27 September 2013
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Assessment report

Ergot derivatives containing medicinal products

International Non-proprietary Name: nicergoline

Procedure number: EMEA/H/A-31/1325

Referral under Article 31 of Directive 2001/83/EC

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

Nicergoline is a semisynthetic ergoline derivative (10-methoxy-1,6-dimethylergoline-8β-methanol 5-bromnicotiant). Nicergoline seems to have an action: (i) as an α1-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 different authorised forms in at least one Member State are the following: oral tablets containing 5 mg, 10mg and 30mg of nicergoline, powder and solvent for solution for injection IM/IV containing 4mg of nicergoline, powder and diluent for solution containing 10mg of nicergoline (no longer marketed).

2.2. Clinical efficacy

The CHMP considered all available data submitted from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation. Only one MAH submitted data in support of the efficacy of nicergoline.

2.2.1. Results

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

The MAH acknowledged that Alzheimer's disease and other dementia is excluded from this referral procedure and that the focus is on the symptomatic treatment of chronic cognitive and neurosensorial impairment in elderly. The MAH mentioned, though, that these symptoms (chronic cognitive and neurosensorial impairment in elderly) are associated with the progressive syndrome of dementia and Alzheimer's (AD) and vascular dementia (VaD) often coexist and there is some evidence to indicate vascular pathology may play a role in the pathogenesis of AD. Early studies conducted with nicergoline included both AD and VaD patients.

Winblad and al, CNS Drugs (2008): This is a meta-analysis covering 13 double-blind, randomised, placebo-controlled, parallel-group studies conducted in patients with a diagnosis of dementia according to criteria accepted at the time the study was conducted (over 3 decades), thus including chronic cerebrovascular disease, mild and moderate cognitive and behavioural disorders in the elderly, multi-infarct dementia, and Alzheimer's dementia. Dementias of the vascular type constituted the majority of the cases. In this study, nicergoline was given by oral administration at a daily dose of 60 mg. The duration of treatment ranged from 4 weeks to 2 years. The most widely used efficacy measurement scale was the Sandoz Clinical Assessment Geriatric Scale (SCAG) in 405 patients treated with nicergoline and 409 with placebo. Other evaluation scales, such as the Geriatric Rating Scale (GRS), Instrumental Activities of Daily Living (IADL), and Multi-Age Cluster Class (MACC), were occasionally used. Cognitive symptoms were evaluated by means of the Mini Mental State Examination (MMSE) scale and Alzheimer's Disease Assessment Scale (ADAS-Cog).

Herrman, and al, Dement Geriat Cogn Disord (1997): Patients with a diagnosis of multi-infarct dementia (Diagnostic and Statistical Manual of Mental Disorders/DSM-III), a Hachinski score> 7, and computed tomography findings compatible with a diagnosis of the vascular type, showing no recent acute focal episodes, and having an MMSE score on enrollment of between 15 and 25 (mean at baseline of 20.25 points) were treated for 6 months with nicergoline 60 mg/day or a placebo in this double-blind controlled trial. The primary endpoints were changes in MMSE and SCAG scores. After 6 months, the mean improvement in the MMSE scores of all 136 patients treated was 3.8 points for those treated with nicergoline and 1.28 points for the group treated with the placebo ($p < 0.001$). Difference between nicergoline and placebo at 6 months on the SCAG was statistically significant ($d=7.94$ points, $p<0.0001$).

Saletu, Psychopharmacology (1995): This study was conducted in 56 patients with senile dementia-Alzheimer type (SDAT) and 56 patients with multi-infarct dementia (MID) treated with nicergoline 60 mg/day ($n = 28$ in each group) or a placebo ($n = 28$ in each group) for 2 months. The diagnosis was made in accordance with the DSMIII-R and the National Institute of Neurological and Communicative Disorder and Stroke – Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria. On admission to the study, the disease was mild to moderate in severity (MMSE of 13 to 25). The principal evaluations were made with clinical global impression (CGI), MMSE, and SCAG. Difference was statistically significant in favour of nicergoline on the CGI at the end of the study ($p < 0.01$). The mean gain on the MMSE observed was 4.2 points in the SDAT group and 3.7 points in the MID group in the patients treated with nicergoline, as compared to 2.2 and 0.9 points respectively after the placebo ($p < 0.01$ in both cases). The SCAG was significantly improved in both groups treated with nicergoline as compared with minimal or no improvement in the groups treated with the placebo ($p < 0.01$ in the SDAT group and $p < 0.05$ in the MID group).

Nappi and al, Clin Drug Invest, (1997): 108 patients meeting the diagnostic criteria for mild to moderate Alzheimer's disease (MINCSD-ADRA) or MID/mixed (DSM-III-R) were randomised to treatment with nicergoline 60 mg/day or a placebo for 12 months in this double-blind study. After 6 and 12 months, the MMSE scores differed significantly between the two treatment groups ($p < 0.001$) in favour of nicergoline. The mean score relative to active treatment remained virtually unchanged for

the entire one-year period, while the placebo group showed a deterioration of 1.63 points after 6 months and 2.84 points after one year. At the end of the study, 25.5% of the patients treated with nicergoline showed improvement of 3 or more points, as compared to 4% of the patients given the placebo (p= 0.004). Sixty one percent (61%) of the patients treated with nicergoline had not shown deterioration, as compared with 36% of those who received the placebo (p = 0.002).

Two randomised, double-blind, placebo-controlled trials investigated the effect of nicergoline in elderly patients aged 50 to 85 with mild to moderate dementia (diagnosed according to the DSM-III-R). The patients were required to meet the diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorder and Stroke – Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria. One study recruited patients from a single centre in the U.S. (***Crook and al, J Neurol Sci, 1997***) while the other involved 31 centres in the U.K., Italy, Sweden, Germany, and Belgium (***Winblad and al, Clin Drug Invest, 2001***). In both of the studies, the ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale) and Alzheimer's Disease Co-operative Study - Clinical Global Impression of Change (ADCS-CGIC) scales were used as the primary efficacy parameters. In the American trial, 149 patients with an MMSE score on enrolment of 10 to 24 were treated with nicergoline 60 mg/day or a placebo for 6 months. At the end of the 6 months of treatment, a significant effect ($p < 0.035$) was observed on the ADCS-CGIC score of the subjects analysed in favour of nicergoline. Effect on the ADAS-Cog score was not found to be statistically different between the two groups of treatment.

In the European multicentre study, 346 patients with MMSE scores ranging from 12 to 23 were enrolled and randomly assigned to treatment with nicergoline (30 mg twice daily) or a placebo. At the end of this period, the patients were asked to continue double-blind treatment on a voluntary basis for an additional six months; 196 patients were given the option of extending the study on a double blind basis, while 153 accepted to continue treatment with nicergoline administered on an open label basis. The difference in ADAS-Cog scale scores between the drug and placebo reached statistical significance after both 3 and 6 months of treatment. At 6 months, it was 1.55 for the cognitive subscale (ADAS-Cog) and 2.0 points for the total ADAS score. The difference in ADCS-CGIC scores was not significant. The ADAS-Noncog, IADL (Instrumental Activities of Daily Living), and Physical Self-Maintenance Scale (PSMS) scores did not show significant changes in any of the treatment groups. In the 196 patients who continued treatment during the extension of the study by 6 months on a double-blind basis, the difference in ADAS-Cog scores in the two groups increased to 1.80 and 2 points at 9 and 12 months respectively.

The MAH further concentrated on the efficacy of nicergoline in restricted clinical practice indication "*symptomatic treatment of mild cognitive impairment of vascular origin in the elderly*", leaving out the neurosensorial impairment indication. In order to support this indication, the MAH provided some limited information of 6 clinical comparative studies (including sub studies) in senile cerebral insufficiency: two sub-studies of study 761i, Granada study, two sub-studies of study 742i and study 743i. In addition, short description of non-comparative study 751i and three observational studies were presented. Only comparative studies are discussed here.

Study 761i

These studies were multicentre double-blind placebo controlled clinical trials comparing the efficacy and safety of nicergoline 20 mg t.i.d. in the treatment of senile cerebral insufficiency. The first trial (trial 1) was performed using a cross-over design and lasted for 8 weeks. The second (trial 2) had a parallel group design and ranged from 3 – 6 months, with a minimum of 3 months. In both trials rating scale for the assessment of efficacy (SCAG scale) was administered and vital signs for the assessment of safety were measured before, 15 days after the beginning of wash-out, then monthly until the end of the study period.

The supposed pathogenesis of the cerebral impairment has been evaluated by the Hachinski Ischemic Score as follows: degenerative (HIS < 4), vascular (HIS > 7) or mixed pathogenesis (HIS = 5, 6). Eighteen centres participated to trial 1 and enrolled 217 patients of which 185 patients were evaluated for efficacy. For trial 2 there were 82 nicergoline and 80 placebo patients evaluated for efficacy. The scores of the individual items were then summed both globally (total SCAG, items from 1 to 18) and in five clusters according to Singer and Hammed as follows: cognitive dysfunction (1+2+3+4), affective disorders (5+6+7), apathy (8+12+13), interpersonal relationships (9+10+11+14), and somatic functioning (16+17+18). Furthermore another cluster (items from 5 to 14) larger than those previously considered was used to evaluate the affective and behavioural disorders.

In both trials an appreciable response to placebo was initially observed and was not substantially different to nicergoline. The MAH noted that after 2-3 months the time course of response to each treatment became very different: the symptoms assessed by SCAG scale showed a further progressive

improvement only on nicergoline, whereas they became stabilised or rose again towards their baseline values on placebo. Statistical analysis confirmed that the active drug was more effective than placebo in both trials with significant differences between treatments with regard to the SCAG total score, which is a valid overall assessment of senile cerebral impairment, and to some main clusters (all but apathy and somatic functioning in trial 1 and that indicative of affective and behavioural disorders of patients in trial 2). The MAH further noted that the size of these differences could seem clinically modest, but not negligible in the light of the specific morbidity involved, where the possibility of stopping or slowing the progressive worsening course of the illness is always considered a positive result.

Granada Study
This was a double-blind, placebo controlled, randomised clinical study. Nicergoline 20 mg t.i.d. was administered for 6 months to 21 institutionalised patients with senile cerebrovascular insufficiency. The SCAG was used to assess therapeutic responses. The scores of the individual items were then summed both globally (total SCAG, items from 1 to 18) and in 6 clusters according to Singer and Hammed as follows: cognitive/intellective dysfunction (1+2+3+4), affective disorders (5+6+7), apathy (8+12+13), interpersonal relationships (9+10+11+14), somatic functioning (16+17+18) and personal care (15).
No statistically significant differences were seen from baseline values in the placebo group for any variable at any observation time. All variables in the nicergoline treated group showed significant changes from the second month of treatment.
For some variables (total SCAG score, cognitive dysfunction, apathy and interpersonal relationships) the observed improvement was statistically significant at one month of treatment.

Study 742i
These were two placebo-controlled clinical trials in patients with senile cerebral insufficiency. The first trial (trial 1) was performed using a cross-over design and lasted for 8 weeks with 12 patients and the second (trial 2) a parallel group design for a minimum of 6 months with 20 patients (with a range of 6-12 months). In both trials rating scale for the assessment of efficacy (SCAG scale) was administered and vital signs for the assessment of safety were measured before, 15 days after the beginning of wash-out, then monthly until the end of the study period. Throughout all the study period monitoring of adverse events were performed.
The scores for the single signs or symptoms were summed up (SCAG total: 1+18) and grouped also as "clusters" based on the particular aspects tested, defined as follows: cognitive disorders (1 + 2 + 3), affective disorders (5 + 6 + 7), apathy (8 + 12 + 13), interpersonal relationships (9 + 10 + 11 + 14), poor self-care (15) and somatic disorders (16 + 17 + 18).
The MAH noted that the overall results obtained with nicergoline in the two experimental groups consisted of a reduction in the symptomatology (SCAG-total) on the average by 25%. Nicergoline efficacy was more evident in the trial conducted according to a cross-over design. The placebo effect - almost absent in the cross-over trial - appeared in the parallel groups with differences with respect to nicergoline in the order of 10% that did not attain the level of significance for all factors. Analysis of variance conducted on monthly measurements vs basal values showed significant differences in favour of the test drug as regards SCAG-total, cognitive disorders, apathy and self-care.

Study 743i
This was a double-blind, randomised placebo controlled trial lasting for a minimum of 3 months with an additional 3 month follow-up in patients with senile cerebral insufficiency of mild degree. Nicergoline was compared to placebo in parallel groups of 20 patients. The scores for the single signs or symptoms were summed up (SCAG total: 1+18) and grouped also as "clusters" based on the particular aspects tested, defined as follows: cognitive disorders (1 + 2 + 3), affective disorders (5 + 6 + 7), apathy (8 + 12 + 13), interpersonal relationships (9 + 10 + 11 + 14), poor self-care (15) and somatic disorders (16 + 17 + 18).
The data resulting from this trial conducted according to a "between patients" experimental design under double-blind conditions, lead to the conclusion that nicergoline administered at the dose of 60 mg/day, even in prolonged courses, is well tolerated and achieves beneficial effects on the disorders associated with senile cerebral insufficiency. Distinctively better responses were obtained in the nicergoline group with statistically significant variations to the better for all items without exception in the order of 20 to 30% compared to basal values. As the treatment proceeds in time, the improvement in the symptomatology becomes progressively more evident, and by the end of the third month is in the order of 20 to 30% with respect to basal values compared to 10% obtainable with placebo. Neglect of self-care and apathy responded best to the treatment.

The MAH also submitted a few studies in support of Parkinson's disease, equilibrium disorders, cochlear and vestibular disorders but these studies were not relevant to the indication under question.

Ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)

No data were submitted in support of this indication. One of the MAHs that have this indication as part of their marketing authorisation has already informed the National Competent Authorities of their intention to stop commercialisation of the product.

Ancillary treatment of Raynaud's syndrome

Raynaud's syndrome is separated into two categories: an idiopathic variant, called Raynaud's disease (RD), and a second variant, which is associated with other diseases or other known causes of vasospasm. Causes of secondary RD are collagen vascular disease, arterial occlusive disease and blood dyscrasias, among others. Recommended treatment comprises different treatment options, including the cessation of smoking, avoiding unnecessary exposure to cold and α-adrenergic blockers.

In a group composed of 219 patients, the differences between nicergoline and dihydroergotoxine were compared. Differences and variation of the following 15 symptoms were taken into account: asthenia, headache, vertigo, tinnitus, impaired vision, decreased concentration, memory disturbances, agitation and mental confusion, personality disorders, affective instability, increased sensitivity to cold in peripheral arteriopathy, sensory processing disorders and intermittent claudication. It was concluded that patients treated with nicergoline showed a higher percentage improvement rate as opposed to cases that remained unchanged or worsened as compared to dihydroergotoxine treated patients. Ten of the 15 symptoms showed an improvement by the following average percentages: asthenia 67%, headache 76%, vertigo 82%, tinnitus 68%, impaired vision 66%, personality disorders 37%, increased sensitivity to cold in peripheral arteriopathy 100%, motor deficit 61%, and intermittent claudication 76%. Moreover, nicergoline showed superior efficiency or at least an equal efficiency to the drug to which it was compared (***Baldoni et al., Mars y Nebuloni, Melini, Corcia, Cavalca***).

Truera et al: The effects of a single intravenous dose of nicergoline 3 mg was studied in patients with peripheral obliterative arterial disease of the lower limbs. An increase in blood flow was observed in arterial disorders, and was greater in arteriosclerotic patients than in diabetic patients. In addition, peripheral blood flow was also evaluated in a patient group with diffuse arteriosclerosis, after being treated with oral nicergoline 15 mg/day for 30 days. This group also showed a clinical improvement with notable vasodilatation, higher blood flow and a decrease on the peripheral resistance.

Meilhac et al: This is a multicenter, randomised, double-blind parallel study using 2 groups to compare the effects of nicergoline (60 mg/day) and naftidrofuryl (300 mg/day) on quality of life and functional discomfort of 131 patients with intermittent claudication. Patients were asked to complete a questionnaire on the quality of life, a visual analogue scale (VAS) to assess the functional disorders, and to quantify the number of steps taken on a flat surface before the onset of pain. After 6 months of treatment, intra-group analysis confirmed a significant improvement ($p < 0.0001$) in both treated groups in quality of life and functional disorders. In the analysis between groups, a statistically significant improvement was observed in favour of nicergoline in the onset of pain ($p = 0.003$), functional discomfort (VAS) ($p < 0.05$), and distance covered in a flat surface ($p = 0.013$). The other variables, in particular the total score on the self-administered questionnaires, confirmed that impression, although this was not a significant difference ($p = 0.136$). The data confirmed the superiority of nicergoline in terms of quality of life. The safety and tolerability was good, similar and comparable, in both groups.

Boismare et al: This is a crossover study with 11 diabetic patients with arteritis to compare the effects of nicergoline (2.5 mg intravenously) or placebo on hemodynamic and metabolic parameters after an aerobic test. The hemodynamic changes after exercise testing with placebo administration were typical: increased systolic blood pressure (SBP), heart rate (HR), and oxygen requirement PO_2max (SBP x HR). Following nicergoline administration, only an increase in arterial systolic pressure was produced, while the cardiac frequency and oxygen requirements remained unchanged. Lactic acid concentrations (H^+) after exercise testing and after treatment were significantly higher ($p < 0.01$) than after exercise without treatment. Overall results showed a hemodynamic and metabolic statistically significant increase ($p < 0.01$) of exercise tolerance in diabetic patients with peripheral artery disease after treatment with nicergoline over placebo, an effect previously observed in healthy subjects.

Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin & acute retinopathies of vascular origin

A summary of the clinical studies submitted in support of the ophthalmological indications is presented below.

Hasslinger (1986): This open-label, long-term study in the context of ambulatory ophthalmological practice with nicergoline (10 mg 3 times daily for 14 days, 5 mg 3 times daily thereafter) included 213 patients with degeneration of the retina, inflamed retina or optic nerve, impaired binocular fusion or occlusions. The treatment lasted for between 6 and 24 months. In a group diagnosed with degeneration of the retina, results from 135 patients were analysed separately, dividing the disease into 2 stages: early stage – macular and para-macular dysphoric foci and pigment irregularities; and late stage – advanced degeneration of the centre of the retina.
Results from Early Stage patients: the improvement in visual acuity was highly significant in this group. No further deterioration in visual acuity occurred up until the end of the period of observation. The improvement in the ophthalmological findings (examination of the fundus) was already highly significant after the first 14 days, but was seen to almost the same extent up to 154 days. Even after that, the pathological retinal changes regressed in a decreasing number of cases. In addition to the unaltered findings, a further deterioration occurred in only 8 right and 14 left eyes.
Results from Late Stage patients: in this group, the increase in the visual acuity was also highly significant and remained almost constant up to the end of the observation period. An improvement in the morphological changes was only seen in a few eyes here. Moreover this was confined to the marginal area around the completed degenerative process and peripheral dysphoric foci.

Several short-term, open-label cohort studies have assessed the efficacy of nicergoline added to topical β-adrenoceptor antagonist therapy in patients with open-angle glaucoma by recording cortical potentials and electro-retinographic signals evoked by patterned stimuli, that is, visual evoked potentials (VEPs) and the pattern electroretinogram (PERG), respectively.

Nicergoline 30 mg twice daily for 30 days induced significant decreases in peak latencies and increases in peak amplitudes in 30 eyes (*Parisi et al, Protti et al*).

Along with these improvements in retinal function and visual cortical responses, a significant reduction compared with baseline values in retinocortical time, defined as the difference between the VEP P100 and the PERG P50 peak latencies, was found after 30 days. This indicated improvements in post-retinal neural conduction. All these effects disappeared within 45 days after discontinuation of the treatment. Interestingly, no significant changes in intraocular pressure, either with respect to any individual patient or in terms of mean values, were found (*Parisi et al*).

Similar changes in PERG latencies (–6.0%, p = 0.0001) and amplitudes (+31.0%, p =0.0002) were observed in a longer term, open-label study of 16 patients (32 eyes) with glaucoma who were treated with nicergoline 30 mg twice daily for 60 days (*Parisi et al, Hasslinger et al*).

Protti (1998): In this study, additional analysis by colour Doppler imaging revealed that nicergoline influenced the resistance index, probably through its α-adrenoreceptor antagonist actions, with consequent enhancement of ocular region perfusion. The mean resistance index for the central retinal artery, the posterior ciliary artery and the ophthalmic artery was reduced from 0.69 to 0.64 (p = 0.01), from 0.68 to 0.65 (p = 0.01) and from 0.73 to 0.72 (p = 0.24), respectively.

Borgioli (1979): In this study, the therapeutic efficacy in 37 patients with various eye diseases was tested by administering nicergoline orally at a dose of 30 mg/day for 30 days and 20 mg/day as maintenance dose for 60-120 days. Positive results were observed in cases of arterial obstructions, venous thrombosis, diabetic retinopathies, senile macular degenerations, papilla ischaemic oedema, and central serous chorioretinopathies.

Ganescu (1982): Over a 40 day period, 46 patients with senile or arteriosclerotic macular degeneration were treated with nicergoline. At the end of the treatment the therapeutic efficacy of nicergoline on the eye background, visual field and visual acuity was tested and a statistical analysis was made of the results. Blood pressure was controlled. Final investigation resulted in no change in the eye background and blood pressure. Thirty-one (31) patients showed a distinctive ($p<0.01$) improvement in visual acuity from 0.1 up to 0.3; visual field improved in 15 patients.

Parisi (1999): The retinal dysfunction and the delayed visual cortex responses shown by patients affected by glaucoma can be objectively assessed by Pattern Electroretinogram (PERG) and Visual Evoked Potentials (VEP) recordings.
This study aimed to evaluate the effects of nicergoline on the retinal function and on the visual cortical responses in glaucoma patients. Sixty (60) patients (mean age 44.6 +/- 3.7 years) with open angle glaucoma were enrolled. The patients were divided into 2 groups: NG Group, where 30 patients were treated with nicergoline (2 cps/day) for 30 days; and CG Group, where 30 patients were not treated. Simultaneous recordings of PERG and VEP were performed in NG patients at the baseline, at 30 days after treatment with nicergoline (day 30), and at 45 days from the end of the treatment (day 75). PERG and VEP were recorded in CG patients at the baseline and after 30 and 75 days. The visual stimulus for recording PERGs and VEPs was a checkerboard whose elements subtended a visual arc of 60' and 15' with a 70% contrast, and alternated at a frequency of 2 Hz.
At the baseline, none of the electrophysiological parameters observed in NG Group patients differed ($p > 0.05$) from those of CG Group patients. At days 30 and 75, in CG Group patients the values of the PERG and VEP parameters were unmodified ($p > 0.05$) with respect to the baseline. In NG Group patients, the 30-day treatment period with nicergoline induced a significant ($p < 0.01$) improvement of the PERG and VEP parameters. At day 75 all the electrophysiological parameters of NG Group did not differ significantly ($p > 0.05$) from those at the baseline. In conclusion, treatment with nicergoline induces an improvement of the retinal function and of the visual cortical responses in patients affected by glaucoma. This effect disappears within 45 days after the suspension of the treatment.

Prophylaxis of migraine headache

Data in support of prophylaxis of migraine headache with nicergoline are limited and are presented below.

Fourty (40) patients with migraine were assessed in an open clinical study (*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 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.

2.2.2. Discussion

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

The CHMP noted that efficacy data were mainly provided from study publications conducted in patients with dementia (Alzheimer disease, MID, 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 MAH 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.

Ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)

The CHMP noted that no data were submitted for this indication and as a result was considered as unsupported.

Ancillary treatment of Raynaud's syndrome

For Raynaud's syndrome, the MAH presented the pathogenesis, and recalled that recommended treatment comprises different treatment options, including the cessation of smoking, avoiding unnecessary exposure to cold, and α-adrenergic blockers, such as nicergoline.

However, the submitted studies did not really assess nicergoline in patients with Raynaud's syndrome, 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 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.

Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin & 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*). In this study, the treatment lasted from 6 to 24 months. Improvements in visual acuity were also reported in Ganescu study (46 patients of various eye conditions) but no English translation is available, and according to the published English summary, 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.

As pointed out also by the MAH, the clinical studies focused on the pharmacodynamic effects of nicergoline: short-term, open-label cohort studies have assessed the efficacy of nicergoline in patients with open-angle glaucoma by recording cortical potentials and electro-retinographic signals (visual evoked potentials (VEPs) /pattern electroretinogram (PERG)) which nevertheless cannot replace the observed deficit of relevant comparative clinical efficacy data.

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.

Prophylaxis of migraine headache

The CHMP commented that the available data in migraine headache are from open label studies in a small number of patients (40 and 17 patients). 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.

2.3. Clinical safety

The MAHs 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.

2.3.1. Results

Risk of fibrosis
A search of cases evocative to fibrotic reactions was performed by the MAHs and the data retrieved are summarised as follows.

A total of 30 cases related to fibrotic events have been reported, where 25 were medically confirmed and 5 were non-medically confirmed. The potential fibrotic events most commonly reported (> 1 occurrence) were pulmonary in nature and included pulmonary fibrosis (9 cases), interstitial lung disease (6 cases), pleural effusion (6 cases) and pleural fibrosis (5 cases).

Four cases of fibrotic events were excluded from the analysis. One case of pleural effusion was attributed to patient's underlying cardiac disorder and one case of eosinophilic pleurisy was attributed to co-suspect donepezil by reporting physician. One case of hydronephrosis was most likely to be related to patient's underlying cervical cancer. The case of myelofibrosis in a patient with a history of breast cancer could also be excluded from the analysis on the type of fibrosis.

Insufficient information was reported in five cases precluding any meaningful assessment. Missing information included patient medical history, any concomitant medications, any laboratory or radiographic test results, action taken in response to event and/or event outcomes.

Among the 21 remaining cases, an association between nicergoline and the fibrotic event or potential fibrotic event could not be excluded. It was noted that:

- One case of interstitial pneumonitis presented a Drug Lymphocyte Stimulation Test with nicergoline
- For the 4 cases retrieved from literature, 3 cases presented bilateral posterior pleural thickening. Of note, two of them presented thickened parietal pleura by parallel layers of fibroblasts and intervening fibrosis with sparse inflammatory cellular infiltrate. For the last published case, the same histology of pleura was observed and it should be underlined that the bilateral pleural effusion was associated with pleural and pericardial thickenings.
- The limited information provided for the case presenting pleurisy/pleural effusion do not allow to exclude a pulmonary fibrotic event.
- The limited information for the case presenting hydronephrosis do not allow to exclude a fibrosis of parietal lamina of urethra.

The 21 reported cases where an association between nicergoline and fibrotic event or potential fibrotic event could not be excluded occurred after 5 months to 30 years of nicergoline treatment 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 documented (3 cases of pulmonary fibrosis, 5 cases of pleural thickening, 1 case of interstitial pneumonitis, 1 case of pulmonary hypertension) 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.

The MAH listed several co-suspect drugs but only amiodarone is suspected to represent confounding factors for pulmonary fibrosis and dantrolene can be suspected to induce pleural effusion. All other concomitant treatments are not co-suspected drugs based on the knowledge up to date. More specifically, the two isolated published cases involving carbamazepine are likely not sufficient to affirm any causal link between carbamazepine and pulmonary fibrosis. Moreover, several risk factors were mentioned by the MAH (such as stroke, organic brain psychosyndrome, Alzheimer disease) but cannot be considered as confounding factors for pulmonary fibrosis.

Outcomes were reported in 17 cases. For 12 cases, improvement has been reported after nicergoline discontinuation. Indeed, it should be noted that for the 4 published cases of pleural thickening, the clinical and radiological improvement after nicergoline withdrawal is in favour of a causal role of nicergoline. The case with the positive Drug Lymphocyte Stimulation Test with nicergoline is in favour of a causal link between nicergoline and interstitial pneumonitis, which is known to possibly worsen in pulmonary fibrosis. Moreover, there was one case of death after diagnosis of pulmonary fibrosis suspected to be linked to nicergoline and amiodarone treatments.

Only one case of hydronephrosis has been reported in an 80 year-old female patient and no case of cardiac fibrotic reaction has been reported. However, in one published case of pleural effusion, pericardial thickening was observed over pleural thickening. It cannot be excluded that the observed cardiac fibrotic event was due to long term treatment with nicergoline.

Overall, among the 30 provided cases, 21 cases reported confirmed fibrotic events or were compatible with fibrotic events probably linked to nicergoline. When documented, the events occurred with recommended daily doses. The main localisation of fibrosis is preferentially pulmonary area and also retroperitoneal and cardiac area.

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.

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.

2.3.2. Discussion

Risk of fibrosis

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 commented 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

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.

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.

Ergotism

Based on the provided data, 90 cases with terms potentially indicative of symptoms of ergotism have been reported. Even if no case was reported with the actual term ergotism, 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.

2.4. Overall benefit/risk assessment

The CHMP has considered the totality of the available data on the safety and efficacy of nicergoline.

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.

Therefore no conclusion on efficacy of nicergoline in the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly"* can be drawn from this data.

The MAH further provided information on six clinical comparative studies in senile cerebral insufficiency and short description of 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.

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 "a*ncillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)*" no data were submitted and as a result it 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 presented studies 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 "a*ncillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin*" and "*acute retinopathies of vascular origin*" the CHMP commented 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). While the studies provided seem to indicate an improvement for patients on nicergoline, 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.

On the safety side, 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.

A total of 30 cases related to fibrotic events have been reported with nicergoline. 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-risl balance 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, even if no case has been reported with the actual preferred term “ergotism”, the CHMP stated that the other preferred terms could also be related to symptoms of ergotism. Ninety (90) cases with terms potentially indicative of symptoms of ergotism have been reported so the CHMP was of the opinion that ergotism cannot be ruled out.

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.

2.5. Communication plan

The CHMP was of the opinion that a ‘Dear healthcare professional’ communication (DHPC) should be disseminated by mid/end of July 2013 to inform prescribers of the main conclusions of this review. The wording of the DHPC is to be agreed between the marketing authorisation holders (MAHs) and the national competent authorities (NCAs).
As part of this referral procedure, the CHMP agreed on some key elements to be included in the DHPC which are described below:

- Restriction of indications for nicergoline-containing medicinal products/ suspension where applicable
- Risk of fibrotic reactions and ergotism
- Limited evidence of efficacy in the indications reviewed
- Benefits of nicergoline-containing medicinal products no longer outweigh their risks

2.6. Changes to the product information

The CHMP concluded that all references to the below mentioned indications should be deleted from the relevant sections of the summaries of product characteristics and package leaflets (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

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, 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.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.