ANNEX II

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

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BROMOCRIPTINE, DIHYDROERGOCRYPTINE AND LISURIDE AND ASSOCIATED NAMES (SEE ANNEX I)

Bromocriptine, dihydroergocryptine and lisuride belong to the class of ergot derived dopamine agonists, which also comprises cabergoline and pergolide. 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on whether the marketing authorisations for all products of the class should be maintained, varied, suspended or withdrawn.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.

Spontaneous cases of fibrotic reactions were reported for all ergot derived dopamine agonists, especially at high doses and after long period of treatment. However, cases of valvulopathy were reported for bromocriptine, cabergoline, dihydroergocryptine and pergolide, but not for lisuride. Overall, data from spontaneous reports indicate that subjects using carbergoline and pergolide are more at risk for fibrotic events and valvulopathy than subjects using bromocriptine, lisuride or dihydroergocryptine. The majority of reported fibrotic events were not completely reversible although symptomatic improvement occurs for various reasons and indeed occasionally fibrosis may regress.

For bromocriptine, dihydroergotamine and lisuride, no fibrotic events have been reported by MAHs from clinical trials or observational studies.

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, 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-HT2B receptor agonists is considered the most plausible mechanism that induces cardiac valvulopathy, although other mechanisms may be involved. The degree of 5-HT2B 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 carbergoline 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 bromocriptine, dihydroergocryptine and lisuride containing medicinal products with amendments to their product information (Summary of product characteristics and Package leaflet), as outlined below.

- For bromocriptine and dihydroergocryptine:
  - A contraindication for patients treated for a long period and with pre-existing cardiac valulopathy .

- For bromocriptine:
  - Restriction of the maximum dose to 30 mg per day.

- For bromocriptine, dihydroergocryptine and lisuride:
  - A warning on the possible risk of fibrosis in patients taking these medicines at high doses for long periods. This warning includes recommendations for the monitoring of patients for signs of fibrosis during treatment.

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

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS 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 fibrotic events, including valvulopathy, is not equal for all ergot-derived dopamine agonists. For bromocriptine, dihydroergocryptine and lisuride, an increased risk of fibrosis, including cardiac valvulopathy, cannot be excluded.

- The CHMP, as a consequence, recommended amendments to the relevant sections of the Summary of product characteristics and Package leaflets for the medicinal products containing bromocriptine, dihydroergocryptine and lisuride (see Annex III).