



## **QUESTIONS AND ANSWERS ON THE REVIEW OF ERGOT-DERIVED DOPAMINE AGONISTS**

The European Medicines Agency (EMA) has completed a review of the safety of the ergot-derived dopamine agonists, a group of medicines that are mainly used to treat Parkinson's disease. The review focused on the risk of fibrosis (the formation of fibrous tissue in some body structures) in patients taking these medicines for long periods, particularly cardiac fibrosis (abnormal thickening of the heart valves). This review was carried out under an 'Article 31' referral<sup>1</sup>.

The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the marketing authorisations for these medicines should be maintained. However, restrictions on the way these medicines are used should be introduced, to reduce the risk of fibrosis developing.

### **What are ergot-derived dopamine agonists?**

Ergot-derived dopamine agonists are a group of medicines consisting of bromocriptine, cabergoline, dihydroergocryptine, lisuride and pergolide. They have been available on the market for many years and are mainly used to treat Parkinson's disease, either on their own or in combination with other medicines. They are also used to treat conditions including hyperprolactinaemia (high levels of the hormone prolactin in the blood) and prolactinoma (a non-cancerous tumour of the pituitary gland at the base of the brain), and to prevent lactation (production of breast milk) and migraine. All five medicines are authorised by regulatory authorities in Member States.

Dopamine agonists work by stimulating brain and nerve cells in a similar way to dopamine, a messenger substance in the nervous system. This group of dopamine agonists are called 'ergot-derived', because they were first produced from a type of fungus called ergot.

### **Why have ergot-derived dopamine agonists been reviewed?**

Fibrosis can affect a number of body structures such as the heart, the lungs or the abdomen. When it affects the heart valves, it can lead to problems with the flow of blood around the heart and, eventually, heart failure (an inability of the heart to pump enough blood around the body). The development of the symptoms of fibrosis has been known as a side effect of ergot-derived dopamine agonists for many years, particularly when the medicines are used for long periods. However, two studies published in scientific journals using echocardiography (ultrasound scans of the heart) have shown that fibrosis of the heart valves can begin to develop well before symptoms start to appear. This suggested that cardiac fibrosis may be more common than previously thought.

Consequently, the United Kingdom's medicines regulatory authority asked the CHMP to review the risk of fibrosis, including cardiac fibrosis, associated with the use of ergot-derived dopamine agonists.

### **Which data has the CHMP reviewed?**

The CHMP reviewed all of the available information on the risk of fibrosis and valve problems from clinical trials, observational studies (studies looking at the effects of medicines as they are used by patients) and 'spontaneous reports' of side effects made by patients or doctors to the companies that make the medicines or to health authorities.

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<sup>1</sup> Article 31 of Directive 2001/83/EC as amended, referral under Community interest.  
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### **What are the conclusions of the CHMP?**

Based on the information available, the CHMP has concluded that the marketing authorisations for the ergot-derived dopamine agonists should be maintained, but changes to the prescribing information for the medicines should be introduced to reduce the risk of fibrosis. The CHMP also concluded that the risk of fibrosis, including fibrosis of the heart valves, does not appear to be the same for all five medicines in the class.

For cabergoline and pergolide, the Committee noted that the risk of fibrosis of the heart valves is well established, that the prescribing information for both products already includes contraindications stating that patients with evidence of heart valve problems should not take them, and that the medicines should only be used for Parkinson's disease in patients who have already taken or cannot take other treatments. Therefore, the CHMP recommended that the prescribing information for these two medicines should be updated to include:

- a warning stating that patients must be monitored for signs of fibrosis with echocardiography before treatment is started and regularly during treatment;
- a reduction of the maximum recommended dose to 3 mg per day;
- 'cardiac fibrosis' as a 'very common' side effect (seen in more than 1 patient in 10 taking either medicine).

The CHMP also recommended that companies that make these two medicines should conduct studies to look at how closely doctors follow the updated prescribing information and the impact that these changes have on the incidence of fibrosis of the heart valves.

In contrast, there is not enough evidence to determine whether there is an increased risk of fibrosis of the heart valves in patients taking bromocriptine, dihydroergocryptine or lisuride. However, since such a risk cannot completely be excluded, the Committee recommended that warnings on the possible risk of fibrosis in patients taking these medicines at high doses for long periods should be included in their prescribing information. The dose of bromocriptine should also be limited to 30 mg a day.

In addition, the CHMP recommended that a contraindication for patients with pre-existing valve problems should be included in the prescribing information for bromocriptine and dihydroergocryptine-containing medicines. There was not enough information available to allow the Committee to recommend a similar contraindication for lisuride.

The Committee noted that there is a plausible mechanism for how these medicines may cause fibrosis, through activation of '5-HT<sub>2B</sub> receptors', leading to cell division and formation of fibrous tissue, although other mechanisms might be involved. Among the ergot-derived dopamine agonists, cabergoline and pergolide activate these receptors most strongly, possibly explaining the greater risk of fibrosis seen with these medicines.

### **What are the recommendations for patients and prescribers?**

- Doctors should prescribe ergot-derived dopamine agonists according to the updated prescribing information.
- Ergot-derived dopamine agonists should not be taken by patients who have had fibrosis in the heart, lungs or abdomen. The absence of fibrosis in the heart should be verified before treatment is started.
- Patients should be monitored for the signs of fibrosis in the heart and elsewhere in the body throughout treatment, using blood tests or chest X-rays as appropriate.
- To reduce the risk of cardiac fibrosis, patients should be prescribed a daily maximum of 3 mg pergolide or cabergoline, or 30 mg bromocriptine.
- Patients or their carers who have any questions or concerns should speak to their doctor or pharmacist.