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**Re.: Cabergoline and recommendations for cardiac monitoring in patients with prolactinomas**

Cabergoline has become the treatment of choice for patients with prolactinomas because of a greater efficacy and tolerability compared to other dopamine agonists. The compound is also used, in much higher doses, as second line treatment in Parkinson's disease (PD). In long-term treatment in PD, an increased incidence of valvular abnormalities has been reported. The recently updated prescribing information for cabergoline, as issued by the EMEA June 2008 (EMEA/CHMP/322395/2008) has raised concern among clinical endocrinologists in Sweden and elsewhere, and the recommendations on detailed, frequent cardiac monitoring for patients with prolactinomas have been questioned.

The Swedish Pituitary Study Group consists of endocrinologists responsible for treatment of pituitary disorders, aiming at improving and harmonizing treatment practice across the country. We have evaluated the existing literature on cabergoline and cardiac valvulopathy in PD and in patients with prolactinomas. In our view, the EMEA recommendations, although valid for the Parkinson's group, do not seem applicable for patients with prolactinomas given the dosing difference. The EMEA recommendations can lead to unjustified use of medical resources (cardiac evaluations, echocardiographies), cause unnecessary patient concern, and may prevent optimal care of patients who benefit from treatment with cabergoline. Further, the group of patients resistant or intolerant to other dopamine agonists, will be at risk to unduly obtain other treatment modalities i.e. surgery or radiotherapy, both known to have a less favourable risk/benefit profile compared to medical treatment.

Therefore, we ask for a modification of the current recommendations. To support our position, we here recapitulate the published literature as of August 2009, and include a power point summary of the studies on prolactinoma patients (1-8), a copy of an Editorial by Mark Molitch, *J Clin Endocrinol Metab* 2008;93:4643-4645, and a response on this issue from ULIC (Uppsala Läkemiddelsinformationscentral).

*Cabergoline in Parkinson's disease*

The use of cabergoline in patients with PD has been associated with an about 5-fold increased risk for valvular abnormalities (9-17). In these papers PD patients had received daily doses ranging from 2.6 to 4 mg, a dose 18-29 times higher than the most common dose in patients with prolactinomas (1.0 mg per week, typically divided as 0.5 mg twice a week, i.e. corresponding to approximately 0.14 mg daily). Less than 20 % of patients require more than 2 mg/week to normalize prolactin levels (18). In some of the studies valvulopathy was associated with the cumulative dose given (from 2600 to 6700 mg).

In the study on the largest number of PD patients (10) the mean cumulative dose in patients with no or mild regurgitation was 2341 mg and 4015 mg in the group with moderate to severe valvulopathy. The relevance, however, of using the cumulative dose as a measure to evaluate risk can be discussed. To our knowledge there is no data to suggest that a pharmacological effect of a drug observed following daily exposure to high doses will automatically translate into a corresponding effect when a much lower dose is given for a longer time. Given similar untoward effects of a low dose regimen in the average prolactinoma patient, 45-77 years of treatment would be needed.

### *Cabergoline in prolactinomas*

Today, the combined data from eight controlled studies on prolactinoma patients (n = 563) treated with cabergoline for 45-81 months do not support an increased proportion of significant valvular abnormalities in patients compared to controls (1-8, slide summary of these studies enclosed). One of the eight studies reported an increased prevalence of moderate tricuspid regurgitation (TR) in patients (5). However, the criteria for valvular abnormalities used in this study has been questioned (see Molitch) given the unexpected high incidence of mild TR in controls and in a group of untreated prolactinoma patients, 42% and 55% respectively, to be compared with a figure around 15-18 % in the large Framingham Heart Study (n = 3589, ref.19). To which extent the higher blood pressure and left ventricular mass index among patients with moderate TR influenced the outcome remains to be clarified.

We ask that recommendations to be modified and adapted to the low dose cabergoline regimens used in the treatment of prolactinoma patients. We share the very insightful view and clinical attitude expressed by Dr Molitch with regards to the current management of patients with prolactinomas.

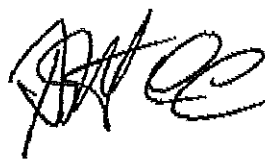
On behalf of the Swedish Pituitary Study Group,



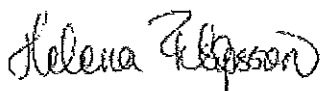
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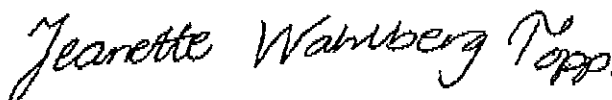
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## Enclosures

- I. Cabergoline and valvulopathy in patients treated for hyperprolactinemia (Slide summary by Katarina Berinder).
- II. Editorial by Mark Molitch, *J Clin Endocrinol Metab* 2008;93:4643-5.
- III. Response from ULIC 2009-05-18 (Sofie Schwan, Pär Hallberg) to a question from Britt Eden Engström on the possible risk of low-dose cabergoline use in prolactinoma patients given the reports of valvulopathy in high-dose treated PD patients.

Translation of the ULIC summary: “One of seven published observational studies in conditions of hyperprolactinemia has shown an increased risk of moderate tricuspid regurgitation, which speaks against that cabergoline would be associated with an increased risk of valvular disease after an average cumulative dose of 300-400 mg (corresponding in average to 5-6 years of treatment). Longer studies and longitudinal studies are lacking.”