Malta, 15 February 2007
Circular No. P02/2007

Dear Healthcare Professional,

Re: Pergolide and the risk of cardiac valvulopahty and fibrotic reactions.

Following reports in the local media that the drug pergolide (marketed locally as Celance® and in other markets as Permax®) is being distributed by the Health Department in spite of certain "dangers" associated with the use of this drug, the Medicines Authority would like to provide an accurate picture about the status of this medicinal product in Malta.

According to the Summary of Product Charactersitics (SmPC) of Celance® (a document which is authorised by the Medicines Authority as part of the evaluation and licensing of a medicinal product in Malta and available on our website www.medicinesauthority.gov.mt) pergolide is indicated in the following:

> "If treatment with a dopamine agonist is being considered, pergolide mesilate 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, in the management of the signs and symptoms of Parkinson's disease. Pergolide mesilate is a dopamine receptor agonist at D1, D2 and D3 receptor sites.
> 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."

This indication was agreed upon after extensive discussions between the regulatory authorities of all Member States at the Pharmacovigilance Working Party organised at the European Medicines Agency (EMEA) where all data available at that time (from literature reports, clinical trials and individual case safety reports) was evaluated to determine the benefit-risk balance of pergolide. It was concluded that the benefit-risk balance of this drug remains positive as long as certain warnings with respect to cardiac valvulopathy and fibrotic disorders were implemented in the SmPC. Apart from the modified indication above, in which it is clearly stated that pergolide is only indicated as a second line therapy, the following information is also listed in the SmPC:

> "*Section 4.3 Contra-indications:*
> History of fibrotic disorders. Anatomical evidence of cardiac valvulopathy of any valve (e.g. echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).
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> *Section 4.4 Special warnings and special precautions for use:*

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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 pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.

Before initiating treatment:
All patients should undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. In patients with valvular regurgitation, it is not known whether pergolide treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with pergolide (see section 4.3)
There is some evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology.

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 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
Appropriate investigations such as erythrocyte sedimentation rate, chest X-ray and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder. 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.
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 least every 6 to 12 months.
Pergolide 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.

Section 4.8 Adverse Reactions:
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 pergolide (see 'Special warnings and special precautions for use').The incidence of valvulopathy with pergolide 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 regurgitaion (vitually all cases asymptomatic) potentially attributable to pergolide may be in range of 20% or greater. There is limited information available on the reversibility of these reactions."

Patients should rest assured that if advice in section 4.3 is followed by prescribers prior to starting treatment (i.e. a full cardiovascular evaluation, including an electrocardiogram) as well as during treatment (monitoring of signs and symptoms of possible cardiac failure or pleuro-pulmonary disease) this medication is no more “dangerous” than other therapy currently available for the treatment of Parkinson’s Disease. Furthermore, the Medicines Authority would like to reassure prescribers and patients alike that safety issues such as the risk of cardiac valvulopathy and fibrotic reactions associated with the use of pergolide are regularly reviewed together with regulatory authorities of all Member States and that various risk minimisation measures are in place as agreed with the marketing authorisation holder of this product.