

## **Annex II**

**Scientific conclusions and grounds for variation to the terms of the marketing authorisations or suspension of the marketing authorisations, as applicable, taking into consideration the approved indications for each product**

## Scientific conclusions

### Overall summary of the scientific evaluation of dihydroergocryptine/caffeine containing medicinal products (see Annex I)

On 18 January 2012, France triggered a referral under Article 31 of Directive 2001/83/EC for the following ergot derivatives containing medicinal products: dihydroergocryptine/caffeine, dihydroergocristine, dihydroergotamine, dihydroergotoxine and nicergoline. Following a national pharmacovigilance review held in 2011 new spontaneous notifications reported with some of those products identified serious cases of fibrosis and ergotism and France considered that this safety concern is not outweighed by the limited evidence of efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications:

- Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)
- Ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)
- Ancillary treatment of Raynaud's syndrome
- Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin
- Acute retinopathies of vascular origin
- Prophylaxis of migraine headache
- Orthostatic hypotension
- Symptomatic treatment of veno-lymphatic insufficiency

Dihydroergocryptine is an ergot alkaloid that has an agonist activity on D2 dopaminergic receptors and a partial agonist activity on D1 receptors. In rats, dihydroergocryptine showed to activate antioxidant enzymatic systems physiologically altered during aging. It is available in combination with caffeine that may improve the digestive absorption of this ergot alkaloid.

From the approved indications of the dihydroergocryptine containing medicinal products the ones that are in the scope of this referral procedure and are approved in at least one Member State are the following (specific wording of the indication may vary from product to product):

- Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)
- Ancillary treatment of Raynaud's syndrome

In fact, dihydroergocryptine being part of the class of ergot derivatives containing medicinal products covered by this procedure is only approved in the above mentioned indications in France and only in combination with caffeine since 1979. Dihydroergocryptine only containing products are approved in other EU Member States but their indications were not in the scope of this referral procedure (e.g. Parkinson's disease) and were excluded from this review.

The marketing authorisation holders (MAHs) submitted all available efficacy data from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation. The MAHs also submitted their own overviews and critical summaries of all spontaneous reports of fibrotic reactions (cardiac with or without pulmonary arterial hypertension, pulmonary, pleural, peritoneal, retroperitoneal, etc) and ergotism with their ergot derivatives-containing medicinal products. A review of all other available data (i.e. literature data, pre-clinical data, and other clinical data including epidemiological studies) that were relevant to evaluate the risk of fibrosis was provided where possible.

The CHMP has considered the totality of the available data on the safety and efficacy of dihydroergocryptine/caffeine.

### Clinical efficacy

Overall, for the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*", the MAHs provided 6 publications (dated from 1983 to 1998) with an adequate design (randomised, double-blind, placebo-

controlled) to support the claim for efficacy, plus one study in vascular cognitive impairment which was not further discussed. The number of patients could be considered sufficient in 4 studies (146, 203, 155 and 324 patients) and small in 2 studies (50 and 49 patients). The duration of these studies was short (2 or 3 months) considering the chronic indication approved. Patients included in most of these studies presented various very different symptoms without standardised diagnosis. In 2 studies patients presented a clinical diagnosis of mild organic brain syndrome (stage 2-3 on the Global Deterioration Scale) (Scarzella study) and an early stage senile cerebral deterioration without dementia or major dependence with respect to the environment, based on DSM-III criteria (Babeau study). This later diagnosis is not any more listed in the DSM-IV-TR. Results were heterogeneous and there was no consistency across studies. In general the CHMP was of the opinion that the methodological flaws and the absence of primary efficacy endpoint do not allow to draw conclusions on clinical efficacy or to support an indication with standardised diagnosis.

A scientific advisory group (SAG) was convened in December 2012 at the request of the CHMP during which the experts discussed, based on their clinical experience, whether this substance plays a role in the symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia). The group highlighted that the claimed indication is not used anymore in the clinical practice and that from a clinical viewpoint there is no evidence at present that there is a therapeutic need for this active substance in the treatment of cognitive and neurosensorial impairment in the elderly.

For the indication "*ancillary treatment of Raynaud's syndrome*", all the studies submitted in support of this indication were considered by the CHMP of poor methodological quality (i.e. uncontrolled, open designed, with a low number of patients (n=20-37)). The studies included young and old patients (18-78 years old) with idiopathic acrosyndrome. Only one study (Vinckier study) mentioned a small group of patients suffering from associated systemic disease. The clinical efficacy endpoints were numerous and heterogeneous with no defined primary efficacy endpoint. The studies mainly assessed functional symptoms, capillaroscopic parameters and plethysmographic parameters whose clinical relevance was considered questionable by the CHMP. There seemed to be a benefit of treatment in approximately 55-75% of patients but the CHMP concluded that these results are in fact difficult to interpret from a clinical point of view and not reliable due to the methodological limitations of the studies. The reliability and the clinical relevance of the study results was therefore questionable and preclude any conclusion on the efficacy of the product.

### **Clinical safety**

Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis. The relationship between fibrosis and serotonergic receptor activation, particularly 5-HT<sub>2B</sub> receptors by ergot derivatives is extensively described in the literature. Agonism to 5-HT<sub>2B</sub> receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. Overall, the varying affinity for serotonergic receptors with the different ergot derivatives and the therapeutic doses used may explain the differences observed for notification rates for the fibrotic reactions. Therefore, even if it is highly pharmacologically plausible that ergot derivatives acting as 5-HT<sub>2B</sub> receptor agonists may induce "serotonergic" valve disease similar to that induced by carcinoid tumours or fibrotic lesions of other tissues, it must be remembered that some ergot derivatives are not 5-HT<sub>2B</sub> receptor agonists. Therefore, other mechanisms inducing fibrosis cannot be excluded, which suggests a causal link between fibrosis and agonism of 5-HT<sub>2A</sub> and 5-HT<sub>1B</sub> receptors and also plausible effect on serotonin transporter.

The data from the reported cases of fibrosis (n=3) are limited in order to draw any firm conclusions, however, the risk cannot be excluded considering the improvement observed when dihydroergocryptine/cafeine was discontinued in one of the three reported cases of pulmonary fibrosis occurring with recommended daily dose. Under-reporting can also be suspected because the substance is marketed for a long time as well as because fibrosis is already mentioned as an adverse drug reaction in the product information.

Data provided during a referral under Article 31 in 2007-2008 (EMEA/H/A-31/881) including dihydroergocryptine showed that several cases of fibrosis either pulmonary or cardiac or retroperitoneal were suspected to be associated to the treatment with dihydroergocryptine use for Parkinson's disease treatment (involving dosage five times higher). As a note, one of the above mentioned three cases of fibrosis was reported in 2009 (i.e. after finalisation of the previous referral) which shows that the risk minimisation measures that were imposed at that point in time are not sufficient to exclude the risk.

Based on these data and based on the pharmacological plausibility, dihydroergocryptine is considered to be associated with fibrotic reactions. Moreover the severity of such adverse effects, their possible fatal outcome and the raised risk for patient to develop a fibrotic disorder with long term use according to the authorised indications should be underlined.

Regarding ergotism, there were several cases reported in the French Pharmacovigilance database where dihydroergocryptine/caffeine was the suspected drug for symptoms related to ergotism. The absence of such reports claimed from the MAH, raised questions to the CHMP with regard to the way that the data collection was performed. Considering the several reported cases of vasoconstriction and the pharmacological structure of this ergot alkaloid derivative product, ergotism cannot be ruled out.

The CHMP considered the MAHs proposals for risk minimisation measures. These included changing the prescription status, limiting treatment duration in certain conditions, contraindicating the product in patients with pre-existing fibrosis or in association with other drugs, the issuing of a DHPC highlighting the risk, a checklist for prescribers, and a pharmacological in vitro study for 5-HT subclass receptors affinity to the product. Although some of the proposed measures could help identify patients with pre-existing fibrosis, relevant concomitant medication and increased risk, the Committee pointed out that they are insufficient to avoid that some patients develop fibrosis and ergotism during treatment.

Overall, the CHMP was of the opinion that no situation could justify exposing a patient to risk of fibrosis and ergotism considering the very limited data on efficacy.

### **Benefit –risk balance**

The Committee concluded that the benefit-risk balance of dihydroergocryptine/caffeine containing products is not favourable pursuant to Article 116 of Directive 2001/83/EC for symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia) and for ancillary treatment of Raynaud's syndrome.

### **Grounds for the variation/suspension to the terms of the marketing authorisations**

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for ergot derivatives containing medicinal products in the concerned indications.
- The Committee considered the overall submitted data provided by the MAHs and the outcome of the scientific advisory group.
- The Committee considered that a potential causal association between fibrotic reactions or ergotism and dihydroergocryptine/caffeine cannot be excluded. Available data is in fact indicative of such causal relationship. The seriousness of such adverse effects and their possible fatal outcome is underlined.
- The Committee is of the opinion that the evidence for clinically significant efficacy of dihydroergocryptine/caffeine in the currently assessed indications is very limited, and therefore the potential benefit for patients in these indications is outweighed by the above identified risk.
- The Committee considered that the benefit-risk balance of dihydroergocryptine/caffeine containing products:
  - Is not favourable for symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia).
  - Is not favourable for ancillary treatment of Raynaud's syndrome.

Therefore, in accordance with Article 116 of Directive 2001/83/EC the CHMP recommends:

- The variation to the terms of the marketing authorisation for dihydroergocryptine/caffeine containing medicinal products referred to in Annex I, to delete the below indications from the Product Information (specific wording of the indication may vary from product to product and country to country) as well as any relevant reference to these indications in the Product Information, when there are other therapeutic indications approved as part of their marketing authorisation:
  - Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer’s disease and other dementia).
  - Ancillary treatment of Raynaud’s syndrome.
- The suspension of the marketing authorisation for dihydroergocryptine /caffeine containing medicinal products referred to in Annex I in the event that no other indications are approved as part of their marketing authorisation. In order to lift the suspension, MAHs must identify a specific patient population for which the benefits of the product outweigh the risk.