

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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

Nicergoline is a semisynthetic ergoline derivative that seems to have an action: (i) as an α 1-adrenoceptor antagonist, it induces vasodilation and increases arterial blood flow; (ii) it enhances cholinergic and catecholaminergic neurotransmitter function; (iii) it inhibits platelet aggregation; (iv) it promotes metabolic activity, resulting in increased utilization of oxygen and glucose; and (v) it has neurotrophic and antioxidant properties.

From the approved indications of the nicergoline 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 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

Dementia and dementia related indications are excluded from 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 nicergoline.

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)*", the efficacy data were mainly provided from study publications conducted in patients with dementia (Alzheimer disease, multi-infarct dementia, vascular dementia, Parkinson disease, etc), while dementia is excluded from the scope of this referral procedure.

Overall, the study designs were adequate (randomised, double-blind, placebo-controlled), diagnoses were established according classification criteria at the time of the studies, primary efficacy scales were defined a priori (MMSE, SCAG, ADAS-Cog). Results show statistically significant difference between nicergoline and placebo in favour of nicergoline.

The MAHs considers that the most comprehensive review of nicergoline efficacy was completed in a meta-analysis performed in 2008 by Winblad et al. Indeed, this publication described the meta-analysis of 13 double-blind, placebo-controlled, randomised studies performed by the Cochrane Collaboration in 2001. This Cochrane review on efficacy of nicergoline was performed in patients with mild to moderate dementia and is therefore also outside the scope of the procedure.

The CHMP noted that none of the studies was designed to address the specific indication under question (*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*), and that the data is further weakened by publication biases and changes in the understanding of proper criteria for current diagnoses.

The MAH further provided information on six clinical comparative studies in senile cerebral insufficiency and a short description of a non-comparative study and three observational studies in support of the efficacy of nicergoline in a specific indication "*symptomatic treatment of mild cognitive impairment of vascular origin in the elderly*". The CHMP was of the opinion that overall based on these data there is some evidence of positive effects of nicergoline on cognition and behaviour in patients with senile cerebral insufficiency of different origins. However, the clinical relevance is unknown. Taking into account the limited information presented from these studies (only summary of these studies were provided), the unclear inclusion/exclusion criteria and statistical analyses employed, no conclusion can be drawn from the data provided.

The CHMP concluded that, as result, no conclusion on efficacy of nicergoline as "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*" can be drawn from the data provided.

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 intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)*" no data were submitted and as a result was considered as unsupported by the CHMP.

For the indication "*ancillary treatment of Raynaud's syndrome*", the submitted studies did not really assess nicergoline in patients with this specific indication, but were rather conducted in patients with peripheral arteriopathy. The population was old and suffered from intermittent claudication. This does not exactly reflect the indication supported by the MAH. However, the CHMP considered whether some of these studies could be used in support of the indication "*ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)*". The studies submitted have assessed nicergoline for oral or parenteral use and had heterogeneous efficacy endpoints such as: sensitivity to cold, peripheral blood flow, walking distance, pain, quality of life. Most of the studies that became available after the granting of the initial marketing authorisation were very old and of poor methodological quality, notably non-randomised and with a low number of patients. As a result, the reliability and the clinical relevance of the studies is questionable. Therefore, the CHMP was of the opinion that these substantial methodological deficiencies preclude any conclusion on the efficacy of nicergoline (oral or parenteral) on Raynaud's syndrome, and more largely in peripheral circulation disorders.

For the indications "ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin" and "acute retinopathies of vascular origin" the CHMP noted that positive clinical results (in particular regarding the progression of visual acuity) were described mainly in one open long-term study in the context of an ambulatory ophthalmological practice that involved 213 patients with heterogeneous pathologies (e.g. retina degeneration, inflammatory diseases of the retina and of the optic nerve, venous and arterial vessels occlusions, glaucoma, etc) (Hasslinger, 1986). Improvements in visual acuity were also reported in Ganescu study (46 patients of various eye conditions) but this study was not comparative. Therefore, despite the positive conclusions of the authors regarding the progression of visual acuity under a treatment with nicergoline, the CHMP considered that, in the absence of a comparison to a placebo control, no reliable conclusion can be drawn from these clinical results which referred to heterogeneous data based on small series of patients of various eye conditions. In conclusion, the CHMP was of the opinion that a couple of studies have some positive findings in the populations tested but considering the inadequate methodology, the reliability and the clinical relevance of the results is questionable. Therefore, none of the studies can be considered as conclusively supporting the evidence of efficacy in the indications under assessment.

For the indication "prophylaxis of migraine headache" the available data in migraine headache are from open label studies in a small number of patients (40 and 17 patients).

Fourty (40) patients with migraine were assessed in an open clinical study that became available after the initial marketing authorisation was granted (Prusinski, *Wiad.Lek*, 1984). The majority of them had been previously treated with various anti-migraine drugs like dihydroergotamine, pizotifen and propranolol with unsatisfactory effects. On admission to the study, patients were suffering from 1-3 attacks per week. Patients were given 10 mg of nicergoline three times daily for the first 10 days followed by 5 mg three times daily for 3-5 weeks. A complete relief of migraine attacks was achieved in 45% of patients, while a reduction of migraine attacks by at least 50% occurred in 18% patients. Nicergoline was also given to 17 patients with migraines for prevention of attacks (Prusinski, *Wiad.Lek*, 1984). In 8 cases full remission was achieved and in 3 cases the frequency and intensity of the attacks were significantly reduced. In 6 cases the treatment was ineffective. These data were considered insufficient by the CHMP to conclude on a beneficial efficacy of nicergoline in the prophylaxis of migraine headache.

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.

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_{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 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_{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.

A total of 30 cases related to fibrotic events have been reported. The main localisation of fibrosis is preferentially pulmonary area and also retroperitoneal and cardiac area.

Four cases of fibrotic events were excluded from the analysis. Insufficient information was reported in five cases precluding any meaningful assessment.

Among the 21 remaining cases, an association between nicergoline and the fibrotic event or potential fibrotic event could not be excluded. In these cases, the event occurred after 5 months to 30 years of

nicergoline treatment and in patients aged between 59 and 90 years. When documented, the reactions occurred with recommended daily dose.

Regarding cases of pulmonary reactions, the emerging number of cases and the improvement observed after nicergoline discontinuation in 10 cases with no confounding factor is in favour of a causal role of nicergoline, especially in 5 cases in which improvement was also confirmed by radiography or scanner. The improvement, when documented, was observed between 3 and 10 months after nicergoline discontinuation, without corticoid treatment in four cases.

Regarding peritoneal and cardiac fibrosis, the CHMP was of the view that the causal role of nicergoline cannot be excluded. The CHMP noted that an under-notification of the adverse events can also be suspected given that:

- Adverse drug reaction with a substance marketed for a long time is generally less reported
- Fibrosis is also a slow and insidious reaction that occurs after a long period of treatment and with delayed diagnosis

To conclude, given the cases reported for a reaction difficult to early diagnose (delayed symptoms) and probably under reported, the use of the drug at an approved dosage, added to a plausible pharmacological profile, nicergoline is considered to be associated with a risk of fibrotic reactions. In addition, given that fibrosis is a serious life threatening reaction, observed after long duration of treatment with nicergoline (a drug used in indications requiring long duration of treatment), this has an impact on the benefit-risk profile of the products. Moreover, recent cases were identified during the French survey conducted in 2011, which show that the risk minimisation measures currently in place are not sufficient to prevent the development of fibrotic reactions.

Regarding ergotism, there were no cases identified in the MAH's safety database reporting the preferred term ergotism associated with nicergoline. Nevertheless, the MAH also provided an analysis regarding all spontaneous reports for the last 40 years (n=390, including 205 medically-confirmed cases). Ninety (90) cases were found to contain terms potentially indicative of symptoms or ergotism, such as 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. Therefore, the CHMP was of the opinion that it is not possible to rule out the possibility that these actually correspond to the development of ergotism.

The CHMP considered the MAH's proposal for risk minimisation measures: the inclusion of information related to fibrosis and ergotism in section 4.4 of the Summary of Product Characteristics. However, provision of information on these events is 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 nicergoline 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 intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II), for ancillary treatment of Raynaud's syndrome, for ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin, for acute retinopathies of vascular origin and for prophylaxis of migraine headache.

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.
- 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 nicergoline 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 nicergoline in the currently assessed indications is very limited, and therefore the potential benefit for patients in these indications is outweighed by the identified risk.
- The Committee considered that the benefit-risk balance of nicergoline 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 intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II).
 - 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 acute retinopathies of vascular origin.
 - Is not favourable for prophylaxis of migraine headache.

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

- The variation to the terms of the marketing authorisation for nicergoline containing medicinal products referred to in Annex I, to delete the below indications (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 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.
- The suspension of the marketing authorisation for nicergoline 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.