



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Ergot derivatives containing medicinal products

International Non-proprietary Name: dihydroergocristine

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.



Table of contents

1. Background information on the procedure	3
1.1. Referral of the matter to the CHMP	3
2. Scientific discussion	3
2.1. Introduction.....	3
2.2. Clinical efficacy	3
2.2.1. Results.....	4
2.2.2. Discussion	6
2.3. Clinical safety	7
2.3.1. Results.....	7
2.3.2. Discussion	8
2.4. Overall benefit/risk assessment.....	9
2.5. Communication plan	11
2.6. Changes to the product information.....	11
3. Overall conclusion	11
4. Annexes.....	12

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/cafeine, dihydroergocristine, dihydroergotamine, dihydroergotoxine and nicergoline. Following a national pharmacovigilance review held in 2011 new spontaneous notifications reported with some of those products identified serious cases of fibrosis and ergotism and France considered that this safety concern is not outweighed by the limited evidence of efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications:

- Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)
- Ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II)
- Ancillary treatment of Raynaud's syndrome
- Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin
- Acute retinopathies of vascular origin
- Prophylaxis of migraine headache
- Orthostatic hypotension
- Symptomatic treatment of veno-lymphatic insufficiency

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

2. Scientific discussion

2.1. Introduction

Dihydroergocristine is a partial agonist of α -adrenoreceptors that decreases the activity of sympathetic centres and is responsible for a peripheral adrenolytic effect with an increased venous wall tone. In addition it has a pharmacological action on the serotonergic and dopaminergic receptors leading to interesting effects on cerebral metabolism. It is available in combination with raubasine that is an adrenolytic and sympatholytic agent with an inhibitory effect on sympathetic centres. It produces a decrease in blood pressure and an increase in peripheral blood flow. Its effect results mainly from its α_1 -blocking properties. In Europe, dihydroergocristine is also available in combination with etofyllinum.

From the approved indications of the dihydroergocristine containing medicinal products, the ones that are in the scope of this referral procedure and are approved in at least one Member State are the following (specific wording of the indication may vary from product to product):

- Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)
- Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin
- Acute retinopathies of vascular origin

Dihydroergocristine products are approved for oral use or intramuscular/intravenous use (IM/IV) in different pharmaceutical forms (tablets, capsules, oral solution, oral drops, solution for injection). 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 MAHs from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation.

Very few of these studies were conducted according to the current medical standards and Good Clinical Practices (CGPs).

2.2.1. Results

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

The following six main studies were provided in support of the efficacy evidence for dihydroergocristine in the above indication.

Hugonot R (1984): This double-blind, randomised, placebo-controlled study included 127 patients older than 60 years (mean age around 72 years) who were diagnosed with a reduction of the intellectual functioning, memory and attention disorders with functional signs such as vertigo, tinnitus, headache often related to cerebral vascular insufficiency. The moderate intellectual disorder was defined as a total score between 12 to 30 on the French L. Israel's clinical evaluation scale of intellectual dynamism. Patients received either dihydroergocristine + raubasine (240 drops per day in 3 divided doses), or placebo during 2 months.

The monthly clinical assessments were multivariate, including rating of 9 functional symptoms, the intellectual functioning using the L. Israel's clinical evaluation scale of intellectual dynamism combined with separate rating tests of attention and vigilance, the assessment of the treatment effects on the activities of daily living and personality and mood assessments. Statistical analysis was performed in the per protocol population (55 patients on dihydroergocristine + raubasine and 43 patients on placebo).

Results were heterogeneous. The L. Israel scale total score was in favour of the dihydroergocristine + raubasine group at day 60 ($p < 0.001$) for some items (recall ability, attention, capacity to express oneself, vigilance, general dynamism and verbal fluidity). Significant difference between groups was observed on psychological symptoms (irritability, lack of well-being, emotional lability and tension). No difference was observed on somatic symptoms. During the tests for attention and vigilance (crossing out tests), only the speed of the tests execution was significantly improved at day 30 and day 60.

Albarède JL (1987): This double-blind, randomised, placebo-controlled study included 89 patients who received either dihydroergocristine + raubasine 240 drops per day in 2 divided daily doses, or placebo for 4 months. Patients were aged over 60 years, with moderate impairment of their intellectual faculties and some somatic disorders (these symptoms inducing psychological and behavioural disorders e.g. withdrawal, irritability, anxiety, or anxio-depressive disorders). There were multiple assessment criteria for cognitive functions, functional symptoms, subjective assessment of the clinical global impression and daily activities, the L. Israel's clinical evaluation scale of intellectual dynamism.

After 3 months of treatment, changes of L. Israel scale total score showed a variation of +27% in the dihydroergocristine + raubasine group as compared to +11% in the placebo group ($p < 0.0001$). Functional somatic and psychological symptoms were statistically significantly improved with dihydroergocristine + raubasine compared to placebo after 90 days of treatment as measured by the percentage of improvement: headache (80% vs 40%; $p < 0.003$), tinnitus (77% vs 45%; $p < 0.02$), tremor (70% vs 31%; $p < 0.03$).

Hugonot L (1990): This double-blind, randomised, placebo-controlled study included 114 patients aged 55 to 70 years (mean age around 81 years), with a progressive decline of memory with an impact on the daily activities (Mini Mental Status (MMS) between 21 and 27). Patients were randomised in 4 groups who received either dihydroergocristine + raubasine 4 tablets per day in 2 divided doses or placebo, with or without training exercises for memory using the L. Israel method, during 3 months.

Two evaluation scales were used: a battery of tests for Fluidity in Elderly was used to assess 4 factors (organised memory, working capacity, perceptive structure, topographic orientation, total score between 7 and 35), and the Mac Nair scale, a self-administered scale assessing daily life difficulties. Statistically significant difference was observed on the total score of the tests for Fluidity in Elderly between dihydroergocristine + raubasine and placebo, respectively +2.14 vs -1.02 ($p < 0.01$). Result was statistically in favour the subgroup receiving the study treatment combined with memory training exercises compared to treatment alone ($p < 0.01$).

Vellas B (1991): This randomised, double-blind, placebo-controlled clinical study enrolled 95 elderly patients (mean age around 75 years). Patients were randomised to receive either dihydroergocristine + raubasine, 240 drops per day in 2 divided doses or placebo, during 3 months. The patients had experienced a fall in the 7 previous days of the study. The fall was due to an obstacle or unexpected step, and it could have been combined with a loss of consciousness, and minor injury.

The group of patients receiving dihydroergocristine + raubasine showed a decreased occurrence of new falls compared to placebo (4% versus 17% between day 30 and day 60). The total score on the French L. Israel intellectual dynamism scale at baseline was consistent with a moderate alteration of intellectual functions (between 12 and 30). The difference between the 2 groups was statistically significant on the L. Israel scale.

Allain H (1992): This double-blind, randomised, placebo-controlled clinical study was conducted in 111 elderly patients who received dihydroergocristine + raubasine (4 tablets per day in 2 divided doses) or placebo for 3 months. The patients were aged between 50 and 70 years (mean age around 61.8 years) and were presenting with memory complaints combined with deficit of the intellectual performances (memory deficit, decrease of attention and concentration), without any vascular disorders, dementia, or depression (Hachinski score <7, MADRS score < 25 and MMS > 25).

The L. Israel Intellectual Dynamism scale was the primary efficacy criterion; the mean total score at baseline was 28.2 and 30.5, in the dihydroergocristine + raubasine and the placebo group respectively. The change from baseline of the total score after 3 months of treatment was +4.87 in the dihydroergocristine + raubasine group and +2.00 in the placebo group, with statistically significant difference ($p < 0.005$). The items: attention, general dynamism, capacity to express oneself and recall ability were statistically improved.

Vellas (Phase IV, 1998 - Not published): This double-blind, randomised, placebo-controlled clinical study was conducted in 216 patients (mean age 72.3 years) who received either dihydroergocristine + raubasine, 2 tablets per day or placebo, during 6 months. Patients had to present a moderate memory deficit, with a Mini-Mental State Examination MMSE > 25 and a score total > 38 and < 70 on the Mac Nair and Kahn auto-questionnaire assessing the difficulties in daily activities. Analyses were performed on per protocol population (202 patients).

Two scales have been identified as primary criterion: the Mac Nair and Kahn auto-questionnaire assessed at day 90 and day 180 and the Gröber and Buschke test assessed at day 180 (number of correct responses makes 16). At day 90 and day 180, no difference between treatment groups was observed.

A total of 27 literature references were submitted to support the efficacy of dihydroergocristine in the treatment of chronic cognitive impairment in the elderly (excluding Alzheimer's disease and other dementia). Of these, 18 concerned placebo-controlled trials, 2 concerned actively-controlled trials and 7 concerned open label studies.

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

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

Two abstracts of two preclinical published studies were submitted in support of these indications. These abstracts reported the effects of topical doses of dihydroergocristine to decrease intraocular pressure (IOP) that were explored in ocular normotensive rabbits and alpha-chymotrypsin-induced ocular hypertensive rabbits by Puras G, 2002 and Melena J, 1998, respectively. Topical dihydroergocristine was reported to lower intraocular pressure (IOP) in both conditions. No study in humans was submitted.

One of the MAHs did not submit any efficacy data to support the ocular approved indications "Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin" (for the oral pharmaceutical form) and "Acute retinopathies of vascular origin" (for the IM/IV pharmaceutical form), considering that, due to the limitations of the data available, the ocular indications cannot be upheld.

Other indications

One of the MAHs submitted a few data in support of the indication "Circulatory conditions in otorhinolaryngology" but these will not be considered in the final outcome as this indication is 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)

In the Hugonot (1984) study, the treatment duration was short (2 months), the definition of the diagnosis was not standardised, and no primary efficacy criterion was selected among the multi-dimensional assessment. The analysis was performed on the per protocol population, not on the intent-to-treat (ITT) population (29 patients i.e. 22.8% discontinued the study). The L. Israel's scale was the only structured scale used in this study which is a French scale assessing intellectual dynamism and is composed by 9 items (vigilance, attention, general dynamism, verbal fluidity, capacity to express oneself, fatigability, orientation in the space, general memory, recall capacity) with 5 decreasing severity levels. This scale is not used anymore. The CHMP noted that effect was observed on several heterogeneous symptoms; however, the methodological flows and the absence of primary efficacy endpoint do not allow drawing efficacy conclusion.

In the Albarède study, the definition of the diagnosis was not standardised, and no primary efficacy criterion was selected among the multi-dimensional assessment. Again, the L. Israel's scale was the only structured scale used but this scale is not used anymore. The CHMP noted that effect was observed on several heterogeneous symptoms; however, the methodological flows and the absence of primary efficacy endpoint do not allow drawing efficacy conclusion.

In the Hugonot (1990) and Vellas (1991) studies, the definition of the diagnosis was not recognised, and no primary efficacy criterion was selected among the multi-dimensional assessment. The scales used are old and not recognized anymore. No efficacy conclusion could be drawn.

In the Allain study, the treatment duration was short (3 months) and the number of patients per group was small (around 55). The definition of the diagnosis was standardized, and the total score on the L. Israel's clinical evaluation scale of intellectual dynamism was identified as the primary efficacy criterion. However, the CHMP noted that this scale is not recognised anymore. The analysis demonstrated statistically significant difference between dihydroergocristine + raubasine and placebo of 2.87 points. However, at D90, scores were not different between dihydroergocristine + raubasine and placebo (respectively 33.1 and 32.5 points). Because of that, the CHMP was of the opinion that the clinical relevance of these results is questionable.

In the most recent study (Vellas, 1998), the treatment duration was longer (6 months) than in the older studies, the number of patients per group was higher (around 110), the definition of the diagnosis was standardised, and the co-primary efficacy endpoints were decided upfront. The tests used are still recognised. However, non-significant difference between the groups of dihydroergocristine + raubasine and placebo was observed.

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

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

activities) and defines the primary efficacy criterion a priori (the Mac Nair and Kahn auto-questionnaire and the Gröber and Buschke test). However, in this study with adequate methodological quality standard, non-significant difference between dihydroergocristine + raubasine and placebo groups was observed.

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

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

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

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

A scientific advisory group (SAG) was convened in December 2012 at the request of the CHMP during which the experts discussed, based on their clinical experience, whether this substance plays a role in the symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia). The group highlighted that the claimed indication is not used anymore in the clinical practice and that from a clinical viewpoint there is no evidence at present that there is a therapeutic need for this active substance in the treatment of cognitive and neurosensorial impairment in the elderly.

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

The few preclinical findings submitted were considered by the CHMP insufficient to support the use of dihydroergocristine as intraocular pressure (IOP) lowering agent in human or for other ocular conditions presumably of vascular origin. Moreover, it was pointed out that topical instillations of dihydroergocristine are out of the scope of this procedure.

The CHMP also noted the position of one of the MAHs that due to the limitations of the data available, the ocular indication cannot be upheld.

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.

No case suggestive of cardiac fibrotic reactions was retrieved and one case was reported as pulmonary hypertension.

Five serious spontaneous cases of pulmonary fibrosis have been reported in patients treated with dihydroergocristine/raubasine. In addition, four spontaneous cases could actually be compatible with pulmonary fibrosis, which was however not reported as such and therefore not coded (i.e. two cases

referring to interstitial pneumopathy, one case referring to interstitial lung disease and one case describing pleural effusion). Finally, three distinct cases retrieved from literature could also be compatible with pulmonary fibrosis. In 4 of the 12 cases, concomitant treatments were administered.

The overall assessment of post-marketing data did not retrieve any reports evocative of peritoneal/retroperitoneal fibrotic reactions; however, one case of retroperitoneal fibrosis was reported in the literature with dihydroergocristine administration. This case of retroperitoneal fibrosis was diagnosed in a 61 year-old man who took dihydroergocristine for two years with dosage higher than the recommended dosage (6mg daily instead of 4.8 mg). A scan revealed a marked reduction of the extension of the fibrotic plaque one year after the withdrawal of dihydroergocristine.

With regard to ergotism, one case coded as ergot poisoning was retrieved. Two cases of intestinal ischemia were reported (one case of ischemic colitis and one fatal case of mesenteric infarction). In addition, five cases, for which symptoms could be suggestive of ergotism, were retrieved; (i) formication, tachycardia, arrhythmia and chest pain, (ii) two cases of paraesthesia and paresis, (iii) limb discomfort and gait disturbance, (iv) strong pain of lower limbs.

2.3.2. Discussion

With regard to the twelve cases of pulmonary fibrosis, treatment duration, when reported (n=7), was between 8 months to 9 years (of note, in the first 16 months of exposure for 4 cases) and no case occurred with higher dose than the recommended dosage: 6 cases occurred with dosage inferior to the recommended therapeutic dose range and 4 cases occurred with doses in the recommended therapeutic dose range (2.4-4.8 mg of dihydroergocristine daily by oral route). The CHMP noted that in 4 of the 12 cases compatible with pulmonary fibrosis, concomitant treatments were taken since an unknown date and therefore represent confounding factors. The other cases did not mention any concomitant treatments.

Outcome after withdrawal of dihydroergocristine was documented for 8 cases and all these cases showed improvement after treatment withdrawal. Among these 8 cases, improvement can be due to confounding factors in 5 cases. Concomitant confounding treatments which were also withdrawn approximately at the same time are making the assessment of causality of dihydroergocristine difficult.

However, the CHMP underlined the reported case of interstitial pneumopathy since positive rechallenge (symptoms re-occurring on re-administration) was twice observed within a short period (1-3 days) after reintroduction of treatment which is in favour of a causal role of dihydroergocristine.

Moreover, in the 3 other cases presenting no concomitant treatment, the improvement seems only due to the withdrawal of dihydroergocristine, which is in favour of a causal link between pleuropulmonary changes observed and dihydroergocristine. The CHMP noted that, in these 3 cases improvement was clinically and radiologically showed: healed after around 3 weeks-1 month in two cases and improvement after 6 months for the case presenting bilateral pleural thickening.

For the one case of retroperitoneal fibrosis that was reported in the literature (concerning fibrotic plaque), a scan performed one year after the discontinuation of dihydroergocristine revealed a marked reduction of the fibrotic plaque which was considered by the CHMP in favour of a causal relationship between the retroperitoneal fibrosis observed and dihydroergocristine.

Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis. The relationship between fibrosis and serotonergic receptor activation, particularly 5-HT_{2B} receptors by ergot derivatives is extensively described in the literature. Agonism to 5-HT_{2B} receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. Overall, the varying affinity for serotonergic receptors with the different ergot derivatives and the therapeutic doses used may explain the differences observed for notification rates for the fibrotic reactions. Therefore, even if it is highly pharmacologically plausible that ergot derivatives acting as 5-HT_{2B} receptor agonists may induce "serotonergic" valve disease similar to that induced by carcinoid tumours or fibrotic lesions of other tissues, it must be remembered that some ergot derivatives are not 5-HT_{2B} receptor agonists. Therefore, other mechanisms inducing fibrosis cannot be excluded, which suggests a causal link between fibrosis and agonism of 5-HT_{2A} and 5-HT_{1B} receptors and also plausible effect on serotonin transporter.

With regard to ergotism the case of ergot poisoning was difficult to assess taking into consideration the concomitant use of clarithromycin which is known to induce vasoconstriction, vasoconstriction of extremities or hypertensive pressure when administered together with ergot derivatives.

Among the two cases of gastrointestinal vasoconstriction, one case of suggestive dechallenge is in favour of a causal relationship with dihydroergocristine. In the other case reporting death from a mesenteric infarction 8 days after dihydroergocristine administration in a patient also treated with dihydroergotamine per os, the relationship with ergot derivatives cannot be excluded (with a possible potentiation of effects of the two ergot derivatives).

Regarding the four cases of paraesthesia, paresis, pain or discomfort of limbs, symptoms occurred rapidly after introduction of dihydroergocristine (immediately to 2 days in case of IM injection; 2 and 7 days in case of per os administration). The positive dechallenge in the case in which dihydroergocristine was administered per os and in which no concomitant treatment has been reported is in favour of a causal role of dihydroergocristine.

In the case of formication, tachycardia, arrhythmia and chest pain occurring when dosage was increased (of note, the maximum recommended dosage per os was respected), the observed improvement after withdrawal of treatment is in favour of a causal role of dihydroergocristine.

In general, the data from the reported cases of fibrosis (n=12) are indicative of the capacity of dihydroergocristine to induce fibrotic reactions, mostly localised in the pulmonary area considering also the improvement of some patients following discontinuation of the product. Under-reporting can also be suspected because the substance has been on the market for a long time and because fibrosis is already mentioned as an undesirable effect in the product information. In addition, on the basis of the reported cases, vasoconstriction induced by dihydroergocristine cannot be excluded.

2.4. Overall benefit/risk assessment

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

The MAH submitted 27 literature references to support the efficacy of dihydroergocristine on the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*". Of these, 18 concerned placebo-controlled trials, 2 concerned actively-controlled trials and 7 concerned open label studies. Of the 6 randomised, double blind, placebo-controlled studies, 5 studies were not considered relevant by the CHMP because the definition of the diagnosis was not standardised, no primary efficacy criterion was selected among the multi-dimensional assessment, the number of patients per group was small (from 47 to 65), and the treatment duration was short (2 and 3 months). Results are heterogeneous and inconsistent. The CHMP was of the opinion that no efficacy conclusion could be drawn based on these studies. The most recent study (Vellas 1998 - Not published) that became available after the granting of the initial marketing authorisation, uses a standardised definition of diagnosis (patients had to present a moderate memory deficit, with a Mini-Mental State Examination MMSE > 25 and a score total > 38 and < 70 on the Mac Nair and Kahn auto-questionnaire assessing the difficulties in daily activities) and defines the primary efficacy criterion a priori (the Mac Nair and Kahn auto-questionnaire and the Gröber and Buschke test). However, in this study with adequate methodological quality standard, non-significant difference between dihydroergocristine/raubasine and placebo groups was observed.

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

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

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

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

A scientific advisory group (SAG) was convened in December 2012 at the request of the CHMP during which the experts discussed, based on their clinical experience, whether this substance plays a role in the symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia). The group highlighted that the claimed indication is not used anymore in the clinical practice and that from a clinical viewpoint there is no evidence at present that there is a therapeutic need for this active substance in the treatment of cognitive and neurosensorial impairment in the elderly.

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

On the safety side, ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis. The relationship between fibrosis and serotonergic receptor activation, particularly 5-HT_{2B} receptors by ergot derivatives is extensively described in the literature. Agonism to 5-HT_{2B} receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. Overall, the varying affinity for serotonergic receptors with the different ergot derivatives and the therapeutic doses used may explain the differences observed for notification rates for the fibrotic reactions. Therefore, even if it is highly pharmacologically plausible that ergot derivatives acting as 5-HT_{2B} receptor agonists may induce "serotonergic" valve disease similar to that induced by carcinoid tumours or fibrotic lesions of other tissues, it must be remembered that some ergot derivatives are not 5-HT_{2B} receptor agonists. Therefore, other mechanisms inducing fibrosis cannot be excluded, which suggests a causal link between fibrosis and agonism of 5-HT_{2A} and 5-HT_{1B} receptors and also plausible effect on serotonin transporter.

The data from the reported cases of fibrosis (n=12) are in favour of the capacity of dihydroergocristine to induce fibrotic reactions, mostly localised in the pulmonary area considering also the improvement of some patients following discontinuation of the product. An under-reporting can also be suspected because the substance is marketed for a long time as well as because fibrosis is already mentioned as an undesirable effect in the product information.

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

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

Based on these data and based on the pharmacological plausibility, dihydroergocristine is considered to be associated with fibrotic reactions. Moreover the severity of such adverse effects, their possible fatal outcome and the raised risk for patient to develop a fibrotic disorder with long term use according to the authorised indications should be underlined.

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

The CHMP considered the MAHs' proposals for risk minimisation measures. These included limiting treatment duration in certain conditions, contraindicating the product in patients with pre-existing fibrosis or in association with other drugs, the issuing of a DHPC highlighting the risk, a checklist for prescribers, and a pharmacological in vitro study for 5-HT subclass receptors affinity to the product. Although some of the proposed measures could help identify patients with pre-existing fibrosis, relevant concomitant medication and increased risk, the Committee pointed out that they are insufficient to avoid that some patients develop fibrosis and ergotism during treatment.

Overall, the CHMP was of the opinion that no situation could justify exposing a patient to risk of fibrosis and ergotism considering the very limited data on efficacy.

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 dihydroergocristine-containing medicinal products/ suspension where applicable
- Risk of fibrotic reactions and ergotism
- Limited evidence of efficacy in the indications reviewed
- Benefits of dihydroergocristine-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 visual acuity decrease and visual field disturbances presumably of vascular origin
- Acute retinopathies of vascular origin

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 dihydroergocristine cannot be excluded. Available data is in fact indicative of such causal relationship. The seriousness of such adverse effects and their possible fatal outcome is underlined.
- The Committee is of the opinion that the evidence for clinically significant efficacy of dihydroergocristine in the currently assessed indications is very limited, and therefore the potential benefit for patients in these indications is outweighed by the identified risk.

- The Committee considered that the benefit-risk balance of dihydroergocristine containing products:
 - Is not favourable for symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia).
 - Is not favourable for ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin.
 - Is not favourable for acute retinopathies of vascular origin.

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

- The variation to the terms of the marketing authorisation for dihydroergocristine containing medicinal products referred to in Annex I, to delete the below indications (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 visual acuity decrease and visual field disturbances presumably of vascular origin.
 - Acute retinopathies of vascular origin.
- The suspension of the marketing authorisation for dihydroergocristine containing medicinal products referred to in Annex I in the event that no other indications are approved as part of their marketing authorisation. In order to lift the suspension, MAHs must identify a specific patient population for which the benefits of the product outweigh the 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.