

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES
OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE
EMA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CABERGOLINE AND PERGOLIDE AND ASSOCIATED NAMES (SEE ANNEX I)

Cabergoline and pergolide belong to the class of ergot derived dopamine agonists, which also comprises bromocriptine, dihydroergocryptine and lisuride. All active substances are authorised at the level of the Member States.

Ergot derived dopamine agonists 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 and prolactinoma, and to prevent lactation and migraine.

Ergot-derived dopamine agonists have been associated with an increased risk of fibrotic disorders and valvular heart disease. This has been subject to previous reviews leading to risk minimisation measures at national level. As a result, cabergoline and pergolide containing medicinal products are indicated only as 2nd line therapy in Parkinson's disease, and their use is contraindicated for patients with evidence of valve problems.

On 21 June 2007, the UK asked the CHMP, under article 31 of Directive 2001/83/EC, as amended, to review the risk of fibrosis and cardiac valvulopathy associated with the use of all ergot-derived dopamine agonists, and to provide an opinion on whether the marketing authorisations for all products of the class should be maintained, varied, suspended or withdrawn.

The CHMP reviewed all of the information made available by marketing authorisation holders (MAH) on the risk of fibrosis and cardiac valvulopathy from clinical trials, observational studies and spontaneous reports.

Data from spontaneous reports indicate that subjects using cabergoline and pergolide are more at risk for fibrotic events and valvulopathy than subjects using bromocriptine, lisuride or dihydroergocryptine. For pergolide and cabergoline, the majority (about two thirds) of case reports of valvulopathy occurred with doses ≥ 3 mg / day.

Cases of fibrotic reactions and valvulopathy have been reported with cabergoline and pergolide during clinical trials (open label study and randomised controlled studies). However, most trials did not include echocardiographic monitoring, thus preventing a reliable estimation of incidence rates. No cases were reported for bromocriptine, dihydroergocryptine and lisuride by MAHs. Comparative trials with non-ergot and ergot derived dopamine agonist are scarce.

The majority of reported fibrotic events were not completely reversible although symptomatic improvement occurs for various reasons and indeed occasionally fibrosis may regress.

Four main observational studies looked into the risk of cardiac valvulopathy in patients treated with dopamine agonists for Parkinson's disease (Zanettini et al., NEJM, 2007; Schade et al., NEJM 2007; Yamamoto et al., Neurology 2006; Peralta et al., Movement Disorders 2006). The Schade study reported higher adjusted incidence rate ratio (IRR) for symptomatic valvular regurgitation for cabergoline, and pergolide (in particular at doses > 3 mg/day), compared to bromocriptine, lisuride, and non ergot derived dopamine agonists pramipexole and ropirinole for which no cases were reported.

The mechanism of fibrotic reaction induced by ergot alkaloids has not been completely clarified yet. The stimulation of the 5-HT_{2B} receptor agonists is considered the most plausible mechanism that induces cardiac valvulopathy, although other mechanisms may be involved. The degree of 5-HT_{2B} receptor agonism varies across ergot derived dopamine agonists and fits well with the difference in incidence rates of fibrotic events for the different ergot-products (C.Hofmann et al., Clin

Neuropharmacol, 2006). Whether this mechanism also applies to the non-cardiac fibrotic events is unclear.

At its June 2008 meeting, the CHMP concluded that the amount of evidence on the risk of fibrotic events, including valvulopathy, is not equal for all ergot-derived dopamine agonists. For cabergoline and pergolide an increased risk of fibrotic events is considered well established. For bromocriptine, dihydroergocryptine and lisuride an increased risk cannot be excluded based on the amount of evidence available.

In view of the above, the CHMP recommended the maintenance of the marketing authorisation for cabergoline and pergolide containing medicinal products with amendments to their product information (Summary of product characteristics and Package leaflet), as outlined below.

- Restriction of the maximum dose to 3 mg/day.
- Strengthening of the contra-indications, warnings and precautions for use, outlining the necessity for patients to be monitored for signs of fibrosis with echocardiography before and during long-term treatment.
- Inclusion of cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion) as “very common” undesirable effects.

The CHMP also recommended that marketing authorisation holders provide a detailed protocol (e.g. drug utilisation studies or survey done by record linkage) for the long term follow-up on the adherence to and effectiveness of the changes to the product information.

In view of the differences in the level risk amongst ergot derived dopamine agonists, the CHMP recommended that a separate opinion is issued for bromocriptine, dihydroergocryptine and lisuride.

GROUND FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLETS

Whereas,

- The CHMP considered the referral made under Article 31 of Directive 2001/83/EC, as amended, for medicinal products containing bromocriptine, cabergoline dihydroergocryptine, lisuride and pergolide,
- In view of the available data, the Committee concluded that the risk of fibrosis, including cardiac valvulopathy, is well established for cabergoline and pergolide, and is higher at doses exceeding 3mg/day. The CHMP also noted that these medicines are already indicated only as 2nd line therapy in Parkinson’s disease, and contraindicated for patients with evidence of valvulopathy.
- The CHMP recommended amendments to the relevant sections of the Summary of product characteristics and Package leaflets of the medicinal products containing cabergoline and pergolide (see Annex III).
- The conditions of the marketing authorisations are set out in Annex IV.