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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

Dihydroergotoxine mesilate is an ergot alkaloid, known also as codergocrine mesilate and ergoloid mesilate, which is composed of equal parts of mesilates of dihydroergocornine, dihydroergocristine, and dihydroergocryptine. The primary mechanism of action of dihydroergotoxine and other ergoloids is unclear at the present time. It acts as an agonist to dopaminergic and serotonergic receptors and an antagonist for alpha-adrenoreceptors. Dihydroergotoxine modulates synaptic neurotransmitter levels and increases blood flow to the brain; at one time, it was believed that the latter mechanism was the primary mode of action by which dihydroergotoxine exerts clinical effects.

From the approved indications of the dihydroergotoxine 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
- Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin
- Prophylaxis of migraine headache
- Symptomatic treatment of veno-lymphatic insufficiency

Dementia and dementia related indications, as well as the acute treatment of migraine, are outside the scope of this referral procedure.

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 dihydroergotoxine.

Clinical efficacy

On the efficacy side for the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*", data were presented by the MAH by sub-areas of the cognitive function diseases: cerebrovascular impairment with arteriosclerosis, cerebrovascular insufficiency and stroke; and other causes with elderly/senile impairment, primary or not otherwise specified impairment, and organic brain syndrome. The MAH submitted a number of papers with efficacy clinical studies, 2 reviews (the medical letter, 1974, Mc Donald, 1979) and one Cochrane review (2009). The Cochrane review is not relevant for the assessment as it focuses on dementia and symptoms consistent with dementia.

The publications on clinical data are old (from 1971 up to 1995). The majority of the papers are not relevant (publications not submitted, studies were open-label, not placebo-controlled and/or with intravenous use of dihydroergotoxine mesilate).

During the review, the MAH has suggested to restrict the indication to 'symptomatic treatment of chronic cognitive impairment in elderly (excluding Alzheimer's disease and other dementia)'. In the 19 clinical studies that are argued to be supportive of this restricted indication, and which included heterogeneous populations, some did not show significant effects of dihydroergotoxine. In others, only certain points of the scale to assess efficacy were significantly improved. Issues such as a high dropout level, unclear or subjective evaluation criterions and low number of patients also preclude a conclusion on efficacy based on these data.

Diagnostic and determination of the origin of cognitive impairments are difficult tasks for the modern medicine. With the current patient evaluation tools, the distinction between mild or moderate cognitive impairment and early stage of Alzheimer or of other dementia is difficult. In such cases, administration of dihydroergotoxine may delay the administration of an appropriate treatment for dementia.

The CHMP noted that patients included in studies presented various symptoms or putative diagnosis, effect was mainly assessed with subjective scores, symptoms observed were very heterogeneous and results were not consistent across studies and long-term data are not in favour of an effect of dihydroergotoxine as compared to placebo. The CHMP was therefore of the opinion that no conclusion on the efficacy of dihydroergotoxine as "Adjuvant symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)" or in another indication could be drawn.

In addition, 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*" the CHMP noted that the indication claimed by the MAH is peripheral vascular disease and that in some Members States the ancillary treatment of Raynaud's syndrome is approved for dihydroergotoxine as part of this more general indication (i.e. "peripheral vascular disease"). However, the presented studies assessed oral dihydroergotoxine in very heterogeneous vein diseases: peripheral and cerebrovascular insufficiency, chronic varicose eczema, ulcus cruris, varicose veins, venous insufficiency, cerebral vascular lesions, thrombophlebitis of the superficial veins, post-thrombophlebitis syndromes. These studies were of poor methodological quality: uncontrolled, open designed and without any well-defined primary efficacy endpoint. Consequently, it was not possible for the CHMP to draw scientific conclusions regarding the benefit of dihydroergotoxine in peripheral vascular disease based on these study results and subsequently no conclusions could be drawn for the ancillary treatment of Raynaud's syndrome.

For the indication "*ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin*", seven clinical studies have been submitted. All these old studies suffered from methodological flaws. Five were uncontrolled, open designed, without any well-defined primary efficacy objective, and they were conducted in patients with heterogeneous ocular disorders. The two comparative studies described by the MAH (Orma, 1958 and Vannas, 1958) were of poor methodological quality; moreover no information is available about the exact design or randomisation in the different groups tested. In addition, both included a small number of patients (n=48 and n=62), both were short-term studies (1-5 months and 8 months, respectively) which short term duration is

considered inappropriate to evaluate the outcome of slow progressing diseases. Based on the overall documentation provided, the CHMP concluded that the studies suffer from substantial methodological deficiencies which preclude any conclusion on the efficacy of the product.

For the indication "*prophylaxis of migraine headache*", two publications describe a double-blind, active, not placebo-controlled study on the effect of dihydroergocryptine (dihydroergotoxine is composed of a third of dihydroergocryptine) as compared to propranolol and flunarizine. In spite of the fact that propranolol and flunarizine are recognized in migraine prophylaxis, the absence of a placebo group does not allow to conclude on the efficacy of dihydroergotoxine in the prophylaxis of migraine.

In addition, 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 prophylaxis of migraine headache. Based on the clinical experience the group considered that no special population exists that could benefit from the treatment with this active substance in the prophylaxis of migraine headache. Therefore, the group was of the opinion that there is not a clearly defined population, which unsatisfactorily responds to standard migraine prophylaxis treatment, where there is a therapeutic need for this substance as alternative/last line treatment.

No data were submitted in support of the indication "*symptomatic treatment of veno-lymphatic insufficiency*" and consequently no conclusion on efficacy could be drawn by the CHMP.

Clinical safety

Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis. The relationship between fibrosis and serotoninergic receptor activation, particularly 5-HT_{2B} receptors by ergot derivatives is extensively described in the literature. Agonism to 5-HT_{2B} receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. Overall, the varying affinity for serotoninergic 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_{2B} 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_{2B} receptor agonists. Therefore, other mechanisms inducing fibrosis cannot be excluded, which suggests a causal link between fibrosis and agonism of 5-HT_{2A} and 5-HT_{1B} receptors and also plausible effect on serotonin transporter.

The data from the reported cases of fibrosis (n=9) are limited in order to draw firm conclusions, however, the capacity of dihydroergotoxine to induce fibrotic reactions, localised in the retroperitoneal, pulmonary and cardiac area cannot be excluded notably based on the absence of any other aetiology for some of the assessed cases and the mechanism of action of ergot derivatives. Moreover, three out of the nine cases were reported during the French Pharmacovigilance survey that was conducted in 2011 which shows that the risk minimisation measures that are currently in place are not sufficient to prevent the risk of fibrotic reactions.

In addition, dihydroergotoxine is composed of dihydroergocryptine and dihydroergocristine which are also considered to be associated with the induction of fibrotic reactions.

Based on these data and based on the pharmacological plausibility, dihydroergotoxine 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.

No reports of ergotism were stated, however, the CHMP questioned the appropriateness of the data collection method (i.e. non exhaustive and thus inconclusive). More specifically, the CHMP stated that apart from "ergotism" other preferred terms are also related to symptoms of ergotism (i.e paraesthesia, formication, tingling, intestinal/cerebrovascular/peripheral/tongue ischaemia, angina pectoris, coronaropathy, thoracic pain, nausea, vomiting, diarrhoea, abdominal pain, cold sensation, thrombosis, stroke, gangrene, necrosis, vasoconstriction/vasospasm, cyanosis, myalgia, muscular cramps, pain in extremities, vertigo, hypoaesthesia, numbness, headache, confusion, hallucinations). In addition, severe cases of peripheral vasoconstrictive symptoms were reported in the literature.

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 dihydroergotoxine 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 Raynaud's syndrome, for ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin, for prophylaxis of migraine headache and for symptomatic treatment of veno-lymphatic insufficiency.

Re-examination procedure

Following the adoption of the CHMP opinion during the June 2013 CHMP meeting, a re-examination request was received from one of the MAH involved in the procedure. The scope of the re-examination focused on the re-evaluation of the benefit-risk balance of dihydroergotoxine in the restricted indication proposed by the MAH which is "*symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia*".

The CHMP reviewed all available data in support of the benefit and safety on dihydroergotoxine and considered the above restricted indication proposed by the MAH.

The CHMP highlighted that "*chronic cognitive impairment excluding Alzheimer's disease and other dementia*" is not considered a generally accepted definition of a pathological condition aimed to benefit from treatment.
The CHMP reiterated that the studies presented in support of the efficacy of dihydroergotoxine were published in the seventies and eighties, with the consequent risk for publication bias, and have several limitations. Indeed, the heterogeneity of the studies submitted is such that no firm conclusions can be drawn. The CHMP considered that these studies did not provide robust evidence supporting the efficacy of dihydroergotoxine in the proposed target population. Furthermore, the fact that these studies have been performed many years ago raises methodological concerns given advances in clinical research methods and the changes in the definition of dementia/ pre-dementia conditions over time. It therefore remains uncertain whether the studied population in the selected clinical studies is representative of the proposed indication. Therefore, concerns about heterogeneity of the studied population remain. Furthermore, those reporting positive results are claiming improvement in different parameters in scales intended to capture important aspects of impaired cognition. The scales used were largely based on subjective assessment rather than formal testing. The outcome in the different components included in these assessment tools vary considerably between the studies and no general conclusions can be drawn neither on the size of possible effects nor on the clinical relevance.
In view of the above, the CHMP was of the opinion that the studies submitted could not demonstrate that dihydroergotoxine has a clinically relevant effect on patients with cognitive impairment.

The CHMP noted that the incidence of adverse events (i.e. retroperitoneal fibrosis, pulmonary fibrosis, cardiac valvulopathy, ergotism) reported by the MAH with dihydroergotoxine is low. However, the CHMP also noted that the MAH provided information only for their product (Hydergine) and that underreporting is likely. The CHMP considered that, although the risk of fibrotic reactions and ergotism associated with dihydroergotoxine is rare, it is established and these are severe adverse events with a possible fatal outcome.
The CHMP took note of the risk minimisation measures proposed by the MAH. Overall, the CHMP reiterated that the risk minimisation measures proposed by the MAH are not considered by the Committee to effectively reduce the risk of fibrotic reactions and ergotism. Fibrotic reactions have been associated to chronic use of ergot derivatives and although the reporting rate for dihydroergotoxine is low, the risk is sufficiently serious not to be dismissed particularly when considering its potential use in long-term treatment in a broad patient population.

In addition, the CHMP convened another meeting of the scientific advisory group (SAG) that took place on 16 October 2013. The SAG unanimously agreed that there is no distinct clinical entity for cognitive impairment no dementia (CIND), the diagnostic criteria and definitions have changed over time and

this wording does not correspond to a current clinically defined group. The SAG further considered that the evidence presented by the MAH was of poor quality. In the view of the SAG, it is not excluded *a priori* that the drug might be efficacious in a subgroup of well- defined patients according to current criteria, but this cannot be determined based on the information provided, which includes highly heterogeneous patient population and study outcome parameters. In general, a drug investigated in the prodromal stages of dementia would need to demonstrate improvement in cognitive function, and additionally, delay of progression to dementia. Overall, the SAG disagreed with the indication and the target population definitions proposed by the MAH.

In view of the above, the Committee considered that there is a risk for rare but severe fibrotic reactions and ergotism associated with dihydroergotoxine treatment. The Committee is of the opinion that the evidence for clinically significant efficacy of dihydroergotoxine in the proposed indication "*symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia*" is very limited. Thus the demonstrated benefit for patients in the proposed indication does not outweigh the above identified risk. The risk minimisation measures proposed were not considered by the Committee to effectively reduce the risk for the two highlighted reactions (fibrosis and ergotism) in the broad indication proposed by the MAH. Thus, the Committee concluded that the benefit-risk balance of dihydroergotoxine containing products in "*symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia*" is not favourable.

Grounds for the suspension / variation 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 and grounds provided by the MAHs and the outcome of the scientific advisory groups.
- The Committee considered that a potential causal association between fibrotic reactions or ergotism and dihydroergotoxine 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 dihydroergotoxine in the currently assessed indications as well as in the indication proposed by the MAH in the re-examination is very limited, and therefore the potential benefit for patients in these indications is outweighed by the above identified risk.
- The Committee maintained its opinion that the benefit-risk balance of dihydroergotoxine containing products:
  - Is not favourable for symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia) and in the latter proposed indication '*symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia'*.
  - Is not favourable for ancillary treatment of Raynaud's syndrome.
  - Is not favourable for ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin.
  - Is not favourable for prophylaxis of migraine headache.
  - Is not favourable for symptomatic treatment of veno-lymphatic insufficiency.

Therefore, the CHMP maintained its opinion of 27 June 2013 and therefore, in accordance with Article 116 of Directive 2001/83/EC the CHMP recommends:

- The variation to the terms of the marketing authorisation for dihydroergotoxine 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, 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.
  - Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin.
  - Prophylaxis of migraine headache.
  - Symptomatic treatment of veno-lymphatic insufficiency.
- The suspension of the marketing authorisation for dihydroergotoxine containing medicinal products referred to in Annex I if 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 medicinal product outweigh the risk.