



Worldwide Pharmaceutical Operations

Dear Healthcare Professional,

This letter is to inform you of important new safety information regarding the occurrence of cardiac valvulopathy/fibrotic disorders for the following medicines:

- **CABASER®** (cabergoline tablets, uncoated: 1 mg, 2 mg and 4 mg) indicated for the treatment of Parkinson's disease.
- **DOSTINEX®** (cabergoline tablets, 0.5mg) indicated for the treatment of hyperprolactinaemic disorders and the inhibition/suppression of physiological lactation.

IMPORTANT SAFETY INFORMATION

Treatment with cabergoline (Cabaser and Dostinex) has been associated with the onset of fibrotic cardiac valvulopathy.

The Summary of Product Characteristics (SPC) for Cabaser in the treatment of Parkinson's disease and Dostinex in the treatment of hyperprolactinaemic disorders will be updated as follows:

Cabaser

- Restriction of the maximum recommended dose to 3 mg/day in the treatment of Parkinson's disease
- Contraindication in patients with a history of fibrotic disorders and evidence of cardiac valvulopathy as determined by pre-treatment echocardiography
- Warnings including mandatory echocardiographic monitoring before initiating treatment and regularly during treatment, and clinical monitoring of other fibrotic events
- Undesirable effects to include cardiac valvulopathy and related disorders (pericarditis and pericardial effusion) as very common side-effects

In line with the Committee for Medicinal Products for Human Use (CHMP) conclusion, Pharmacia Laboratories Limited will discontinue the production and distribution of the Cabaser 4mg tablets for the European Union from 31st October 2008.

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Dostinex—treatment of hyperprolactinaemic disorders

- Contraindication in patients with a history of fibrotic disorders and evidence of cardiac valvulopathy as determined by pre-treatment echocardiography
- Warnings including mandatory echocardiography monitoring before initiating treatment and regularly during treatment and clinical monitoring of other fibrotic events
- Undesirable effects to include cardiac valvulopathy and related disorders (pericarditis and pericardial effusion) as very common side-effects
- The recommended initial dose remains 0.5 mg per week given in one or two doses per week and titrated according to prolactin levels. The therapeutic dose is usually 1 mg per week.

Prescribers are reminded that pregnancy should be excluded before administration of Dostinex. Women seeking pregnancy should discontinue Dostinex at least one month before intended conception.

Further information

On 21 June 2007 the European Medicines Agency (EMA) initiated a safety review of ergot-derived dopamine agonists, including cabergoline.

The safety review arose from published articles (Zanettini¹ and Schade²) that reported 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 the SPC includes the contraindication "anatomical evidence of cardiac valvulopathy of any valve."

The CHMP concluded that the following sections of the SPC were to be amended: contraindications; special warnings and precautions for use; and undesirable effects (see annex 1).

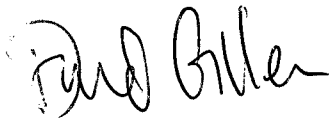
Reporting of adverse reactions

Please report any suspected serious or unexpected adverse reactions associated with the use of Cabaser or Dostinex to the Medicines and Healthcare products Regulatory Agency (MHRA) using a Yellow Card (see www.yellowcard.gov.uk). Adverse reactions should also be reported to Pfizer Medical Information on 01304 616161.

If you have any enquiries or require further information, please contact Pfizer Medical Information on 01304 616161.

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Yours sincerely,



Dr David Gillen

Medical Director

Pfizer Ltd

Annex 1

SPC wordings adopted by the CHMP for cabergoline at its June 2008 meeting

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.

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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.”

Section 4.4 Special warnings and precautions for use (for cabergoline-containing medicinal products authorised in the indication of anovulation and infertility only)

...[]...

“Before administration of cabergoline pregnancy should be excluded. Because clinical experience is still limited and the product has a long half-life, as a precautionary measure it is recommended that once regular ovulatory cycles have been achieved women seeking pregnancy discontinue [product name] one month before intended conception.”

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).”

References

1. Zanettini R et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson’s Disease, N Engl J Med 2007; 356-39
2. Schade R et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation, N Engl J Med 2007; 356-29

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