

18 December 2013 EMA/750630/2013

Assessment report

Ergot derivatives containing medicinal products

International Non-proprietary Name: dihydroergotoxine

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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

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.

Dihydroergotoxine products are approved for oral use in different pharmaceutical forms (tablets, capsules, oral drops, oral solution). The approved strengths and recommended doses are not harmonised across the EU.

2.2. Clinical efficacy

The CHMP considered all available data submitted by the MAH from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation.

2.2.1. Results

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

In support of this indication, clinical data were presented under the following sub-areas of the cognitive function diseases: arteriosclerosis, cerebrovascular insufficiency, stroke, elderly/senile impairment, primary cognitive impairment, "organic brain syndrome", memory impairment. In addition, some results following a review from Cochrane were presented.

Arteriosclerosis

The MAH referred to 6 papers reporting the results of clinical trials (which were not actually presented in detail) as well as two reviews ("The Medical Letter", 1974 – no Author mentioned and a publication by McDonald, 1979). Among the 6 papers, two involved old and open-label studies, i.e. Garagnani Sciarretta B et al, 1974 and Memin Y, Rigal P, 1971. The rest of the papers mentioned were the following.

Bazo AJ (1973): This double-blind, not placebo-controlled study included 66 elderly patients with various "complaints of the aged" attributable to cerebral arteriosclerosis with cerebrovascular insufficiency. Patients received dihydroergotoxine (3 mg) or papaverine (300 mg) during 12 weeks. Effects were evaluated on a 17-item rating scale.

Thibault A (1974): This randomised, double-blind, placebo-controlled, 12-weeks study included 48 institutionalised elderly patients with symptoms attributable to cerebral arteriosclerosis or chronic brain syndrome. No primary efficacy endpoint was defined. Eighteen target symptoms were evaluated with a 7-point rating scale per symptom. Comparing the 2 treatment groups, significant differences in favour of the dihydroergotoxine group occurred in 13 target symptoms (appetite, dizziness, sleep difficulties, fatigability, mobility, degree of nursing time, irritability, restlessness, sadness or depressed, recent memory, interest in activities, appearance, initiative) with a mean score difference between 0.67 and 2.15 points.

Rehman SA (1973): Two double-blind, randomised, placebo controlled studies were conducted in patients with mild to moderate symptoms of cerebral arteriosclerosis or senile dementia. Selection for inclusion was made on the 10 factors 5-point Crichton Royal Behavioural Rating Scale. The first trial was a cross-over study, included 60 patients and failed to demonstrate superiority of dihydroergotoxine.

The second trial was on parallel groups and randomised 43 patients to dihydroergotoxine or placebo group during 12 weeks. No primary efficacy endpoint was defined. Statistically significant difference in favour of dihydroergotoxine was observed on the number of patients showing a 1 or 2 point improvement for 5 symptoms among 10 (mobility, orientation, restlessness, dressing, and continence).

Bargheon J (1973): This double-blind, randomised, placebo-controlled, 12-weeks study included 120 patients between 60 and 85 years old with cerebral arteriosclerotic or cerebral degeneration. Effect was evaluated on the Crichton Geriatric Behaviour Rating Scale. After 12 weeks of treatment, the mean global improvement was 15% in the dihydroergotoxine group and 1.8% in the placebo group. The difference between groups was statistically significant on the per cent (%) change of score for 13 items out of 17. Numerical scores were not provided and clinical relevance could not be assessed.

On the two supplementary reviews provided by the MAH, in the first publication ("The Medical Letter", 1974 – no Author mentioned) the conclusions were that: "There is no convincing evidence that dihydroergotoxine has any value in the treatment of cerebral arteriosclerosis or senile behaviour".

The second publication (*McDonald*, **1979**) is a review of 26 double-blind studies (20 placebo-, 4 papaverine-, 1 piribedil- and 1 multivitamins- controlled studies) which investigated the efficacy of dihydroergotoxine in a total of 1,409 patients with mild to moderate degree of symptoms attributed to or associated with either cerebral arteriosclerosis, cerebrovascular insufficiency, or senile mental deterioration. Fifty-two percent (52%) of patients received dihydroergotoxine. The most common

dosage was either 1 mg three times daily (t.i.d) or 1.5mg t.i.d. the study duration was 12 weeks for 18 studies, 3-6 weeks for 3 studies and up to 15 months for 5 studies. The main assessment methods employed were either clinical rating scales (for example the Sandoz Clinical Assessment Geriatric and the Crichton Royal Behavioural Rating Scale), mental status evaluation (Mental Status Check List), electroencephalography, cerebral circulation time or a combination of two or more of these methods. No difference was observed between dihydroergotoxine and placebo in 2 studies and between dihydroergotoxine and placebo in 2 studies and between dihydroergotoxine and placebo in 2 studies and between

Cerebrovascular insufficiency

The MAH referred to 19 papers reporting the results of clinical trials (which were not actually presented in detail). Of the 19 studies, 11 were open-label and without comparator. Eight were randomised, double-blind and placebo-controlled studies. One of them is presented in the above paragraph on arteriosclerosis (Bargheon, 1973) and another (Steurer, 1989) was not provided by the MAH. In addition, the most relevant trial as claimed by the MAH (Wolmark, 1982) is again an open-label study without comparator. The remaining 6 randomised, double-blind and placebo-controlled studies could be summarised as follows.

Banen (1972): This study was conducted in 78 patients (65-96 years old) with mild to moderate symptoms of cerebrovascular insufficiency (CVI). Patients received placebo or dihydroergotoxine (1 mg t.i.d) for 12 weeks. Twenty (20) symptoms were evaluated on cognitive and intellectual capacities, clinical status (physical complaints), and attitude and behaviour. Difference between dihydroergotoxine and placebo was statistically significant for 7 items (irritability, sociability, depressive mood, anorexia, emotional lability, bothersomeness, and cooperativeness).

Ditch (1971): This study included 40 patients (mean age 84.7 years) with mild to moderate degrees of mental deterioration diagnosed as due exclusively to either cerebral arteriosclerosis or simple senile cerebral degeneration. They received dihydroergotoxine (1 mg t.i.d) or placebo for 12 weeks. Difference between dihydroergotoxine and placebo was considered significant by the authors with p<0.10 or better for 6 items on a total of 32.

Jennings (1972): This study included 50 patients (mean age 80.5 years) with moderate degree of symptoms of CVI. They received dihydroergotoxine (1 mg t.i.d) or placebo for 12 weeks. Changes in clinical status were determined by the rating of 17 symptoms on a Clinical Status Check List. Difference between dihydroergotoxine and placebo was considered significant by the authors with p<0.10 or better for 12 items.

McConnachie (1973): This study included 58 patients (mean age around 81.5 years) with mild to moderate symptoms of CVI or senile dementia. They received dihydroergotoxine (1.5 mg t.i.d) or placebo for 12 weeks. Several symptoms/factors on physical manifestations, daily living activities, attitude and mood, and motor activity were evaluated. Difference between dihydroergotoxine and placebo was statistically significant (p<0.05) on 3 symptom complexes (Physical, Mood and Motor activity).

Paux (1975): This study included 50 patients with CVI for 12 weeks. Thirteen (13) symptoms were assessed. Difference between dihydroergotoxine and placebo was statistically significant for 5 symptoms.

Rao (1972): This study included 57 patients (mean age 78.3 years) with CVI associated with cerebral arteriosclerosis for 12 weeks. Several methods were used to evaluate the patient's response to treatment: one checklist of 19 symptoms and signs (difference significant between dihydroergotoxine and placebo for 12 items), the Mental Status Check List with 6 items (difference significant for 2 items), and clinical judgment.

<u>Stroke</u>

The analysis of the literature yielded 4 specific papers reporting the results of clinical trials (3 of which double blind and placebo controlled). The age of the patients started from 55 years, while the daily dose went from 3 to 6 mg for treatment duration between 2 weeks and 6 months.

A paper (*Tohoku, 1990*) reports that three female patients aged from 74 to 79 with multi-infarct dementia were studied using positron emission tomography (PET) to assess the effect of dihydroergotoxine mesilate on cerebral glucose metabolism. The cerebral glucose utilization (CMRGIc) of each patient was evaluated by PET scan using 2-deoxy-[18F]-2-fluoro-D-glucose (FDG). Following the first PET study, 0.04 mg/kg of dihydroergotoxine mesilate was injected intravenously with 250 ml

saline solution, and then the second PET study was performed. The CMRGIc was determined from the images of the PET scan and the radioactivity of 18F in the plasma. After the administration of dihydroergotoxine mesilate, the value of CMRGIc increased significantly in the cerebral cortex and basal ganglia (p less than 0.05) compared with values before the administration, but no significant increase was found in the centrum semiovale. According to the authors, these results suggest that dihydroergotoxine mesilate stimulates glucose metabolism of neurons in the human brain.

Elderly/Senile impairment

The MAHs mentioned eleven papers on elderly/senile cognitive impairment and considered the Huber's publication (1986) as the most relevant one. Of the eleven papers mentioned by the MAH, two were not submitted.

Huber (1986): This study was a 5-year, double-blind, placebo-controlled study conducted in 148 healthy elderly volunteers who received prophylactic treatment of 1.5 mg t.i.d of dihydroergotoxine or placebo. 89 subjects remained in the double-blind trial after 5 years. This study was still on-going at the date of publication. After 5 years, many of the subjects had an improvement compared to the beginning, irrespective of the treatment (dihydroergotoxine or placebo). The frequency of subjective neurological and psychological symptoms and subjective somatic symptoms was not different between the two treatment groups. No difference versus placebo was observed on mental change, blood pressure, electrocardiogram (ECG) findings, laboratory tests, major diagnoses, and psychometric variables (Wechsler Adult Intelligence Scale (WAIS), General comprehension, Coloured Progressive Matrices test, Maudsley Personality Inventory).

Roubicek (1972): This publication described one acute/sub-acute study and one chronic study. The acute study was performed in only 4 women (68.5 years) who received 0.6 mg of dihydroergotoxine intravenously over a 2-hour period, and then 0.6 mg subcutaneously for 13 days. The chronic study was double-blind, randomised and placebo-controlled, and was performed in 62 patients (78 years) with mild to moderate degrees of senile mental deterioration. Patients received placebo or 1.5 mg of dihydroergotoxine orally t.i.d. for 12 weeks. Statistically significant difference was observed between treatment groups on various symptoms as emotional withdrawal, conceptual disorganisation, depressive mood, motor retardation, blunted affect, disorientation, activity wakefulness, mood, physical condition, psychiatric assessment.

Rouy (1989): This paper described a double-blind, randomised, placebo-controlled study performed in 97 elderly patients (mean 82 years) with age-related mental deterioration. The authors noted the lack of precision in the demarcation between normal and pathological cerebral ageing. Patients received 4.5 mg of dihydroergotoxine per day or placebo for 6 months. Clinical assessment was performed with the EACG scale (a French version of the Sandoz Clinical Assessment Geriatric scale) and the NOSIE (Nurse's Observation Scale for In-Patients). After 6-month treatment, a statistically significant difference in favour of the dihydroergotoxine group was observed for cognitive deficits (p<0.05), anxiety and mood depression (p<0.01), unsociability (p<0.01), retardation (p<0.05) and irritability (p<0.001).

Spiegel (1983): This paper described a 3-year, placebo-controlled study conducted in 148 healthy elderly volunteers. Dihydroergotoxine was administrated preventively at 1.5 mg t.i.d. After 3 years, 99 subjects were still being treated under double-blind conditions. The authors concluded that many subjects in both groups were healthier after the 3 years.

Van Loveren-Huyben (1984): This paper described a double-blind, 24-week, placebo-controlled study conducted in 58 patients (mean 83 years) with mild to moderate forms of senile mental deterioration determined on the Sandoz Clinical Assessment Geriatric Scale (SCAG). The drug dosage was 4.5 mg t.i.d for 12 weeks and then 1.5 mg once morning and 3 mg twice daily for the subsequent 12 weeks. No statistical analysis was performed on the difference between the 2 treatment groups.

Matjecek (1979): This paper described a double-blind trial, 3-month, placebo-controlled study conducted in 16 elderly patients (mean 75.4 years) with mild to moderate form of deterioration determinated by the SCAG rating scale. Treatment regimen was one 1.5 mg capsule orally three times daily for 12 weeks. Statistical significance of dihydroergotoxine was only obtained in two of the 19 items evaluated in the SCAG ration: mood depression and irritability.

Lazzari (1983): This paper described a multicentre, double-blind, placebo-controlled long-term (1 year) clinical trial including 559 patients where 388 patients achieved a 6-month treatment and only

204 completed a year. Result after 3, 6 and 12 months of treatment was significantly positive for dihydroergotoxine.

Loria (1989): This paper described a double-blind, double-placebo, randomised trial comparing dihydroergotoxine 4.5 mg capsules and dihydroergotoxine 4.5 mg tablets. The treatment period was 4-month. The 193 patients who were included were aged from 55 to 85 years with mental and behavioural disturbances due to cerebral aging, with an MMS score greater than 10 and equal or less than 25. Intra-group analysis on day 120 showed significant improvements in the dihydroergotoxine 4.5 mg tabets group for 2 factors, 6 items and the overall score, and in the dihydroergotoxine 4.5 mg tabets group for 3 factors, 7 items and the overall score. The two formulations are considered to be equivalent and this slow release formulation seems better tolerated by the patients.

Pere (1989): This paper described a double-blind multicentre, two parallel groups study with patients with mental and behavioural disturbances due to aging. The 183 patients included in the study were given either dihydroergotoxine 4.5mg capsule or dihydroergotoxine 4.5mg tablets plus one capsule of placebo or one capsule of dihydroergotoxine 4.5mg plus one placebo tablet once daily for a period of 4 months. The two formulations were comparable in term of efficacy.

Primary cognitive impairment

The MAH mentioned 5 papers. Two papers are open-label studies (Albanese, 1987; Mongeau, 1974), and one paper was not submitted (anonymous, 1975). The last paper (*Kuskowski, 1990*) is about a randomised, double-blind, placebo-controlled study conducted in 18 patients (mean age 67.6 years) who meet the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-III criteria) for Primary Degenerative Dementia. They received 4.5 mg or 9 mg/day of dihydroergotoxine mesilate or placebo for 24 weeks. Effect was observed on electroencephalogram (EEG) changes (the late positive component (P300) latency of event-related brain potentials and smooth pursuit eye movement). No difference between treatment groups was observed on the P300 wave. There were some significant differences in favour of dihydroergotoxine mesilate on pursuit eye movement performance (higher pursuit gain on the low condition). However, the authors concluded that the lack of significant group differences on the other measures of pursuit quality does not support efficacy.

Organic Brain Syndrome

According to the MAH, in practice, organic brain syndrome is still conceptually useful to the practicing emergency physician by highlighting a sizable list of diagnoses to be considered before a patient with abnormal mentation and/or behaviour is presumed to solely have a psychiatric illness (Medscape, 2012). Five papers on "Organic Brain Syndrome" cover a total of 185 patients of whom 131 treated with dihydroergotoxine at the daily dosage of 3 mg for periods ranging from 3 to 15 weeks. In the most relevant paper according to the MAH (Biel, 1976) the efficacy of dihydroergotoxine was compared against placebo in a 15 weeks cross-over trial in 51 patients with "organic brain psychosyndrome". The daily dosage was 3 mg of dihydroergotoxine. Criteria of evaluation consisted of clinical rating and electroencephalographic registrations, which were evaluated visually and partly automatically.

The clinical symptoms and the electroencephalographic criteria (base line activity, theta- and delta activity) were both positively influenced by dihydroergotoxine. The base-line activity was stabilised and the alpha activity of the power spectrum increased. According to the authors, the most impressive result was the carryover effect of dihydroergotoxine, which could still be demonstrated in the post-trial period. In case of "dizziness", however, the good results were limited to the period of active treatment.

Memory impairment

The MAH mentioned 3 papers of which 2 are described on the previous sections (Thibault, 1974 in section arteriosclerosis; and Paux, 1975 in section CVI).

Thienhaus (1982): This paper described a double-blind study conducted in 41 outpatients aged 55 to 80 years with mild memory impairment. The effect of dihydroergotoxine at 6 mg per day, administered orally, was tested during a twelve-week period. Specific aetiologies for the amnesic syndrome were ruled out by history, physical examination, and laboratory tests. Subjects with a Hamilton Depression Scale rating above 18, i.e. possible pseudodementia, were excluded. Physician rating of memory, employing the Inventory of Psychic and Somatic Complaints in the Elderly (IPSC-E), indicated statistically significant improvement of memory function in dihydroergotoxine treated subjects (N = 22) vs those on placebo (N = 19), (F = 3.34; df = 1,39; p< 0.04). In contrast, structured testing of recent memory using digit symbol substitution and Zahlenverbindungs test (ZVT) showed improvement in both groups with no significant intergroup differences. According to the authors, these

results indicate that in cases of mild, though subjectively distressing impairment, dihydroergotoxine mesilate at higher doses may help to enhance short-term memory function.

Cochrane review

A Cochrane review for dihydroergotoxine was recently published (Schneider, 2009). In this review, trials to be included had to be randomised, double-blind, parallel-group, and unconfounded comparisons of dihydroergotoxine with placebo for a treatment duration of greater than one week in subjects with dementia or symptoms consistent with dementia.

There were a total of 19 trials that met inclusion criteria and that had data sufficient for analysis. Thirteen trials reported sufficient information to use a global rating of improvement and nine trials provided information on a comprehensive rating scale. Three trials provided both outcome measures. The therapeutic areas identified by the reviewers were Alzheimer's Disease, Vascular dementia, Primary dementia of undetermined type, Cerebral insufficiency, and Cerebral or senile deterioration.

For the trials that used global ratings, there was a significant effect favoring dihydroergotoxine (OR 3.78, 95% CI, 2.72 to 5.27). For the nine trials that used comprehensive ratings, there was a significant mean difference favoring dihydroergotoxine (WMD 0.96, 95%CI, 0.54 to 1.37).

Ancillary treatment of Raynaud's syndrome

In some Members States the ancillary treatment of Raynaud's syndrome is approved for dihydroergotoxine as part of a more general indication, i.e. "peripheral vascular disease". The MAH submitted data in order to support the indication "peripheral artery disease". However, the terms "peripheral vascular disease" and "peripheral arterial disease" are often used interchangeably and as a result the data provided by the MAH were considered within the scope of the referral with regard to the indication for Raynaud's syndrome.

An overview of clinical trials published with dihydroergotoxine in association with other compounds in peripheral vascular disease is presented below.

Bruning (1975): In this open controlled study, 74 male patients with peripheral and cerebrovascular insufficiency were treated with dihydroergotoxine for 6 weeks. An improvement of the early symptomatology of cerebral blood circulation reduction and a decrease of pathological EEG changes after the treatment was noticed. No unwanted side effects were mentioned.

Horakova-Nedvidkova (1970): In this study, 59 patients with diagnosis chronic venous insufficiency, chronic varicose eczema and ulcus cruris were treated with dihydroergotoxine, esculoside & rutoside. Their peripheral circulation was investigated by measurement of skin temperature on both legs, measurement of the circumference of the calf and supramalleolar region, and measurement of blood pressure; in 10 patients with postphlebitic syndrome plethysmography was used to investigate the vasomotor reactions to the used pattern of standard impulses. Eighteen (18) cases were found to be clinically highly improved, 31 patients were improved, the subjective improvement being also accompanied by an objective reduction in the leg circumference. The vasomotor reactions, which had in 50% of cases an inversely vasodilating character prior to therapy, normalised by 7.3%, being in full agreement with the clinical improvement.

Gordon (1972): Thirty five (35) patients with symptoms of varicose veins were treated with dihydroergotoxine, esculoside & rutoside. The dosage was 2 tablets three times daily for 5 days, thereafter one tablet three times a day for 8 weeks. An improvement was noticed in 27 cases (12 extremely good, 5 very good, 10 good). In 4 patients there was no relief in therapy.

Lambelet (1973): In this uncontrolled study in 52 patients suffering from venous insufficiency, 77% of subjective symptoms responded favourably to dihydroergotoxine, esculoside & rutoside, while improvement in objective symptoms was also showed in a number of patients. These results promped the authors to undertake a subsequent double blind study. Fifty (50) patients were treated in 2 groups, 26 receiving the active component, and 24 placebo for 15 days. Dosage was 6 tablets daily. Dihydroergotoxine, esculoside & rutoside proved decidedly superior to placebo both in global evaluation and in the evaluation of the subjective symptoms and objective symptoms of venous insufficiency.

Losson (1969): The clinical effects of "papaverine, ergoloid mesillates & sparteine" have been studied in elderly patients suffering from cerebral vascular lesions. There were 48 patients hospitalized for 2

years. These subjects included 43 women and 5 men. Their ages ranged between 63 and 98 years, they all had a general condition fairly well preserved, although not all "valid". Their degree of vascular injury was variable; patients were divided into four categories according to the classification of Geraud. The "papaverine, ergoloid mesillates & sparteine" was given in a dosage of two tablets per day, one in the morning, one in the evening at the beginning of meals, for 6 weeks. Patients were unaware of the clinical trial, and the questionnaire was presented as a game made by a psychologist. The first series of tests was made 1 month before the administration of the product, and the second series at the end of 6 weeks of treatment, both sets of tests were conducted at two and a half months apart. Two thirds (2/3) of patients showed an improvement in intellectual capacity.

Obeid-Ruggli (1971): In a population of 235 ambulatory patients, spasms, pain and heaviness in the legs decreased or disappeared in more than 90% of the cases following administration of dihydroergotoxine, esculoside & rutoside. Objective improvements, especially significant reduction or total reduction of venous leg oedema were about 80%.

Ourgaud (1975): Dihydroergotoxine, sparteine & papaverine was administered to 26 arteriosclerosis retinal patients. In 12 patients the angiography was the same before and after treatment. Results showed an improvement in 17 patients. One case of dizziness was reported.

Schwaar (1969): In this trial 172 patients aged from 16 to 70 years suffering varicose diseases and their complications were treated with dihydroergotoxine, esculoside & rutoside. All patients improved their diseases. Author concluded that dihydroergotoxine, esculoside & rutoside improve arterial circulation, tissue oxygenation and vein tonicity.

Uminska (1960): In 16 cases of thrombophlebitis of the superficial veins of inferior extremities and deep crural veins and in 14 cases of post-thrombophlebitis syndromes with and without ulcerations dihydroergotoxine, esculoside & rutoside coated tablets were used. Very good and good results were obtained in 23 cases out of 30 treated ones. In 2 cases of post thrombotic syndromes non improvement was obtained. Beginning of treatment with dihydroergotoxine, esculoside & rutoside inmediately after the onset of thrombosis is followed by a more rapid and more complete therapeutic effect. In 16 cases dihydroergotoxine, esculoside & rutoside & rutoside had a more rapid and better effect compared with the results with other therapies in 10 randomly selected cases treated. No side effects were observed during the treatment with dihydroergotoxine, esculoside & rutoside.

Weitgasser (1968): The pharmacological action of dihydroergotoxine, esculoside & rutoside was investigated in a series of 208 outpatients with prevaricosis, varicose syndromes associated and/or not associated with ulcera cruris, and post thrombotic complaints. Dihydroergotoxine, esculoside & rutoside was found to exert a twofold beneficial effect on the peripheral circulatory system, its action being directed to the arteries (adrenolytic effect) and the veins (tonic effect). After very good results had been obtained in a pilot study on 39 patients, the efficacy of the preparation was demonstrated in a double blind test using placebo on the control group, and subsequently corroborated by analytical evaluation.

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

Seven studies have been submitted in support of the above indication and are summarised as follows.

Shukla (1989): Dihydroergotoxine mesilate was clinically evaluated in 161 eyes of 96 patients suffering from different types of neuro-retinal disorders which included various forms of optic atrophy, retinitis pigmentosa, pathological myopia, dry senile macular degeneration and heredomacular degeneration. While all the patients received this treatment with tablets, 32 patients, in addition, received this therapy in injectable form also. Beneficial results in terms of improvement in visual acuity were noticed in 52 (32.30%) eyes after three months of treatment. Long-term visual improvement or stabilisation of visual acuity was seen in 40 eyes at 6 months and 29 eyes between six months-one year respectively. The best visual results were obtained in pathological myopia, anterior ischaemic optic neuropathy, primary optic atrophy and typical retinitis pigmentosa. According to the authors, while the initial results of dihydroergotoxine mesilate treatment are quite encouraging in the treatment of certain neuro-retinal disorders primarily with a neuronal transmission defect and/or vascular ischaemic pathology, the cost factor is a positive drawback particularly in cases requiring long-term treatment.

Vannas (1958): Sixty-two patients with impaired vision, field defects and sclerotic fundal changes were placed in 4 groups to permit comparison of methods of treatment. Improvement of vision by at least 2 lines or complete disappearance of metamorphopsia was classed as a positive result. In the group receiving alternating periods of heparin and vitamins A and E, 2/3 were positive. In the group given vitamin therapy alone, and in the dihydroergotoxine group, 1/3 were positive. In the placebo group, none was positive. The experience gained indicated that alternating long-term heparin and vitamin A and E therapy was suitable for both the wet and dry forms of arteriosclerotic chorio-retinopathy. Dihydroergotoxine, on the other hand, was suitable especially for the wet forms, requiring treatment for several months and relatively large doses. Vitamin A and E therapy alone had a favourable effect principally on the incipient dry form.

Simkova (1954): In this trial, twenty cases of severe hypertensive retinopathy (stage III and IV), which were refractory to the usual forms of treatment, were tentatively treated with dihydroergotoxine for about one year. Judging not only by the fundus of the eye, but also by the blood pressure, the visual acuity, the disappearance of subjective symptoms and the improvement of working capacity, the results can be considered good in 11 cases, satisfactory in 4, doubtful in 3 and bad in 2. Arterial tension decreased on an average by 34 mm/Hg systolic and 18 mm/Hg diastolic; retinal arterial tension decreased 22-24 mm/Hg. Retinal venous pressure was normalized in 11 of 14 cases.

In another open trial (*Bronner*, **1979**) in a population of 25 aged patients with atherosclerosis and visual trouble (47 eyes) the treatment with oral dihydroergotoxine at the dosage of 4.5 mg/day for a period of one month caused improvements in visual acuity, in hemodynamic flow and in the electrophysiology.

Sixteen unselected cases with different conditions were treated with dihydroergotoxine. In cases with fixed hypertension and severe changes of the retinal blood vessels no influence upon the vascular conditions was obtained (*Remler, 1954*). Young patients with disturbance of the arterial blood flow allowed improvement of the ophthalmoscopically visible changes and also of their visual function. Independently of the blood pressure the subjective symptoms were reduced owing to the increased cerebral blood circulation.

Dihydroergotoxine mesilate was administered also to 26 arteriosclerosis retinal patients. In 12 patients the angiography was the same before and after treatment. Results showed an improvement in 17 patients. There was only one case of dizziness (*Ourgaud*, *1975*).

Panthesine has a spasmolytic, anti-allergic and ganglion-blocking ability and persists intact for some hours after parenteral administration. It is combined with dihydroergotoxine in the preparation PH 203 (panthesine hydergine) (*Orma, 1958*). Forty-eight patients were studied, including 18 venous or arterial occlusions and 30 non-thrombotic cases of vascular sclerosis of the fundus. Fifteen of the latter were given a placebo.

This material does not warrant definite conclusions, but since some severe cases made unexpectedly good recoveries the authors considered that the use of PH 203 and dihydroergotoxine therapy for peripheral circulatory disturbances of the eye might be a subject for more thorough investigation. In occlusion, a positive result seemed to depend on the relaxation of spasm. The best response to therapy was in chorioretinopathies of the 'wet', i.e. exudative, type.

Dihydroergotoxine therapy, when continued for several months, obviously promoted the resorption of haemorrhages, and sometimes stimulated retinal function.

Prophylaxis of migraine headache

The MAH submitted four publications. Two publications describe a double-blind, active, not placebocontrolled study on the effect of dihydroergocryptine (dihydroergotoxine is composed of a third of dihydroergocryptine) as compared to propranolol (Micieli et al, 2001) and flunarizine (Bussone et al., 1999). The third study (Heydenreich, 1989) compared 3 treatment groups: association of iprazochrom and dihydroergotoxine, acupuncture, and punctiform transcutaneous nervestimulation. The last publication (Voisin and Paquelin, 1962) is a description of 17 cases of migraine treated by dihydroergotoxine where improvements were noticed.

Symptomatic treatment of veno-lymphatic insufficiency

This indication is approved in only one Member State (Czech Republic) but no data were submitted by the MAH in support of its efficacy.

Other indications

One of the MAHs submitted a few data in support of the indication "cervical syndrome" and "hypertension" but these will not be considered in the final outcome as these indications are outside the scope of this referral procedure.

2.2.2. Discussion

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

Overall, data on efficacy in cognitive dysfunction 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.

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.

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

Seven clinical studies have been submitted in support of this indication. 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 (Ourgaud, 1975; Remler, 1954; Shukla, 1989; Bronner, 1979; Simkova, 1954). Among these, one study referred to a combination with papaverine and sparteine (Ourgaud, 1975) and therefore, is out of the scope of the procedure when considering the combination of actives tested. Similarly, the reduction of angioscotoma observed in Simkova study (1954) in patients treated by the injectable drug is out of the scope of the procedure as no formulation for injection is registered nowadays for dihydroergotoxine.

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. These studies also included patients presenting very heterogeneous pathologies of various severities. In both studies, an injectable formulation of dihydroergotoxine was associated to treatments while no injectable formulation is currently approved in the EU.

Finally, in Vannas study, comparisons used active ingredients that are no more considered as therapies of choice to treat or prevent retinal diseases (heparin, vitamins A and E) and in Orma study, panthesine was combined with dihydroergotoxine in the preparation PH 203.

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 in the treatment of visual trouble presumably of vascular origin.

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 recognised 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.

Symptomatic treatment of veno-lymphatic insufficiency

No data were submitted in support of this indication and consequently no conclusion on efficacy could be drawn by the CHMP.

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

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

A total of four cases of retroperitoneal fibrosis were reported since 1997; three spontaneous reports concerning dihydroergotoxine mesilate (of which only 2 were medically confirmed) and one literature case concerning a patient treated with dihydroergocristine, one of the compounds contained in dihydroergotoxine.

A total of two case of pulmonary fibrosis were reported since 1997 as well as one case of interstitial pneumonia and one case of acute respiratory distress syndrome.

No cases of cardiac valvulopathy have been reported apart from a non-medically confirmed report received in 1991 from a consumer.

A French pharmacovigilance survey was performed in 2011 on dihydroergotoxine which showed that three additional cases of fibrosis occurred with dihydroergotoxine containing products and more specifically one case of retroperitoneal fibrosis and two cases of pulmonary fibrosis.

No reports of ergotism have been retrieved from the MAH's search but a search of the literature yielded two possibly related episodes. A case in which the medicinal product produced symptoms and signs of iatrogenic ergot vasospastic angiitis and a case where peripheral gangrene occurred in a patient treated with dihydroergotoxine for nine years.

2.3.2. Discussion

Overall, the three spontaneous cases of retroperitoneal fibrosis have been reported with dihydroergotoxine mesilate in patient aged between 55 and 87 years old. Two patients were elderly patients as per the authorised indications. The CHMP noted that one case was not confirmed by a health care professional and its narrative contained limited information. Treatment duration was unknown and in all cases the prescribed dosages were not higher than the recommended daily dose. In one case where chronic renal insufficiency is known, retroperitoneal fibrosis leads to acute renal insufficiency and secondary heart failure. In the second case, retroperitoneal fibrosis is diagnosed after occurrence of renal insufficiency. The CHMP noted that since no aetiology was found in the third case, the role of dihydroergotoxine could be suspected.

Even if dihydroergotoxine is composed of a third of dihydroergocristine, the literature report could not be assessed by the CHMP because it occurred with a product which only contains dihydroergocristine.

Regarding pulmonary fibrosis, two cases have been reported, one of which was described with very limited information to allow a proper assessment. For the second case where thickening of interstitial septa was observed, it could not be be excluded that dihydroergotoxine taken for several years could be responsible for the pulmonary fibrosis, especially as the other concomitant treatments are not known to induce fibrosis.

For the two other provided cases (acute respiratory distress syndrome and interstitial pneumonia), there is no relevant information since for one case the time to onset is in favour of the responsibility of the concomitant treatment, and for the other poorly documented case no exploration was performed to diagnose pulmonary fibrosis.

With regard to the unconfirmed report of cardiac valvulopathy the CHMP commented that the limited information and the lack of diagnosis confirmation by a healthcare professional make the assessment difficult. However, given the young age of the patient the fact that no other suspected medication was administered and the listed event, cardiac fibrosis could be suspected to be due to dihydroergotoxine.

Apart from the data provided by the MAH the CHMP noted the events reported in the French Pharmacovigilance database following a national inquiry performed in 2011 on ergot derivatives. Three additional cases of fibrosis occurred with dihydroergotoxine containing products and more specifically one case of retroperitoneal fibrosis and two cases of pulmonary fibrosis. 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 CHMP noted that no spontaneous reported cases of acute intoxication with dihydroergotoxine showed ergotism symptoms. However, some ergotism symptoms such as peripheral vasoconstriction have been reported in the literature. The MAH provided two publications (Kapoor 1976 and Hubens 1987) highlighting that peripheral vasoconstriction could occur with dihydroergotoxine. For one case the dosage was not specified making difficult to assess if the event occurred in a context of recommended daily dose or chronic intoxication, nevertheless it is underlined for the other case that the dosage was not higher than the recommended dose.

In general, 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. In addition, dihydroergotoxine is composed of dihydroergocryptine and dihydroergocristine which are associated with the induction of fibrotic reactions. 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.

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 have been reported in the literature.

2.4. Overall benefit/risk assessment

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

Overall, data on efficacy in cognitive dysfunction 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.

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.

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 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.

2.5. 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 indication proposed by the MAH which is *"symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia"*.

Details grounds for re-examination submitted by the MAH

The MAH disagreed with the negative benefit risk assessment of the CHMP for dihydroergotoxine. The grounds for re-examination are the following:

- The MAH considered that the benefit-risk of dihydroergotoxine is positive in the restricted indication "symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia" which is presently known as cognitive impairment no dementia (CIND). The MAH considered that there is an unmet medical need for elderly people for CIND.
- The MAH considered that published evidence on the effects of dihydroergotoxine in cognitive impairment is extensive, both in terms of the overall number of trials and of enrolled patients and of the percentage of controlled trials or relevant sample size.
- The MAH highlighted that the incidence of reports of adverse events like fibrotic reactions (including valvulopathy) and ergotism is very low for their dihydroergotoxine containing product (Hydergine) considering the patient exposure.
- The MAH proposed risk minimisation measures including changes to the product information, a DHPC and check list designed to inform prescribers on the risk of fibrotic reactions and ergotism, and to assist them in determining the patient's suitability for treatment. The MAH also proposed measures for the long term follow-up on the adherence to and effectiveness of the changes to the product information.

CHMP discussion on grounds for re-examination

The CHMP reviewed all available data in support of the benefit and safety on dihydroergotoxine and considered the restricted indication proposed by the MAH, i.e "symptomatic treatment of cognitive impairment in elderly, excluding Alzheimer's disease and dementia". The MAH has proposed this restricted indication already during the initial review of this referral.

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. Out of over 42 studies reviewed, 8 studies were considered by the MAH to be robust evidence with a well-defined population, a dropout rate below 20% and a sample size above 50 (Bargheon (1973); Janssen (1985); Lazzari (1983); McConnachie (1973); Rao (1972); Rouy (1989); Van Loveren (1984); McDonald (1985)). However, the CHMP considered that these studies did not provide robust evidence supporting the efficacy of dihydroergotoxine in the proposed target population. The included studied populations are often poorly described, the majority of the studies included a limited number of patients (only the study by Lazzari et al. 1983 included more than 100 patients) and lasted less than 6 months. 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. In fact, some of these studies included patients with dementia. Therefore, concerns about heterogeneity of the studied population remain, even if the restricted dataset of 8 'robust studies' is considered. 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 had a clinically relevant effect on patients with cognitive impairment.

The CHMP noted that the incidence of adverse events reported by the MAH with dihydroergotoxine is low: three spontaneous reports of retroperitoneal fibrosis and one literature case were reported, two cases of pulmonary fibrosis and one report of interstitial pneumonia and one report of acute pneumopathy were reported, and no case of cardiac valvulopathy and ergotism were reported. 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.

In order to maximise benefit and minimise risk associated with dihydroergotoxine, the MAH proposed to limit the treatment duration (i.e. to stop treatment if no evidence of efficacy is found after 3-month of treatment). This limitation is considered by the MAH to be supported by the literature. The MAH also proposed to contraindicate dihydroergotoxine in case of evidence of pre-existent valvulopathy and pulmonary or retroperitoneal fibrosis.

The CHMP noted that fibrotic reactions and valvular heart diseases can be asymptomatic for a long time after the fibrotic process has started. Therefore proposals to limit treatment duration or contraindicate in case of pre-existing fibrosis are not considered sufficient measures to minimise the risk for patients. Furthermore, the CHMP highlighted that even if fibrotic reactions could be diagnosed at an early stage, reversibility is not certain. 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 and cannot be dismissed particularly when considering its potential use in long-term treatment in a broad patient population.

The CHMP also highlighted concerns on the indication proposed by the MAH, i.e. "chronic cognitive impairment excluding Alzheimer's disease and other dementia", given that it is not considered a generally accepted clinical entity aimed to benefit from treatment. At present, the validity of certain diagnosis referring to cognitive impairment in its pre-dementia stages is controversial. In fact, the proposed definition represents a rather heterogeneous population, including subjects with symptoms of normal ageing.

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 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 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. Since the SAG disagreed with the proposed indication and target population definitions proposed by the MAH, any discussion on the risk minimisation measures proposed was considered hypothetical.

Finally the CHMP considered the data presented by the MAH during the oral explanation held on 22 October 2013.

Benefit-risk conclusion within the re-examination procedure

The Committee considered the overall submitted data provided by the MAH and the outcome of the SAG meeting.

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.

2.6. Communication plan

The CHMP was of the opinion that a 'Dear healthcare professional' communication (DHPC) should be disseminated 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 dihydroergotoxine-containing medicinal products/suspension
 where applicable
- Risk of fibrotic reactions and ergotism
- Limited evidence of efficacy in the indications reviewed
- Benefits of dihydroergotoxine-containing medicinal products no longer outweigh their risks

2.7. 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 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

3. Overall conclusion

Having considered the submitted data and grounds provided by the MAHs in writing and in the oral explanation, 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 in the Product Information, when there are other therapeutic indications approved as part of their marketing authorisation:
 - Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia).
 - Ancillary treatment of Raynaud's syndrome.
 - 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.

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.