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Pfizer Global Pharmaceuticals

2 April 2007

Direct Healthcare Professional Communication regarding CABASER (cabergoline tablets, uncoated: 1, 2 and 4 mg) in the treatment of Parkinson's disease and pathological gambling and increased libido including hypersexuality.

Cabergoline (Cabaser®) and pathological gambling and increased libido including hypersexuality: Possible class effects of dopamine agonists.

Safety update for CABASER® (cabergoline) tablets

The Medicines and Healthcare Products Regulatory Agency (MHRA) have requested, that in line with the recommendations of the Pharmacovigilance Working Party (PhVWP) of the European Committee for Medicinal Products for Human Use (CHMP), the following wording is added to the Cabaser Summary of Product Characteristics (SPC):

4.4 Special warnings and precautions for use

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including Cabaser.

4.8 Undesirable effects

Patients treated with dopamine agonists for treatment of Parkinson's disease, including Cabaser, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

Reporting of adverse reactions

Please report any cases of suspected adverse reactions in association with use of Cabaser to the *Medicine and Healthcare Products Regulatory Agency via the Yellow Card Scheme or call 020 7084 3080* and the *Pfizer Medical Information Department on 01304 616161*.

If you have any enquiries or want additional information, please contact *Pfizer Medical Information Department on 01304 616161*. The following number is available for providing Medical Information during normal working hours as well as for out of hours medical emergencies: *01304 616161.*

Yours sincerely,

DK Lloyd

Dr Kate Lloyd
Medical Director
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Direct Healthcare Professional Communication regarding CABASER (cabergoline tablets, uncoated: 1, 2 and 4 mg) in the treatment of Parkinson's disease and cardiac valvulopathy/fibrotic disorders.

Cabergoline (Cabaser®) and fibrotic cardiac valvulopathy: Important information comprising second line indication, contraindications for use and new monitoring requirements.

Summary

The 4 Jan 2007 issue of the New England Journal of Medicine (NEJM) contained two publications on the increased risk for, and frequency of, clinically important valve regurgitation in patients taking pergolide or cabergoline, but not in patients taking non-ergot-derived dopamine agonists.

These results have led to an update of the SPC of cabergoline in the treatment of Parkinson's disease, including:

- **Restriction of the indication for use of cabergoline in the management of the signs and symptoms of Parkinson's disease (PD) to second line therapy in patients who are intolerant to or fail treatment with a non-ergot compound, as monotherapy, or as adjunctive treatment to levodopa plus dopa-carboxylase inhibitor;**
- **Contraindication in patients with a history of pulmonary, pericardial, and retroperitoneal fibrotic disorders and/or anatomical evidence of cardiac valvulopathy of any valve;**
- **Warnings regarding fibrosis and cardiac valvulopathy, as well as patient monitoring requirements.**

Sections 4.1, 4.3, 4.4 and 4.8 have been amended accordingly.

Additionally

- **Reporting of suspected adverse reactions in association with the use of Cabaser is encouraged.**

The highlighted changes in the revised SPC (see Annex 1) have been endorsed by the EU national regulatory authorities.

Information on the safety concern

On 4 January 2007 two clinical papers on the relationship of anti-Parkinson's disease drugs (dopamine agonists) and cardiac valvulopathy were published in the New England Journal of Medicine (NEJM) by Zanettini[1] and Schade[2]. Zanettini concluded that the frequency of clinically important valve regurgitation was significantly increased in patients taking the ergot-derived dopamine agonists pergolide or cabergoline, but not in patients taking non-ergot-derived dopamine agonists, as compared with control subjects.

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The frequency of valvulopathy reported by Zanettini, 23.4% and 28.6 % for pergolide and cabergoline respectively, was consistent with that seen for pergolide in other studies. Schade concluded that the use of pergolide and cabergoline was associated with an increased risk of newly diagnosed cardiac-valve regurgitation. The reported excess risks of cardiac-valve regurgitation for current use of pergolide and for current use of cabergoline were 33 and 21 additional case patients per 10,000 persons exposed per year, respectively. Schade showed that cabergoline administered in doses of 3 mg or less or for fewer than 6 months duration irrespective of dose was not associated with a statistically significant increased risk of valvulopathy. The Zanettini and Scade clinical papers and Pfizer´s spontaneously reported adverse event data provide limited information on regression of valvulopathy following discontinuation of cabergoline.

After review of safety data and the clinical publications, it was considered the risk of valvulopathy and fibrotic adverse events (AEs) of Cabaser to be similar to that of pergolide. Cabaser SPCs are being updated in line with the pergolide SPC in the following sections: limitations to the indication, i.e. second line treatment, addition of contraindications, addition of further detail regarding warnings for use, and addition of monitoring requirements.

Reporting of adverse reactions

Please report any cases of suspected adverse reactions in association with use of Cabaser to the *Medicine and Healthcare Products Regulatory Agency via the Yellow Card Scheme or call 020 7084 3080* and the *Pfizer Medical Information Department on 01304 616161*.

If you have any enquiries or want additional information, please contact *Pfizer Medical Information Department on 01304 616161*. The following number is available for providing Medical Information during normal working hours as well as for out of hours medical emergencies: *01304 616161*.

Yours sincerely,

Dr Kate Lloyd
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Annex 1

Summary of Product Characteristics updates, March 2007

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

ANNEX 1

Safety update for CABASER® (cabergoline) tablets

The Pharmacovigilance Working Party (PhVWP) of the European Committee for Medicinal Products for Human Use (CHMP) have requested that the following wording is added to and/or replaces previous text in the Cabaser Summary of Product Characteristics (SPC):

Section 4.1, Indications

If treatment with a dopamine agonist is being considered, cabergoline is indicated as second line therapy in patients who are intolerant or fail treatment with a non-ergot compound, as monotherapy, or as adjunctive treatment to levodopa plus dopa-decarboxylase inhibitor, in the management of the signs and symptoms of Parkinson's disease.

Treatment should be initiated under specialist supervision. The benefit of continued treatment should be regularly reassessed taking into account the risk of fibrotic reactions and valvulopathy (see sections 4.3, 4.4 & 4.8)

Section 4.3, Contraindications

Hypersensitivity to cabergoline, other ergot alkaloids or to any of the excipients.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders.

Anatomical evidence of cardiac valvulopathy of any valve (e.g., echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

Section 4.4, Special warnings and special precautions for use

Fibrosis and Cardiac Valvulopathy

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 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.

Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorder.

Valvulopathy was associated with cumulative doses.

Before initiating treatment:

All patients should undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. 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:

• Pleuropulmonary 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, as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear.

• Cardiac failure, as cases of valvular fibrosis have often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should occur at a 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, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

4.8 Undesirable effects

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking cabergoline (see 'Special warnings and special precautions for use'). The incidence of valvulopathy with cabergoline is not known, however based on recent studies of the prevalence of valvular regurgitation (the most sensitive echocardiographic marker for restrictive valvulopathy), the prevalence of regurgitation (virtually all cases asymptomatic) potentially attributable to cabergoline may be in the range of 20% or greater.

There is limited information available on the reversibility of these reactions.