

## **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 dihydroergocristine 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marketing authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

Dihydroergocristine is a partial agonist of  $\alpha$ -adrenoreceptors that decreases the activity of sympathetic centres and is responsible for a peripheral adrenergic effect with an increased venous wall tone. In addition it has a pharmacological action on the serotonergic and dopaminergic receptors leading to interesting effects on cerebral metabolism. It is available in combination with raubasine that is an adrenergic and sympatholytic agent with an inhibitory effect on sympathetic centres. It produces a decrease in blood pressure and an increase in peripheral blood flow. Its effect results mainly from its  $\alpha_1$ -blocking properties. In Europe, dihydroergocristine is also available in combination with etofyllinum.

From the approved indications of the dihydroergocristine 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 visual acuity decrease and visual field disturbances presumably of vascular origin
- Acute retinopathies of vascular origin

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 dihydroergocristine.

### Clinical efficacy

The MAHs submitted 27 literature references to support the efficacy of dihydroergocristine on the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*". Of these, 18 concerned placebo-controlled trials, 2 concerned actively-controlled trials and 7 concerned open label studies.

Of the 6 randomised, double blind, placebo-controlled studies, 5 studies were not considered relevant by the CHMP because the definition of the diagnosis was not standardised, no primary efficacy criterion was selected among the multi-dimensional assessment, the number of patients per group was small (from 47 to 65), and the treatment duration was short (2 and 3 months). Results are heterogeneous and inconsistent. The CHMP was of the opinion that no efficacy conclusion could be drawn based on these studies. The most recent study (Vellas 1998 - Not published) that became available after the granting of the initial marketing authorisation, uses a standardised definition of diagnosis (patients had to present a moderate memory deficit, with a Mini-Mental State Examination MMSE > 25 and a score total > 38 and < 70 on the Mac Nair and Kahn auto-questionnaire assessing the difficulties in daily activities) and defines the primary efficacy criterion a priori (the Mac Nair and Kahn auto-questionnaire and the Gröber and Buschke test). However, in this study with adequate methodological quality standard, non-significant difference between dihydroergocristine + raubasine and placebo groups was observed.

There were 3 placebo controlled studies with a study population of 200-240 patients. Among these 3 studies, the publications by Lazzaroni et al and Aranda et al indicated superiority over placebo, while the study by Vellas et al demonstrated similar efficacy to placebo.

There are 2 further studies by Hugonot et al with population of 114-127 patients, both showing superiority over placebo. In six of the evaluable studies with population under 100 patients there were similar findings.

While it is agreed that the medical terminology used nowadays and in the past differs and that the data needs to be assessed bearing this aspect in mind, the clinical symptom of dementia is a result of various pathophysiological processes which makes pooling and comparison of the data difficult, especially when the individual studies used slightly different inclusion criteria.

All the data submitted were reviewed and considered, and though it can be interpreted as suggestive of mild efficacy of dihydroergocristine in the "*treatment of chronic cognitive impairment in the elderly*", efficacy cannot be considered as sufficiently demonstrated namely due to the inconsistency of the data generated in the larger trials.

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 indications "*ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin*" and "*acute retinopathies of vascular origin*", the few preclinical findings submitted reporting the effects of topical doses of dihydroergocristine were considered by the CHMP insufficient to support the use of dihydroergocristine as intraocular pressure (IOP) lowering agent in human or for other ocular conditions presumably of vascular origin. Moreover, it was pointed out that topical instillations of dihydroergocristine are out of the scope of this procedure. The CHMP also noted the position of one of the MAHs that due to the limitations of the data available, the ocular indication cannot be upheld.

### **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=12) are indicative of the capacity of dihydroergocristine to induce fibrotic reactions, mostly localised in the pulmonary area considering also the improvement of some patients following discontinuation of the product. Under-reporting can also be suspected because the substance has been on the market for a long time and because fibrosis is already mentioned as an undesirable effect in the product information.

Even if in some cases, confounding treatment (known to induce fibrotic reaction) have been co-administrated, the relationship between fibrotic reactions observed and treatment with dihydroergocristine cannot be excluded. It should also be underlined that reports of reduction of the extension of the fibrotic plaque a long time after dihydroergocristine withdrawal, improvements after dihydroergocristine discontinuation and positive rechallenge (symptoms re-occurring on re-administration) have been reported. This is indicative of a causal relationship between fibrosis and dihydroergocristine.

Additionally one case of retroperitoneal fibrosis was reported in the literature (concerning fibrotic plaque), and a scan performed one year after the discontinuation of dihydroergocristine revealed a marked reduction of the fibrotic plaque which was considered by the CHMP in favour of a causal relationship between the retroperitoneal fibrosis observed and dihydroergocristine. Based on these data and based on the pharmacological plausibility, dihydroergocristine 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.

In addition, on the basis of the reported cases, vasoconstriction induced by dihydroergocristine cannot be excluded.

The CHMP considered the MAHs' proposals for risk minimisation measures. These included 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 dihydroergocristine 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), for ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin and for acute retinopathies of vascular origin.

### **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 dihydroergocristine 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 dihydroergocristine 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 dihydroergocristine 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 visual acuity decrease and visual field disturbances presumably of vascular origin.
  - Is not favourable for acute retinopathies of vascular origin.

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

- The variation to the terms of the marketing authorisation for dihydroergocristine 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 from 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 visual acuity decrease and visual field disturbances presumably of vascular origin.
  - Acute retinopathies of vascular origin.
- The suspension of the marketing authorisation for dihydroergocristine 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 identified risk.