27 September 2013
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Assessment report

Ergot derivatives containing medicinal products

International Non-proprietary Name: dihydroergocryptine/caffeine

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

Referral under Article 31 of Directive 2001/83/EC

Note

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

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 18 January 2012, France triggered a referral under Article 31 of Directive 2001/83/EC for the following ergot derivatives containing medicinal products: dihydroergocryptine/caffeine, dihydroergocristine, dihydroergotamine, dihydroergotoxine and nicergoline. Following a national pharmacovigilance review held in 2011 new spontaneous notifications reported with some of those products identified serious cases of fibrosis and ergotism and France considered that this safety concern is not outweighed by the limited evidence of efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications:

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

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

2. Scientific discussion

2.1. Introduction

Dihydroergocryptine is an ergot alkaloid that has an agonist activity on D2 dopaminergic receptors and a partial agonist activity on D1 receptors. In rats, dihydroergocryptine showed to activate antioxidant enzymatic systems physiologically alterated during aging. It is available in combination with caffeine that may improve the digestive absorption of this ergot alkaloid.

From the approved indications of the dihydroergocryptine 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

In fact, dihydroergocryptine being part of the class of ergot derivatives containing medicinal products covered by this procedure is only approved in the above mentioned indications in France and only in combination with caffeine since 1979. Dihydroergocryptine only containing products are approved in other EU Member States but their indications were not in the scope of this referral procedure (e.g. Parkinson's disease) and were excluded from this review.

Two oral forms are available: one tablet (4 mg of dihydroergocryptine and 40 mg of caffeine per tablet), and one oral solution (2 mg of dihydroergocryptine and 20 mg of caffeine per 2 ml).

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)

The MAH provided the seven following studies as supporting evidence of the efficacy of dihydroergocryptine in the above indication. All the studies were double-blind, placebo-controlled, and enrolled a total of 995 patients of which 541 were exposed to dihydroergocryptine/caffeine. One of the studies (in vascular cognitive impairment) was provided but not discussed as supportive in the MAHs' responses.

Berthaux study (1983): This randomised, double-blind, placebo-controlled trial included 154 patients aged between 50 and 70 years (mean age around 62 years), and with at least 3 of the 10 functional symptoms (dizziness, headache, tinnitus, insomnia, memory disorders, relational disorders, a decrease in intellectual capacity, paraesthesia in the lower limbs, night-time cramps and fatigue). Treatments were either dihydroergocryptine/caffeine or placebo. The evaluation for each of the functional symptoms when they existed was performed jointly by the doctor and by the patient himself. The severity of each symptom reported corresponded to a point on a questionnaire rating scale used before the start of the trial (M0), after one month (M1 or D30) and after two months of treatment. A qualitative evaluation was associated with this quantitative criterion in the capacity of a control which evaluated the notion of worsening, improvement, stability or possibly the occurrence of the symptom in question.

Analysis of results, using the statistical method of comparison of results between the group treated with dihydroergocryptine/caffeine and the group treated with placebo was performed with a Student t test. A statistically significant difference between groups was observed for dizziness ($p=0.04$) and relations with a subject's family ($p=0.05$). No difference was observed between dihydroergocryptine/caffeine and placebo on the remaining 8 out of the 10 functional symptoms.

Babeau study (1986): This randomised, double-blind, placebo-controlled trial included 350 patients (60-80 years) with early stage senile cerebral deterioration without dementia or major dependence with respect to the environment, based on clinical criteria of the American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders - DSM III): alteration of previously acquired intellectual abilities, memory disorders, alteration of at least 2 intellectual functions (abstract thinking, cognitive judgement, self-control, mood). Eligible patients had to present with mild or moderate symptoms of chronic cerebral vascular insufficiency defined by the EACG (clinical appreciation scale in geriatrics) scale, complying with conditions for validation of this scale: symptom scores had to be between 3 and 5 for 11 of the 17 items and necessarily for the first 6 items of the scale, that is: mental alertness, memory for recent events, orientation, confusion, anxiety, depression and emotional stability.
Patients received placebo or dihydroergocryptine/caffeine (8 ml/day in 2 doses) during 3 months.

The evaluation was performed with the EACG geriatric clinical assessment scale at D-10, D0 and D90, with a margin which could not exceed 4 days (more or less). The statistical analysis was conducted on 324 subjects, 163 in the dihydroergocryptine/caffeine group and 161 in the placebo group. Effect of dihydroergocryptine/caffeine was different from that of placebo for mental alertness ($p < 0.03$), memory for recent events ($p < 0.0008$), dizziness ($p < 0.002$), and headache ($p < 0.01$). Significant difference between dihydroergocryptine/caffeine and placebo ($p=0.04$) was observed at D90 for total score. This corresponded to a numerical difference of 2.5 points in the EACG scale in favour of dihydroergocryptine/caffeine.

***Poynard et al (1986)*:** This randomised, double-blind, placebo-controlled study of 165 patients (mean around 64 years) who presented at least 3 of 10 subjective symptoms of the so-called cerebrovascular insufficiency were included and treated with dihydroergocryptine/caffeine for 60 days. A statistically significant difference was observed for vertigo and unsociability and a trend was found for headache and paresthesia.

Le Poncin study (1988): This randomised, double blind, placebo controlled study included 50 patients (50-90 years) with mild or moderate symptoms of chronic cerebrovascular insufficiency with no visible organic damage as seen on computerised tomography (CT) scan. Dihydroergocryptine/caffeine was administered at a dose of 8 ml per day during 90 days.

Evaluation was based on clinical, psycho-clinical and psychometric tests. Twenty-one (21) different tests with several items by test were performed. No difference between groups was observed on the majority of the tests. A significant difference between groups was observed on only 5 items. It should be noted that patients in this study presented several symptoms without a standardised diagnosis, and received twice the recommended dose of dihydroergocryptine/caffeine.

Khalil study (1990): This randomised, double blind, placebo controlled study included 140 patients (mean around 63 years), who presented memory disorders of gradual onset (disorders in the recall of recent events or in long-term memory, and difficulties in memory retention). Duration of memory disorders was 4.5 ± 0.2 years on average. Dihydroergocryptine/caffeine was administered as two daily doses of 4 ml during 90 days.

The effects of treatment were evaluated by a psychological test battery to examine memory in the elderly. The memory test battery consisted of the following 7 psychometric tests: memory performance profile (Rey dynamic visual-verbal tests), memory recall of a narrative (Barbizet an auditory-verbal dynamic test), measurement of the faculty for retrieval of a narrative (Wechsler digit span test, Jung's word association test, Wechsler's mental control test, Israel's paired pictures test, Rey's repeated word test). A statistically significant difference between dihydroergocryptine/caffeine and placebo was observed in various psychometric parameters.

Derouesne et al (1998): This study involved 203 patients (65-75 years) who complained about amnesic episodes, problems of attention and concentration. Dihydroergocryptine/caffeine was administered at a dose of 8 ml per day during 12 weeks. Evaluation was based on test of cognitive difficulties of Mc Nair. A significant difference between groups was observed on only 5 items. A 34% improvement of the efficacy criteria was observed in the dihydroergocryptine/caffeine group.

Scrazella study (1992): This double-blind, placebo-controlled, randomised study included 52 patients (56-75 years) with a clinical diagnosis of mild organic brain syndrome (stage 2-3 on the Global Deterioration Scale). During 3 months, patients received placebo or dihydroergocryptine (5 mg and 10 mg twice a day during the first and the second fortnight, respectively; 20 mg twice a day during the second and the third month).
The assessed parameters of efficacy were Rey's words (short and long-term verbal memory), Digit Span (short-term verbal memory), Corsi's test (short-term verbal memory), Digit Symbol Substitution Test (DSST) (visuo-motor abilities), Toulouse-Pieron (selective and sustained attention), Word fluency (semantic memory), and Parkside Behaviour Rating Scale (PBRS) (daily living activities).
The study protocol was completed by 49 patients, 25 of them in dihydroergocryptine group and 24 in the placebo group.
The difference between the treatment was significant in the dihydroergocryptine group, for the following tests: Rey's words after short time (p=0.0001), Digit span (p=0.0045), Corsi (p=0.0199), the word fluency (p=0.0003), Parkside behavior rating scale (p=0.0181). For the remaining 4 tests, no statistically significant difference was found.

Ancillary treatment of Raynaud's syndrome

The MAH provided the five following studies as supporting evidence of the efficacy of dihydroergocryptine in the above indication.

Heuberger study (1982): The aim of this study was to evaluate the clinical effects of dihydroergocryptine/caffeine in the treatment of microcirculatory disorders.
Dihydroergocryptine/caffeine was used as monotherapy in 37 patients with acrosyndrome at a dosage of 8 ml daily. Patients were seen after thirty days of treatment. A repeat Doppler examination of the extremities was performed before initiation of treatment and on day thirty. The chosen patients were broken down as 27 women and 10 men, ranging from 18 to 78 years of age.

The beneficial effect of the studied product was observed in three quarters of patients, all causes combined. A relatively good correlation was observed between clinical improvement and improvement in the arteriolar-capillary circulation visualised by Doppler method: 22 cures and improvements and clinical improvements – 19 improvements in velocimetric tracings. Improvement in functional symptoms and local signs was correlated with Doppler measurements.

Sarrat study (1983): The aim of this study was to evaluate the action of dihydroergocryptine/caffeine based on clinical, rheological and capillaroscopic criteria in vascular

acrosyndrome. The study was conducted on 20 patients (16 women versus 4 men; whose mean age was 40 years with a range of 18 to 60 years) with vasomotor acrosyndrome of the extremities. Capillaroscopy did not demonstrate any major morphological changes; in 6 patients, the diameter of capillaries thin or dilated in the baseline examination appeared normal after 6 months of treatment. More representative were cases with a rheological feature. Thus, out of 18 patients, vasomotricity was improved in 8, and erythrocyte aggregation which existed in 7 patients, was reduced in 5 of them. The background skin color, which was pale in 6 cases at D 0, was pink in 5 cases after treatment, violet in 5 cases, and paradoxically, was also improved in 3 cases at D 180.

Improvement in rheological phenomena, on one hand, relaxation of an arteriolar spasm, on the other hand, was sufficient to explain the decrease or even disappearance of vascular sludge. Out of 20 patients in the study results were considered good in 11, average in 7, and poor in 2 cases.

Gros study (1984): The aim of this study was to evaluate the action of dihydroergocryptine/caffeine in patients with a vascular acrosyndrome of the lower limbs. This study was conducted with open-label design. Dihydroergocryptine/caffeine was administered during the cold weather period for 3 months at a dose 8 ml daily. The patients were followed clinically and para-clinically with vascular functional investigations. Assessments were performed at D0, D30, D90. A total of 20 patients were included (14 women and 6 men; age range was 20 to 70 years).
The evaluation was based on baseline assessment, and the final evaluation concerned the following:

- Clinical evaluation: color of the digits, condition of the tegument, existence of dysaesthesia or not.
- Plethysmography: amplitude of waves under baseline conditions and response to reactive hyperaemia
- Capillaroscopy: micro-circulatory background status, capillary density, morphology of capillary loops, existence of atypical and/or dysmorphic findings, existence of petechiae and vasomotor response after a cold provocation test.

It was noted that there was a very good correlation between improvement in symptoms (14 out of 18 patients) for paroxystic pallor in response to cold. Improvement in amplitude of plethysmographic waves (13 out of 19) translating a microvascular vasospasm and improvement in vasomotor response, after a cold provocation test, with capillaroscopy (15 out of 19), an anatomical corollary of functional response measured by plethysomography.

Vinckier study (1985): The aim of this study was to evaluate the utility of dihydroergocryptine/caffeine in vasomotor symptoms of the extremities, with a paroxystic feature such as Raynaud's phenomenon evolving with purely physical symptoms. Each patient underwent a cold provocation test performed with plethysmography with cooling. The humero-digital gradient provided information on the degree of severity of organic arterial disease and guided the aetiological investigation. The population consisted of 19 women and 6 men mean age 42 ± 5.72 years. The study was conducted with "open-label design". The patients were followed during nine months; they were included in the study during the cold season (between January and March) and were seen again in the cold season (between October and January). Interim tests were systematically performed between April and September (month three) and between June and October (month six).
Dihydroergocryptine/caffeine was prescribed at a dose of 8 ml in two daily doses. Results were scored from 0 to 3 depending on severity observed in each patient at the successive visits.
Plethysmography at 15°C demonstrated a statistically significant improvement in all of the 4 periods during treatment ($p < 0.025$) without this being related to an inter-subject difference. The humero-digital gradient was significantly improved.

Allegra study (1989): The aim of this study was to evaluate the effects of dihydroergocryptine/caffeine on plethysmography and capillaroscopic parameters in patients with idiopathic Raynaud's syndrome. This was an open study on 20 patients, females, with essential Raynaud's phenomenon. A daily dose of 8 ml dihydroergocryptine/caffeine was administred for 3 months during cold season.
The results showed a good correlation between symptoms improvement (number and duration of vasospastic crises), variations of impedance plethysmograpy and capillaroscopic parameters at nail fold.

2.2.2. Discussion

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

The design of the Berthaux study was considered adequate by the CHMP (double-blind, randomised, compared to placebo in 154 patients). However, the duration of treatment (60 days) was considered short according to the indication (i.e. chronic treatment). Patients included in the study presented several different symptoms without standardised diagnosis (at least 3 functional symptoms between dizziness, headache, tinnitus, insomnia, memory disorders, relational disorders, a decrease in intellectual capacity, paraesthesia in the lower limbs, night-time cramps and fatigue). In addition, the CHMP commented that no primary efficacy criterion was defined. Difference between dihydroergocryptine/caffeine and placebo at day 60 was only observed on 2 symptoms (dizziness and relation) out of a total of 10 symptoms. The CHMP was of the opinion that no efficacy conclusion could be drawn.

The design of the Babeau study was also considered adequate by the CHMP (double-blind, randomised, compared to placebo in 350 patients). Patients presented early stage senile cerebral deterioration without dementia or major dependence with respect to the environment, based on DSM-III criteria published by the American Psychiatric Association. However, the CHMP noted that this diagnosis is not any more listed in the latest DSM-IV-TR. Efficacy evaluation was based on the French EACG scale which is composed by 17 items on cognitive symptoms, daily activity, or mood criteria. At day 90, difference between dihydroergocryptine/caffeine and placebo was observed on the total score ($p=0.04$) with a numerical difference between placebo and treatment of 2.5 points which could not be considered clinically relevant according to the scores of EACG scale which could vary between 29 and 107 points.

The design of the Le Poncin study was considered adequate by the CHMP (double-blind, randomised, compared to placebo). However, patients included in the study presented several different symptoms without standardised diagnosis and no primary efficacy criterion was defined. In addition, the patients were administered twice the recommended dose of dihydroergocryptine/caffeine and a significant difference was only observed in 5 out of 21 tests. The CHMP was of the opinion that no efficacy conclusion could be drawn.

With regard to the Khalil study, the CHMP commented that a statistically significant difference between dihydroergocryptine/caffeine and placebo was observed in several psychometric parameters. However, the methodological flaws (e.g. patients included in the study presented memory disorders of gradual onset without standardised diagnosis) and the absence of primary efficacy endpoint do not allow drawing conclusions on clinical efficacy.

For the Scarzella study, the CHMP stated that the number of patients was small (52 patients) and that no primary efficacy criterion was defined. The results were heterogeneous with statistically significant difference in 5 out of the 9 tests. No efficacy conclusions could be drawn.

Regarding the Derouesne study, again a significant difference between groups was only observed in 5 items and the patients were being administered twice the recommended dose of dihydroergocryptine/caffeine.

Overall, the MAHs provided 6 publications (dated from 1983 to 1998) with an adequate design (randomised, double-blind, placebo-controlled) to support the claim for efficacy, plus one study in vascular cognitive impairment which was not further discussed. The number of patients could be considered sufficient in 4 studies (146, 203, 155 and 324 patients) and small in 2 studies (50 and 49 patients). The duration of these studies was short (2 or 3 months) considering the chronic indication approved. Patients included in most of these studies presented various very different symptoms without standardised diagnosis. In 2 studies patients presented a clinical diagnosis of mild organic brain syndrome (stage 2-3 on the Global Deterioration Scale) (Scarzella study) and an early stage senile cerebral deterioration without dementia or major dependence with respect to the environment, based on DSM-III criteria (Babeau study). This later diagnosis is not any more listed in the DSM-IV-TR. Results were heterogeneous and there was no consistency across studies. In general the CHMP was of the opinion that the methodological flaws and the absence of primary efficacy endpoint do not allow to draw conclusions on clinical efficacy or to support an indication with standardised diagnosis.

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

All the studies submitted in support of this indication were considered by the CHMP of poor methodological quality (i.e. uncontrolled, open designed, with a low number of patients (n=20-37)). The studies included young and old patients (18-78 years old) with idiopathic acrosyndrome. Only the Vinckier study mentioned a small group of patients suffering from associated systemic disease. The clinical efficacy endpoints were numerous and heterogeneous with no defined primary efficacy endpoint. The studies mainly assessed functional symptoms, capillaroscopic parameters and plethysmographic parameters whose clinical relevance was considered questionable by the CHMP. There seemed to be a benefit of treatment in approximately 55-75% of patients but the CHMP concluded that these results are in fact difficult to interpret from a clinical point of view and not reliable due to the methodological limitations of the studies.

Based on the submitted clinical data, the CHMP considered that the methodology of these studies was not acceptable, with a low number of patients and no primary efficacy endpoint. The reliability and the clinical relevance of the study results was therefore questionable and preclude any conclusions on the efficacy of the product.

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

Since the launch of the product until March 2012 a total of 70 case reports (41 serious and 29 non-serious) were received. From these cases the ones related to fibrotic reactions were summarised as follows.

One single case of valve disease has been reported where dihydroergocryptine/caffeine was administered concomitantly with another drug product and the intake of dihydroergocryptine/caffeine was unknown. Three cases of pulmonary fibrosis were spontaneously reported during the reference period, including one case in which another aetiology was suspected (silicosis in a tiler). In addition, a single case of pleural fibrosis was described in the literature. No case of cardiac or retroperitoneal fibrosis has been reported with dihydroergocryptine/caffeine.

According to the MAH, no case of ergotism was reported and no pre-clinical or clinical data or epidemiological studies are available with dihydroergocryptine/caffeine.

2.3.2. Discussion

The CHMP was of the opinion that the only case of valve disease should be excluded from this assessment due to the concomitant administration of another product and the lack of confirmed information regarding the treatment with dihydroergocryptine/caffeine.

With regard to the three cases of pulmonary fibrosis the CHMP noted that in one of them another aetiology was suspected. In the two other cases, only idiopathic cause can be suspected based on the provided data. Patients experienced pulmonary fibrosis after several years of treatment (6 years in one case and 10 years in the other). The data about the indications treated and the posology with regard to these cases are not robust. In general, the information was insufficient to conclude to any causality link between dihydroergocryptine and pulmonary fibrosis. Nevertheless, the CHMP commented that the risk of pulmonary fibrosis cannot be excluded taking into consideration that in one of the reported cases improvement was observed after discontinuation of dihydroergocryptine. It was also mentioned

by the CHMP that the small number of reported adverse drug reactions (ADRs) compared to the large exposed population could suggest an under-reporting of the ADRs.

Regarding the published case of pleural fibrosis the CHMP noted that it occurred in the context of the treatment for Parkinson's disease, which is not within the scope of this review. However, it was mentioned that improvement of the patient was observed after discontinuation of dihydroergocryptine which was is favour of a causality link between pleural fibrosis and dihydroergocryptine.

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.

In the French Pharmacovigilance database there were several cases reported where dihydroergocryptine/caffeine was the suspected drug for symptoms related to ergotism. The absence of such reports claimed from the MAHs, raised questions to the CHMP with regard to the way that the data collection was performed by the MAHs.

In general, the data from the reported cases of fibrosis (n=3) are limited in order to draw any firm conclusions, however, the risk cannot be excluded considering the improvement observed when dihydroergocryptine/caffeine was discontinued in one of the three reported cases of pulmonary fibrosis occurring with recommended daily dose. Under-reporting can also be suspected because the substance is marketed since a long time as well as because fibrosis is already mentioned as an adverse drug reaction in the product information.

2.4. Overall benefit/risk assessment

The CHMP has considered the totality of the available data on the safety and efficacy of dihydroergocryptine/caffeine.

Overall, for the indication "*symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in elderly (excluding Alzheimer's disease and other dementia)*", the MAHs provided 6 publications (dated from 1983 to 1998) with an adequate design (randomised, double-blind, placebo-controlled) to support the claim for efficacy, plus one study in vascular cognitive impairment which was not further discussed. The number of patients could be considered sufficient in 4 studies (146, 203, 155 and 324 patients) and small in 2 studies (50 and 49 patients). The duration of these studies was short (2 or 3 months) considering the chronic indication approved. Patients included in most of these studies presented various very different symptoms without standardised diagnosis. In 2 studies patients presented a clinical diagnosis of mild organic brain syndrome (stage 2-3 on the Global Deterioration Scale) (Scarzella study) and an early stage senile cerebral deterioration without dementia or major dependence with respect to the environment, based on DSM-III criteria (Babeau study). This later diagnosis is not any more listed in the DSM-IV-TR. Results were heterogeneous and there was no consistency across studies. In general the CHMP was of the opinion that the methodological flaws and the absence of primary efficacy endpoint do not allow to draw conclusions on clinical efficacy or to support an indication with standardised diagnosis.

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*", all the studies submitted in support of this indication were considered by the CHMP of poor methodological quality (i.e. uncontrolled, open designed, with a low number of patients (n=20-37)). The studies included young and old patients (18-78 years old) with idiopathic acrosyndrome. Only one study (Vinckier study) mentioned a small group of patients suffering from associated systemic disease. The clinical efficacy endpoints were numerous and heterogeneous with no defined primary efficacy endpoint. The studies mainly assessed functional symptoms, capillaroscopic parameters and plethysmographic parameters whose clinical relevance was considered questionable by the CHMP. There seemed to be a benefit of treatment in approximately 55-75% of patients but the CHMP concluded that these results are in fact difficult to interpret from a clinical point of view and not reliable due to the methodological limitations of the studies. The reliability and the clinical relevance of the study results was therefore questionable and preclude any conclusion on the efficacy of the product.

On the safety side, ergot derivatives are long been 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=3) are limited in order to draw any firm conclusions, however, the risk cannot be excluded considering the improvement observed when dihydroergocryptine/caffeine was discontinued in one of the three reported cases of pulmonary fibrosis occurring with recommended daily dose. 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 adverse drug reaction in the product information.

Data provided during a referral under Article 31 in 2007-2008 (EMEA/H/A-31/881) including dihydroergocryptine showed that several cases of fibrosis either pulmonary or cardiac or retroperitoneal were suspected to be associated to the treatment with dihydroergocryptine use for Parkinson's disease treatment (involving dosage five times higher). As a note, one of the above mentioned three cases of fibrosis was reported in 2009 (i.e. after finalisation of the previous referral) which shows that the risk minimisation measures that were imposed at that point in time are not sufficient to exclude the risk.

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

Regarding ergotism, there were several cases reported in the French Pharmacovigilance database where dihydroergocryptine/caffeine was the suspected drug for symptoms related to ergotism. The absence of such reports claimed from the MAHs, raised questions to the CHMP with regard to the way that the data collection was performed. Considering the several reported cases of vasoconstriction and the pharmacological structure of this ergot alkaloid derivative product, ergotism cannot be ruled out.

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. 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 dihydroergocryptine-containing medicinal products/ suspension where applicable
- Risk of fibrotic reactions and ergotism
- Limited evidence of efficacy in the indications reviewed
- Benefits of dihydroergocryptine-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 Raynaud's syndrome

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 dihydroergocryptine/caffeine 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 dihydroergocryptine/caffeine 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 dihydroergocryptine/caffeine 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 Raynaud's syndrome.

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

- The variation to the terms of the marketing authorisation for dihydroergocryptine/caffeine 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 country to country) as well as any relevant reference to these indications, when there are other therapeutic indications approved as part of their marketing authorisation:

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

- The suspension of the marketing authorisation for dihydroergocryptine/caffeine 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.