget impact expected to have an incremental increase, that a de novo review is justified?	YES: ; NO: X Cost of monthly treatment (per patient) at 0.5mg/week: R250.44** ***Single Exit Price – April 2022_Arrow Generic*
6	Equitable access across the country is essential, and is limited only by the availability of adequately trained staff and availability of equipment.	YES: X; NO: Comment:

** The Essential Drugs Programme (EDP) of South Africa was established in terms of the National Drug Policy (NDP), which was implemented in 1996*

Recommendation

It is recommended that cabergoline be included on the Tertiary Essential Medicines List for the treatment of prolactinoma for patients intolerant or refractory to bromocriptine, for initiation by a specialist.

REFERENCES

[1] Chanson P, Maiter D. The epidemiology, diagnosis and treatment of prolactinomas: The old and the new. Endocrinology & Metabolism. 2019, 33(2)

[2] National Department of Health, South Africa. Essential Drugs Programme. Hospital level (Adults) Standard Treatment Guidelines and Essential
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[3] Velázquez-Chávez FJ, Tapia-González M, González-Bárcena D. Usefulness of cabergoline in patients with prolactinemia and resistant or intolerant to bromocriptine. Cir Cir. 2009, 77(3):173 – 177.

[4] Delgrane E, Maiter D, Donckier J. Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. European Journal of Endocrinology. 1996, 134 (4):454-456.

[5] Huang HY, Lin SJ, Zhao WG, Wu ZB. Cabergoline versus bromocriptine for the treatment of giant prolactinomas: A quantitative and systematic review. Metabolic Brain Disease. 2018 (https://doi.org/10.1007/s11011-018-0217-3)

[6] Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JAH. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinolo Metab. 2011, 96: 273-288.

[7] Rabinovich IH, Gomez RC, Mourtz MG, Garcia-Agullo DO. Clinical guidelines for diagnosis and treatment of prolactinoma and hyperprolactinemia. Endocrinol Nutz. 2013, 60(6): 308-319.

[8] Delgrange E, Maiter D, Donckier J. Effects of the dopamine agonist cabergoline in patients with prolactinoma intolerant or resistant to bromocriptine. Eur J Endocrinol 1996;134:454–6. ISSN 0804–4643