

**ANNEX III**

**AMENDMENTS TO THE SUMMARIES OF PRODUCT CHARACTERISTICS AND  
PACKAGE LEAFLETS**

## AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR CABERGOLINE CONTAINING MEDICINAL PRODUCTS

### 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:

...[ ]...

*“For long-term treatment: 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<sub>2B</sub> 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 long-term 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 long-term 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).”*

## AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET FOR CABERGOLINE CONTAINING MEDICINAL PRODUCTS

### Section 2 “Before you take [product name]”:

Do not take [product name] if you:

...[ ]...

*“-will be treated with [product name] for a long period and have or had fibrotic reactions (scar tissue) affecting your heart.”*

### Take special care with [product name]’

...[ ]..

*“- If you have or had fibrotic reactions (scar tissue) affecting your heart, lungs or abdomen.”*

*In case you are treated with [product name] for a long period, your physician will check before starting treatment whether your heart, lungs and kidneys are in good condition. He/she will also have an echocardiogram (an ultrasound test of the heart) taken before treatment is started and at regular intervals during treatment. If fibrotic reactions occur treatment will have to be discontinued.”*

### Section 2 “Before you take [product name]”:

The following should be included under Pregnancy and breast feeding (for cabergoline-containing medicinal products authorised in the indication of anovulation and infertility only):

*“Before you can start using cabergoline you have to exclude that you are pregnant. Additionally you should take care not becoming pregnant for at least one month once you have stopped treatment with cabergoline.”*

### Section 4 “Possible side effects”:

...[ ]...

*“Very common side effect (affecting more than one person in ten): heart valve and related disorders e.g. inflammation (pericarditis) or leaking of fluid in the pericardium (pericardial effusion).*

*The early symptoms may be one or more of the following: difficulty breathing, shortness of breath, chest or back pain and swollen legs. If you experience any one of these symptoms you must tell your doctor immediately.”*

## AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR PERGOLIDE CONTAINING MEDICINAL PRODUCTS

### 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 Contraindication:

...[ ]...

*“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<sub>2B</sub> receptor, such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.*

*There is evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology. However, valvulopathy and fibrotic reactions have been reported during treatment with pergolide at doses less than 0.5mg/day.*

*Before initiating treatment:*

*All patients must 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).*

*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.*

*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 valvular disease or fibrosis, 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.*

*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 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).”*

## AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET FOR PERGOLIDE CONTAINING MEDICINAL PRODUCTS

### Section 2 “Before you take [product name]”:

Do not take [product name] if you:

...[ ]...

*“- have or had fibrotic reactions (scar tissue) affecting your heart.”*

Take special care with [product name]”

...[ ]...

*“If you have or had fibrotic reactions (scar tissue) affecting your heart, lungs or abdomen.*

*Before treatment your physician will check whether your heart, lungs and kidneys are in good condition. He/she will also have an echocardiogram (an ultrasound test of the heart) taken before treatment is started and at regular intervals during treatment. If fibrotic reactions occur treatment will have to be discontinued.”*

### Section 3 How to take [product name]

...[ ]...

*“Do not take more than 3 <if relevant include colour of the tablet> tablets (3 x 1000 microgram tablets) per day.”*

### Section 4 “Possible side effects”:

...[ ]...

*“Very common side effect (affecting more than one person in ten): heart valve and related disorders e.g. inflammation (pericarditis) or leaking of fluid in the pericardium (pericardial effusion).*

*The early symptoms may be one or more of the following: difficulty breathing, shortness of breath, chest or back pain and swollen legs. If you experience any one of these symptoms you must tell your doctor immediately.”*