Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24.
Telephone: 01-4676500 Facsimile: 01-4676501
Freephone: 1800-460-900
www.pfizer.ie

28th July 2008

IMPORTANT SAFETY INFORMATION

Dear Healthcare Professional,

Following discussions with the EU regulatory authorities, including the Irish Medicines Board (IMB), this letter is to inform you of important new safety information for Cabaser, (cabergoline tablets, uncoated: 1 mg, 2 mg and 4 mg) in the treatment of Parkinson's Disease as regards the occurrence of cardiac valvulopathy/fibrotic disorders.

IMPORTANT SAFETY INFORMATION

Treatment with Cabergoline (*Cabaser* ®) has been associated with the onset of fibrotic cardiac valvulopathy.

The recent Referral procedure will lead to an update of the current Summary of Product Characteristics (SPC) of cabergoline in the treatment of Parkinson's Disease including:

- **Limitation of the daily dose to a maximum of 3 mg**
- **Contraindication in patients with a history of fibrotic disorders and evidence of cardiac valvulopathy as determined by pre-treatment echocardiography**
- **Warnings including mandatory regular echocardiography monitoring pre- and during treatment and clinical monitoring of other fibrotic events**
- **Amendment of the list of undesirable effects to include cardiac valvulopathy and related disorders**

Information on the safety concern

On the 21 June 2007 the European Medicines Agency (EMEA) initiated a review of safety under Article 31 of Directive 2001/83/EC (as amended) in order to reassess the risk profile of ergot-derived dopamine agonist medicinal products including cabergoline.

The safety review stems from concerns reported in published articles about an increased risk of fibrotic disorders and cardiac valvulopathy in patients treated for Parkinson's disease with ergot dopamine agonists including cabergoline.

Cabergoline is already restricted to second line therapy for the treatment of Parkinson's disease and its SPC includes a contraindication if there is evidence of cardiac valvulopathy in any valve.

The EMEA's Scientific Committee (the Committee for Human Medicinal Products – CHMP) concluded that the following sections of the SPC were to be amended: contraindications, special warnings and precautions for use and undesirable effects.

In line with the CHMP conclusion Pharmacia Laboratories Limited will discontinue the production and distribution of the cabergoline 4mg tablets for the European Union.

Reporting of adverse reactions

If you become aware of any suspected adverse reactions in association with use of Cabaser please report the event promptly to Pfizer Drug Safety group at Pfizer Limited, Walton Oaks, Dorking Road, Walton on the Hill, Surrey KT20 7NS, United Kingdom or to the Irish Medicines Board in the usual way. Pfizer Limited UK can be contacted by freephone 1800 633 363.

If you have any enquiries or want additional information, please contact the Pfizer Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Walton on the Hill, Surrey, KT20 7NS, United Kingdom. The following number is available for providing Medical Information during normal working hours as well as for out of hours medical emergencies: 1800 633 363.

Yours sincerely,

Dr John Farrell
Medical Director
Pfizer Healthcare Ireland

Annex 1

The following changes to the SPC were adopted by the CHMP for cabergoline at its June 2008 meeting and will be implemented over the coming months:

4.2 Posology and method of administration
The following should be reflected as appropriate:
Restriction of the maximum dose to 3 mg/day

4.3 Contraindications:
...[ ]...
"Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography."

4.4 Special warnings and precautions for use:
...[ ]...
"Fibrosis and cardiac valvulopathy and possibly related clinical phenomena:
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin $5HT_{2B}$ receptor, such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Valvulopathy has been associated with cumulative doses, therefore, patients should be treated with the lowest effective dose. At each visit, the risk benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

Before initiating treatment:
All patients must undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.
In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (see section 4.3).

During treatment:
Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.

Therefore, during treatment, attention should be paid to the signs and symptoms of:
- *Pleuro-pulmonary disease such as dyspnoea, shortness of breath, persistent cough or chest pain.*
- *Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.*
- *Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.*

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see Section 4.3).

The need for other clinical monitoring (e.g. physical examination including, cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.
Additional appropriate investigations such as erythrocyte sedimentation rate, and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder."

4.8 Undesirable effects:

The following should be included under Cardiac disorders:

"Very common: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)."