Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Evidence review for Area Prescribing Committee (APC)

Medicine details	
Name, brand name	**Cabergoline,** Dostinex®1 - 0.5mg tablets only licensed for Inhibition/suppression of physiological lactation and for Treatment of hyperprolactinaemic disorders (Carbaser®2 – 1 and 2mg tablets only licensed for Parkinson's) **Bromocriptine** 2.5mg tablets (generic)
Manufacturer	Cabergoline (Pfizer Limited), Bromocriptine (generic)
Proposed indication	Focus on the treatment of hyperprolactinaemic disorders
Requested by	Initially by Professor David Russel-Jones (For endocrine indications), then various

SUMMARY

Clinical Effectiveness

Cabergoline and Bromocriptine are established medicines and the clear supporting guidelines will be described in this paper. A clear treatment algorithm has been proposed in the Pituitary Society international Consensus Statement (September 2023): Diagnosis and management of prolactin-secreting pituitary adenomas[16]

Cabergoline is the preferred dopamine agonist owing to its long half-life, high efficacy and good tolerability (strong). Bromocriptine and quinagolide are less commonly used[16].

Bromocriptine has been included in this paper as traditionally bromocriptine is preferred in women planning pregnancy, but this may be changing: Although bromocriptine might reduce foetal exposure due to its shorter half-life, cabergoline is now preferred by the majority of centres owing to increasing safety data (weak)[16] Both options are to be made available unless there is a strong recommendation either way from specialists during the consultation.

This APC paper has been written as an evidence review as there is the need for careful consideration of the safety and monitoring of patients on this treatment:

In October 2008, the MHRA published a Drug Safety Update specifically on ergot-derived dopamine agonists (cabergoline and bromocriptine) for endocrine disorders[11] which stated: 'Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine. This related to the high doses used in Parkinson's disease.

This has a significant monitoring burden (echocardiography within 3–6 months of starting treatment and subsequently at 6–12-month intervals)

In 2011, the MHRA warning was extended to include treatment of hyperprolactinaemic disorders, even though the doses used are much lower (Parkinson's Disease, usually 2mg per day, hyperprolactinaemia, 0.5- 1mg per week). At the time the Society of endocrinology[10] supported this statement but indicated more research was required

In practice, these monitoring requirements are not being carried out in people taking the lower doses of Cabergoline and Bromocriptine for hyperprolactinaemic disorders and the APC will be asked to take a position on this, based on the evidence, various professional guidelines, and specialist recommendations so that an entry can be added to the PAD, with an appropriate traffic light classification, especially as this is a non-compliance with an MHRA safety alert. This is somewhat

supported by:

- A cross-sectional study of the prevalence of cardiac valvular abnormalities in hyperprolactinemic patients treated with ergot-derived dopamine agonists, 2013, https://pubmed.ncbi.nlm.nih.gov/24187407/
- A Follow-Up Study of the Prevalence of Valvular Heart Abnormalities in Hyperprolactinemic Patients Treated With Cabergoline, 2016, https://pubmed.ncbi.nlm.nih.gov/27571182/
- Cardiac valvular abnormalities associated with use and cumulative exposure of cabergoline for hyperprolactinemia: the CATCH study, 2020, https://pubmed.ncbi.nlm.nih.gov/32075620/

As can be seen in the Interactive Drug analysis Profiles (Appendix 1), incidence is very low, even when the MHRA safety alert launched, and therefore these analysis may not be sensitive enough to make conclusive findings.

After the alert, the incidence of Yellow card reports has decreased, but not disappeared.

A request as been made from the Specialist Pharmacy Service (SPS) to add Cabergoline and Bromocriptine to its' monitoring recommendations in 2022 and again in 2024

Clinical Benefits of treating hyperprolactinemia:

Potential complications of hyperprolactinemia are primarily related to tumor size and the physiologic effects of the condition. These include blindness, hemorrhage, osteoporosis, and infertility.
In the limited studies available, fracture prevalence was increased in patients with untreated hyperprolactinemia compared to those on treatment, independent of gonadal function

Safety

See Appendix 1, interactive Drug Analysis Profiles (iDAPs) for cabergoline (it does not differentiate between high and low doses)

Monitoring options:

Monitoring in line with the MHRA recommendations:

This has a significant monitoring burden:

Echocardiography within 3–6 months of starting treatment and subsequently at 6–12-month intervals

There is a broad consensus that this is not necessary see traffic light classification in other areas listed under 'Relevant guidance / reviews'

No Monitoring:

There are currently around 466 patients on Cabergoline and Bromocriptine in primary care Surrey Heartlands, it is unlikely that they are being monitored for fibrotic reactions (verbal communication Professor David Russel-Jones). This is somewhat supported by a cross-sectional study of the prevalence of cardiac valvular abnormalities in hyperprolactinemic patients treated with ergot-derived dopamine agonists, 2013, https://pubmed.ncbi.nlm.nih.gov/24187407/

Reduced Monitoring:

In 2018, the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology Echocardiography published a joint position statement recommending a pragmatic approach to monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia[10]

Rather than the more frequent monitoring recommended by the MHRA, the consensus document recommends the following:

- A standard transthoracic echocardiogram should be performed before a patient starts DA therapy for hyperprolactinaemia.
- Repeat transthoracic echocardiography should then be performed at 5 years after starting Cabergoline and Bromocriptine in patients taking a total weekly dose less than or equal to 2 mg.
- If there has been no change on the 5-year scan, repeat echocardiography could continue at 5-yearly intervals.

If this option would be selected, due to waiting times for echocardiography of around 6 months, the proposal is to modify this recommendation so that as the treatment will be initiated immediately and the first echocardiogram will be booked at that point by the specialist.

Recommendation:
As a result of this work, it is proposed that the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology Echocardiography joint statement recommendations[9] are adopted. A request was made to the Specialist Pharmacy Service (SPS) drug monitoring team to review the recommendations as this is a national problem.

The 'Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement'[18] states that 'Patients should be informed about the potential for the rare adverse effect of cardiac valve changes with long-term and/or high-dose cabergoline treatment (strong). Intervals for screening echocardiography vary in different countries. Baseline and follow-up screening is suggested in patients considered for long-term or high-dose therapy (weak).'

Differentiating between reports from patients with high or low doses of dopamine agonists:
A query was made to the manufacturer's (Pfizer) medicines information department to enquire if there were any reports of fibrosis in patients receiving the lower doses of cabergoline indicated for Treatment of hyperprolactinaemic disorders, but the reply was not helpful:

'Unfortunately, Medical Information is unable to assist you and we can only provide information that is already in public domain.
All appropriate safety information including information regarding fibrosis/cardiac fibrosis is included in the label.'

Patient factors

Monitoring in line with the MHRA recommendations be the option approved, this would difficult to implement in view of the pressures on the echocardiogram services and would represent a high monitoring burden to the patients. This does not seem to be occurring elsewhere in the NHS.
If this is a true risk, however even at the low doses used for the management of hyperprolactinemia, patients are at risk of not monitored for severe adverse effects
Prescribers not following MHRA advice may be at risk of litigation.

Cost implications

Cabergoline
Last 12 months (Jun '23—May '24) 1,769 items, Costing £59,418

There are some patients for whom primary care prescribers have not accepted transfer of care without a PAD entry and traffic light classification, it is a mixed picture and numbers are not known, but a small proportion of that which is currently prescribed in primary care;

Cost per patient:
Drug tariff, Cabergoline 500microgram tablets, £15.64 for 8 tablets

Dose range 500miccrograms to 2 milligrams per week, equivalent to £30.83 to £203.32 per patient per year, lower doses, 500micrograms to 1 milligram being the usual doses.

Bromocriptine
Last 12 months (Jun '23—May '24) 174 items, £20,507, approximately £120 per item (wide dosage range)

Potential increase by 10% when transferring patients to primary care where this was not previously accepted due to lack of traffic light classification

Cost of transthoracic echocardiogram (PbR, 2021/22) £200-£500 per appointment

Relevant guidance / reviews

Relevant Guidelines:

Society for Endocrinology position statement on the use of dopamine agonists in endocrine disorders, originally issued February 2009; reviewed November 2011, https://pubmed.ncbi.nlm.nih.gov/30818417/

Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nature Reviews Endocrinology, [online] pp.1–19. September 2023 doi: https://doi.org/10.1038/s41574-023-00886-5

Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: A joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology, Clin Endocrinol (Oxf) . 2019 May;90(5):662-669. doi: 10.1111/cen.13940. Epub 2019 Feb 28, https://pubmed.ncbi.nlm.nih.gov/30818417/

Likely place in therapy relative to current treatments

Cabergoline is the preferred Ergot derived dopamine agonist for several indications, bromocriptine may be required as a second choice:

- Parkinson's disease, Treatment (**RED**) and Prevention (Black/ Non Formulary)
- For the inhibition and suppression of lactation after birth or after stillbirth or abortion (see attached established medicines paper) **RED**
- **For the treatment of hyperprolactniaemic disorders (this paper)**
- For the treatment of medication induced hyperprolactinaemia where alternative treatments are not available (mainly in mental health) – The recommendation is that the Mental Health Trust should provide governance around monitoring and ongoing care, before prescribing is approved for Primary care and therefore, until then, give a RED traffic light classification. A request was made and the feedback was that the Maudsley Guidelines were followed.
- Bromocriptine is also licensed for the treatment of infertility and acromegaly which are not being addressed in this paper.

Recommendation to APC

For hyperprolactinaemic disorders:
Approve for prescribing in primary care, after initiation by specialists, with reduced monitoring in line with the 'British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology Echocardiography published a joint position statement recommending a pragmatic approach to monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia[10] Noting that the first echocardiogram should be booked at the time of treatment initiation, but not necessarily completed.
The APC is asked to consider the traffic light classification which could either be an

Amber Shared care OR Blue

- **Amber** shared care:
  - Advantages:
    - Although the treatment itself is not complex, the underlying condition requires long term monitoring with occasional, non-urgent requests for dosage changes of treatment doses, so the patients are not actually discharged from specialist care
    - Clear delineation of the responsibilities could be identified, this includes frequency of prolactin level testing and echocardiography, as well as monitoring the underlying disease
  - Disadvantages:
    - Shared care agreements are usually used where complex monitoring is required in primary care, this is not the case here
    - The paperwork around Amber shared care is more burdensome than Blue traffic light classification
    - Other APC/ DTCs appear to have selected the equivalent of Blue or Green traffic light classification

OR

- **Blue**
  - Advantages:
    - The treatment itself is not complex, only requiring infrequent prolactin level monitoring, and, because levels take several months to settle, recommendations to change doses are not urgent[19]
  - Disadvantages:
    - Shared care agreements provide very clear responsibilities for Secondary care, primary care and patients with regards to monitoring, without these agreements it is important to decide whether these responsibilities can be made clear another way, for example on the PAD statement.

For drug induced hyperprolactinaemia

- 1st line is to select alternative medicine, this is most likely not to be possible in mental health treatments
- Guidelines available in The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry
- **RED** traffic light classification until governance around monitoring is presented to APC

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	**Traffic light Classification in other areas:** **SWL:** **Amber 2** (Initiation by a specialist, stabilisation for a specified time, then continuation in primary care under an individual management plan) **Sussex:** Suppression of Lactation - **GREEN** (Coastal West Sussex ONLY) All other indications - **PURPLE** (Coastal West Sussex) All indications - **PURPLE** (Brighton and Hove, East Sussex and Crawley, Horsham and Mid Sussex) Ergot-derived dopamine agonists: risk of fibrotic reactions - GOV.UK (www.gov.uk) **Frimley** **GREEN**

	Derbyshire **GREEN** after consultant/specialist initiation **Lothian Formulary** To be initiated on specialist advice Prescribing Notes: 1. Bromocriptine is the treatment of choice for hyperprolactinaemia during pregnancy or those planning pregnancy. 2. Cabergoline and bromocriptine are associated with a low risk of fibrotic disorders and heart valve damage associated with ergot-derived dopamine agonists. Periodic echocardiography is recommended. 3. For suppression of lactation, see the Obstetrics, gynaecology, and urinary-tract disorders chapter of the formulary. 4. For Parkinson's disease, see the Central nervous system chapter of the formulary.
Recommendations from national / regional decision making groups	Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline Shlomo Melmed, Felipe F. Casanueva, Andrew R. Hoffman, David L. Kleinberg, Victor M. Montori, Janet A. Schlechte, John A. H. Wass The Journal of Clinical Endocrinology & Metabolism, Volume 96, Issue 2, 1 February 2011, Pages 273–288, https://doi.org/10.1210/jc.2010-1692 Published: 01 February 2011
Stakeholder views	
ICB priorities	As there is no entry on the PAD for this indication, there is variable agreement to prescribe in primary care. Feedback is that monitoring in line with the MHRA safety alert is not being done, governance. Surrey Heartlands is not unique in this situation nationally.

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Declaration of Interest:

None

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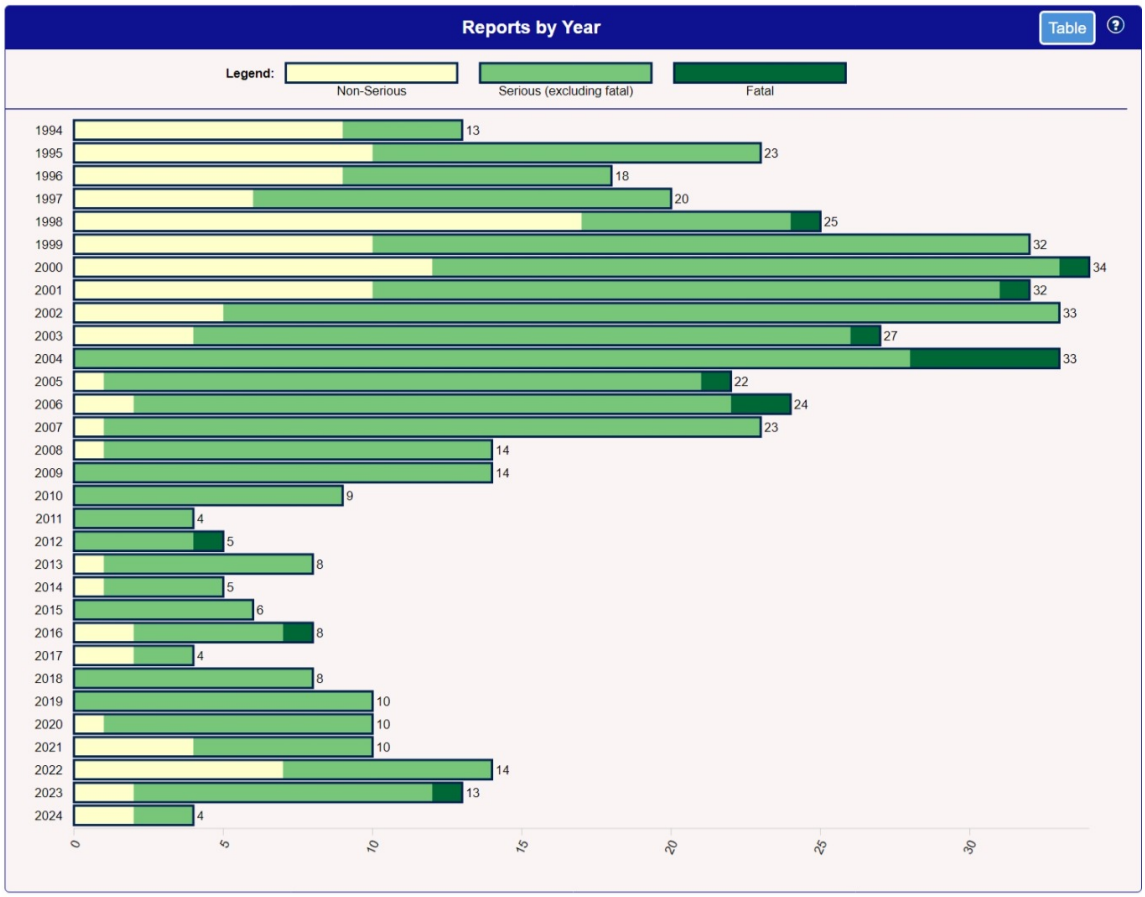
Appendix 1

interactive Drug Analysis Profiles (iDAPs) for Cabergoline, accessed August 2024



Interactive Drug Analysis Profile for BROMOCRIPTINE

Yellow Card
Making medicines safer

Reports by Year