EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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CHMP referral assessment report

Ergot derivatives containing medicinal products

International Non-proprietary Name: dihydroergotamine

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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Table of contents

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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

Dihydroergotamine mesilate (dihydroergotamine - DHE) is a semi-synthetic derivative of ergotamine. It has long been used in the treatment of migraine on the grounds of its vasoconstrictor activity, which is milder than that of ergotamine. In the preventive treatment of migraine, dihydroergotamine is administered orally for long term. In the acute treatment of migraine, it is administered parenterally or in the form of a nasal spray because of the low bioavailability of the unchanged drug by the oral route.

The efficacy of dihydroergotamine in the acute treatment of migraine attack is not within the scope of this referral and will not be discussed. Likewise, the efficacy of dihydroergotamine administered by subcutaneous, intramuscular or intravenous injection or intranasal spray is not within the scope of this referral and will be not discussed.

From the approved indications of the dihydroergotamine 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):

- Prophylaxis of migraine headache
- Orthostatic hypotension
- Symptomatic treatment of veno-lymphatic insufficiency

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

Prophylaxis of migraine headache

The following studies were provided by the MAHs as supporting evidence of the efficacy of dihydroergotamine in the prophylaxis of migraine.

Neuman M (1984): This was a double-blind, randomised, placebo-controlled study to assess the preventive efficacy and safety of dihydroergotamine in patients suffering from migraine. The patients enrolled in the study had to require a maintenance treatment for migraine, the migraine diagnosis was confirmed and they were presenting at least 3 migraine attacks per month and had not taken any preventive treatment for migraine in the previous 15 days. Twenty patients were included in each group and received a twice daily administration of either dihydroergotamine 10mg/day or matching placebo, for one month. The treatment efficacy was assessed by the investigator using the patient's diary cards recording the presence of attacks, the intensity and duration of each migraine attack and a clinical global assessment of the treatment efficacy. The population randomised in the 2 groups was comparable: 45% females in both groups and the mean age was 49.5 / 46.7 years in the dihydroergotamine and placebo groups, respectively. The monthly frequency of migraine attacks at baseline was comparable between the 2 groups: 3.30 ± 0.68 and 3.31 ± 0.60 in the dihydroergotamine and the placebo groups respectively. The reduction in the number of attacks in the dihydroergotamine group and in the placebo group was -1.95 vs -0.42 ($p < 0.0001$). The severity and the number of attacks with a duration longer than 6 hours were statistically lower under dihydroergotamine than under placebo. These objective results were confirmed by both the patient and the investigator global assessments, showing a statistically significant difference in favour of dihydroergotamine (sufficient efficacy reported in: 65% patients in the dihydroergotamine group and 15% in the placebo group; $p < 0.001$).

Buscaino GA (1991): This was a double-blind, randomised study comparing 2 treatment regimens, dihydroergotamine once daily and twice daily administration. The study period was 3 months: the first month was a run-in period without drugs and the double-blind treatment was administered during the subsequent 2 months, patients were receiving dihydroergotamine either 5 mg twice daily or 10 mg once daily. Patients suffered from common migraine with a monthly frequency of 2 to 8 attacks during the 3 months before study entry. The assessment of treatment efficacy was using the monthly migraine attacks frequency, the severity and the duration of the attacks over one month. Ninety patients (63 women and 27 men; mean age, 37 years) were randomly assigned to either group (n=45 per group). The results showed the preventive treatment to be effective, with a reduction ($p < 0.01$ between times) in the severity and frequency of headache and the associated symptoms, independent of the dosage scheme. The author concluded that dihydroergotamine may be administered either in a single dose or twice a day with comparable therapeutic efficacy.

Cabrières F (1988): This open-label study was assessing the efficacy and safety of dihydroergotamine for the prophylaxis of migraine as a chrono-treatment, being prescribed as a function of the time of onset of the migraine attacks: 10 mg, once a day in the evening when attacks were occurring in the morning, 10 mg once a day in the morning when attacks were occurring at fixed times during the day, and in a twice daily administration for other patients. The treatment duration was 3 months, with a visit at 2 and 3 months. The efficacy criteria were the attacks frequency and the clinical global assessment of the efficacy. A total of 1900 patients with migraine were divided in 2 subpopulations either with a circadian rhythm in migraine onset (n=885, 46.6%; mainly in the morning, 68%) or migraine attacks occurring randomly during the day (n= 1015, 53.4%). The mean attack frequency per month was higher in the sub-group of "chrono-migraineurs" (6.5) compared to patients presenting attacks with no fixed time of onset (5.4). In the patient population the gender distribution was 1 male for 4 females and the mean age was 41 years; the baseline mean attack frequency was 5.9/month and the mean duration of attacks was 24 hours. About half of the population (n=885) reported chrono-migraine attacks, mainly in the morning (68%), 10% had attacks in the afternoon, 15% in the evening, and 4% during the night. The analysis considered 2 groups: patients receiving the once daily and those receiving the twice daily regimens. Dihydroergotamine had a fast onset of action, showing a 40% decrease in the number of migraine attacks over the first month, which increased over time and was 75% at 3 months. The percentage of responders at 3 months, defined by a 50% reduction of the migraine frequency from baseline, was 76% and 74% in patients receiving the once daily treatment or the twice daily treatment, respectively. Regarding the migraine attacks freedom rate, 37% and 39% of patients were free of migraine over the last 3rd month in the respective two sub-populations.

Vergeade C (1991): This was an open-label study of dihydroergotamine prescribed as a single morning dose of two 5 mg capsules for 3 months in the maintenance treatment of migraine. Patients, diagnosed with migraine, did not have any migraine attacks with a fixed time of onset. The attack frequency, the duration, the combined symptoms and the daily activities during the attacks were recorded during the study. The patient population was recruited in a general practice setting; 914 patients were enrolled, 81% were females, the mean age was 40 years, the mean duration of migraine history was 8.5 years and 70% had already received preventive treatment in the past. The mean attack frequency was 6.7/month, and in 44% patients their duration was longer than 6 hours. A single morning dose of dihydroergotamine was followed by a clinically significant decrease in the frequency of attacks, being already equal to 30% after 1 month and reaching 73% after three months; 89% of patients were responders (50% reduction of attack frequency from baseline) and 32% were free of attacks over the last 3rd month. In addition, the duration of attacks and the accompanying symptoms also diminished.

Schott (1977): This study of dihydroergotamine capsules in the treatment of chronic migraine syndrome included 38 subjects (average age 35 years) for a period of 2 months. A reduction in the number of attacks per month was observed ($p<0.00001$); of the 20 subjects who suffered from morning migraines, 18 of them showed a reduction in the number of attacks ($p<0.001$).

Boudouresques (1977): This study of dihydroergotamine capsules in the treatment of chronic migraine syndrome included 33 subjects (16 cases with migraine, 17 with vascular headache) and assessed the efficacy in a controlled study versus placebo in accordance with 6 assessment criteria: severity of attacks ($p<0.01$); frequency of attacks ($p<0.001$); duration of attack ($p<0.01$); prodrome of attack ($p<0.01$); accompanying signs ($p<0.001$); impact on social life ($p<0.001$).

PROMISE (2004): This recent post-authorisation study is a multicentre, randomised, double blind, placebo-controlled trial including 363 subjects. The efficacy of dihydroergotamine was compared to placebo in the reduction of the frequency of migraine attacks. However, no statistical significance between dihydroergotamine and placebo in the attack frequency was reached (primary efficacy criterion). The secondary criteria evaluated (average duration of an attack, average total duration of attacks, use of emergency analgesics during attacks, overall assessment score by the patient) were in favour of dihydroergotamine. Migraine attack frequency difference did not reach statistical significance because the attack frequency (primary efficacy criterion) decreased markedly in the two treatment groups (Pradalier, Lantéri-Minet et al 2004). A post-hoc analysis of subgroups (functional handicap and eligible for basic treatment in accordance with the recommendations of ANAES-MSQ<80) was carried out retrospectively. After 4 months of treatment, dihydroergotamine, used at a dosage of 10 mg per day, demonstrated its superiority over a placebo with regard to the main criteria:

- Reduction in the frequency of attacks per month: -2.02 vs. -1.65 ($p=0.04$)
- Increase in the response rate 50%: 68% vs. 55% ($p=0.03$)
- Reduction in the average duration of attacks: 4.8 hours vs. 0.5 hours ($p<0.05$)

The literature data submitted by the MAHs showed both positive and negative results with regard to the efficacy of oral dihydroergotamine in the prevention of migraine.

An overview of the efficacy studies conducted with oral dihydroergotamine in the prophylaxis of migraine and their weaknesses can be found below.

Study	**n**	**duration**	**placebo**	**active control**	**results**	**weakness**
Pradalier, 2004	363	5 months	yes	no	similar as placebo	
Neumann, 1984	40	1 month	yes	no	better than placebo	st*
Martucci, 1983	90	45 days	yes	no	better than placebo	st*
Boudouresques, 1977	33	15 days	yes	no	better than placebo	ig*
Autret, 1987	115	2 months	yes	no	similar as placebo	
Bousser,1988	38	8 weeks	yes	no	better than placebo	ct*
Buscaino, 1991	90	3 months	no	no	no difference between two treatments	ne*
Cabrière, 1988	1900	3 months	no	no	"good safety and efficacy"	uc*
Danic, 1991	914	3 months	no	no	"good efficacy"	uc*
Schott, 1977	38	2 months	no	no	"good efficacy"	uc*

Bonuso, 1983	41	2 months	no	amitryptyline	mixed	ig*
Frediani, 1991	30	4 months	no	dihydroergocryptine	dihydroergotamine inferior to dihydroergocryptine	

*st: statistics, ig: inhomogeneous study population, ct: combination therapy, ne: no efficacy endpoint, uc: uncontrolled design

Orthostatic hypotension

Two studies that were included in the initial registration dossier were submitted by one of the MAHs and are summarised below.

Benoit (1977): Thirty-six (36) patients suffering from orthostatic hypotension in psychiatric patients (probable cause was the medication they received for their condition) were studied between April 1976 and January 1977. Dosing was 5 mg dihydroergotamine twice daily (of this 1.5 mg immediately releasing and 3.5 mg as timed release micro granules). No statistical analyses were made of the results, but the author reported 66.5% (24 patients) having a good response to dihydroergotamine medication.

Boudouresques (1977): The effects of dihydroergotamine in orthostatic hypotension were evaluated. Seventeen (17) out of 28 patients suffered of clinostatism or orthostatic hypotension. Fourteen (14) (82%) out of those patients responded well to treatment with dihydroergotamine.

The rest of the evidence provided by the MAHs was based on literature data and the most significant studies are described below.

Thulesius, Berlin (1986): This double-blind, placebo controlled study with 10 mg per day dihydroergotamine was conducted in patients with orthostatic hypotension induced by treatment with psychotropic drugs. Treatment showed a significant effect in preventing immediate drop in blood pressure after standing up. It also showed an effect in preventing an abrupt drop in blood pressure with change of posture hinders symptoms of dizziness and faintness.

Lübke *(1976)*: Thirty-six (36) outpatients with a manifest orthostatic syndrome were the subject of this double-blind study to investigate the influence of dihydroergotamine and placebo over a 4-week period. In the majority of subjects, the dosage was 1 tablet (2.5 mg) 3 times a day. In the test group with dihydroergotamine (17 subjects), a normalisation of circulatory regulation occurred in all cases. In contrast, the placebo group (19 patients) showed no changes.

Krüger, Neff (1974): This double-blind study was conducted in 20 subjects with essential orthostatic syndrome. The treatment duration with dihydroergotamine was 128 days. The superiority of dihydroergotamine both with regard to its effect on the changed cardiovascular parameters occurring in the orthostatic syndrome (pulse rate, systolic and diastolic blood pressure, pulse pressure) and to its beneficial effect on the subjective symptoms accompanying these changes was found to be statistically significant (p=0.05–0.01) to highly significant (p=0.001).

An overview of the efficacy studies, conducted with oral dihydroergotamine in orthostatic hypotension and their weaknesses can be found below.

Study	**n**	**duration**	**placebo**	**active control**	**results**	**weakness**
Thulesius, 1986	58	1 week	yes	no	better than placebo	short
Lübke, 1976	36	4 weeks	yes	no	better than placebo	
Lang, 1976	40	1 month	(no)*	no	"good efficacy"	ig,(uc)
Gemeinhard, 1981	51	90 days	no	etilefrine/etilefrine+DHE	DHE inferior to etilefrine	
Said, 1987	16	1 month	no	no	"good efficacy"	ig,sg,uc
Conté, 1976	40	90 days	no	no	"good efficacy"	ig,uc
Bevegard, 1976	5	7 weeks	no	anti gravity suit	equal anti gravity suit	sg,uc
Jansen, 1980	42	2 months	no	etilefrine	combination of etilefrine+DHE better than etilefrine	ct

Bojanovsky, 1974	20	14 days	yes	no	DHE efficacious after amitryptiline	ig, sg
Boismare, 1974	15	7 days	yes	heptaminol,neosynephrin	inconclusive	sg
Krüger, 1974	20	128 days	yes	no	better than placebo	sg

st: non reproducible statistics, ig: inhomogeneous study population, ct: combination therapy, ne: no efficacy endpoint, uc: uncontrolled design, sg: small study groups
*with a placebo washout phase

Several MAHs considered that there is not enough evidence to support the efficacy of dihydroergotamine in orthostatic hypotension.

Symptomatic treatment of veno-lymphatic insufficiency

In general, no clinical studies have been performed by the MAHs and several MAHs commented that there is a lack of robust published clinical data to support efficacy of dihydroergotamine in the symptomatic treatment of veno-lymphatic insufficiency. The studies that provide the most important results on the clinical experience of dihydroergotamine in this indication are summarised below.

Wenzel-E et al (1989): The background of this clinical study was a previous report on the treatment of two patients with Klippel-Trenaunay syndrome in clinical practice, which brought interesting observations of the efficacy and the side effects of dihydroergotamine. This led to the decision to carry out a validation study in 12 patients suffering from chronic venous insufficiency (CVI). The patients were treated with 0.25 mg or 0.5 mg dihydroergotamine intravenously, and after that with 7.5 mg orally for one week. Before and after treatment measurements of venous capacity, microcirculatory parameters and rheological parameters were performed. Following the intravenous injection of 0.25 to 0.5 mg dihydroergotamine the venous capacity decreased significantly in a dose-dependent relationship. The flow of erythrocytes in capillaries measured under resting condition was significantly lower and peak flow of reactive hyperaemia decreased. No relation was found between the dose of dihydroergotamine administered and the particular side effects (stomach trouble, increase in diastolic blood pressure) in 2 of the 12 patients. After oral treatment patients showed signs of subjective improvement of their complaints.
The MAH commented that in this open-label study, the number of patients was low, which limit the reliability of the clinical study. In addition, the effects are mainly reported with the intravenous administration which is not in the scope of this referral procedure for dihydroergotamine.

Bjerle et al (1979): This is a small placebo-controlled study to demonstrate efficacy of dihydroergotamine in the treatment of venous insufficiency. The effect of oral treatment with 10 mg dihydroergotamine was evaluated during a 4 week double blinded study on 18 patients with primary varicouse veins. It was reported that venous pooling and venous reflux were significantly reduced in the dihydroergotamine group.

2.2.2. Discussion

Prophylaxis of migraine headache

In the Neuman study, patients were treated with 10 mg of dihydroergotamine or placebo. At the baseline, monthly frequency of migraine was 3.30 in the dihydroergotamine group and 3.31 in the placebo group. After 1 month of treatment it was 1.35 in the treated group and 2.98 in the placebo group. The difference after the treatment was -1.95 for the dihydroergotamine group and -0.42 in the placebo group ($p<0.0001$). The CHMP pointed out that even if the difference between the two groups is statistically significant, in this study a small number of patients per group ($n=20$) were treated and the treatment duration was short (one month). According to the European Guidelines on clinical investigation of medicinal products for the treatment of migraine, the recommended treatment period should be at least 3 months after titration and an observation after the treatment for continuing efficacy is essential.

The Buscaino GA study compared two treatment regimens (dihydroergotamine 10 mg one daily and dihydroergotamine 5 mg twice daily) over 2 months. The assessment of efficacy parameters showed that there was no difference between the 2 treatments groups. However, no validated non-inferiority design was used, a small number of patients were included and the treatment duration was short and

in the absence of placebo group for internal validation, this study was not considered contributive by the CHMP.

In the open-label studies (Cabrières and Vergeade) a large number of patients were enrolled (1900 and 914 respectively). Due to the lack of a controlled group in these studies and considering the high placebo effect in migraine patients the CHMP was of the opinion that no conclusion on the efficacy of dihydroergotamine in migraine prophylaxis could be drawn and the results can only be considered of supportive character.

The Schott and Boudouresques studies were not carried out with an up-to-date methodology: open design, cross-over comparative studies without placebo group, small number of patients included, short time treatment duration, type of migraine was not clearly defined. Based on these data the efficacy of oral dihydroergotamine in the prevention of migraine could not be confirmed.

The most recent study, i.e. the PROMISE study, was considered by the CHMP to have an appropriate design (double-blind, placebo controlled). A total of 363 subjects were treated with dihydroergotamine or placebo during 4 months after 1 month of placebo "run-in". The frequency of attacks of migraine (the primary efficacy criteria) was not statistically significant (dihydroergotamine group (-1.84 ± 1.55) vs placebo group (-1.67 ± 1.49) (p=0.220)). For the percentage of responders (61.1% in the dihydroergotamine group vs. 55.9% in the placebo group) the difference was not statistically significant.
A post-hoc analysis was performed in the sub-group of patients (n=288) with functional handicap and quality of life (QOL) decrease (defined by Migraine Specific Quality of Life, MSQ<80). After 4 months of treatment, the attack frequency decreased by 2.0 ± 1.6 (–60.0%) with dihydroergotamine versus 1.7 ± 1.5 (–48.8%) with placebo (p = 0.014 for the relative variations). No significant improvement over placebo was observed in the subset of patients with unaffected QOL. The efficacy of dihydroergotamine in the prevention of migraine in this study has not been demonstrated taking into account that there was no statistically significant difference between dihydroergotamine and placebo with respect to the reduction of the frequency of migraine attacks (the primary efficacy criterion) in the overall population. The CHMP noted that according to the European Guidelines the use of QOL measures are not fully established in migraine and the analyses in the subpopulation should be pre-planned. The results of subgroups effects should be interpreted with caution when primary criteria are not met. As proposed by the authors, a large, randomised, double-blind, placebo-controlled trial investigating dihydroergotamine for the prevention of migraine specifically in patients with impaired QOL should be required to confirm the efficacy. This was endorsed by the CHMP and in conclusion, the efficacy of dihydroergotamine in the prophylaxis of migraine was not considered demonstrated.

The literature data indicate a possible efficacy of oral dihydroergotamine in migraine prophylaxis, but definite scientific proof remains weak. There is little evidence from double-blind, placebo-controlled clinical trials and no uniform picture of the efficacy of oral dihydroergotamine in the prevention of migraine emerges from these studies since studies reported both positive and negative results.

In conclusion, the studies provided by the MAHs were not carried out with up-to-date methodology. The number of patients included was small and the duration of treatment was too short. In the only recent, large study with appropriate design (PROMISE study) there was no statistically significant difference between dihydroergotamine and placebo with respect to the reduction of the frequency of migraine attacks (the primary efficacy criterion) in the overall population.

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.

Orthostatic hypotension

The uncontrolled open label trial of Benoit included 36 psychiatric patients with orthostatic hypotension. The CHMP noted that no statistical analysis of any kind was performed and was of the opinion that this study does not meet current standards to prove efficacy of oral dihydroergotamine in the treatment of orthostatic hypotension.

For the Boudouresques study the CHMP commented that in this uncontrolled trial, the study population was limited to 37 patients who were under the treatment of antipsychotic drugs. The duration of dihydroergotamine treatment varied between 30 and 90 days and only a fractional part of the patients was suffering from orthostatic hypotension. The CHMP was of the opinion that this study does not meet current standards to prove efficacy of oral dihydroergotamine in the treatment of orthostatic hypotension.

The CHMP stated that only one study, Thulesius (1986), demonstrated a significant decrease of immediate drop in blood pressure after standing up with 10mg per day dihydroergotamine compared to placebo, in patients with hypotension induced by treatment with psychotropic drugs. The design of this study was considered acceptable by the CHMP (i.e. controlled, randomised, double-blind) but the size of the study was considered small (n=58). In addition, patients were included in the study if they displayed a reduction of systolic blood pressure of more than 10 mmHg, which does not comply with the established definition of orthostatic hypotension (at least 20 mm Hg below baseline). Systolic blood pressure of the placebo and the dihydroergotamine group differed already at baseline. Efficacy was assessed by comparing absolute blood pressure measurements after treatment rather than comparing the differences between supine and standing position which was not considered acceptable.
The CHMP also stated that the study population, consisting only of drug induced orthostatic hypotension patients, is not representative to conclude on the efficacy of dihydroergotamine in the total population of orthostatic hypotension patients.

The Lübke study showed significant reduction in blood pressure falls from supine to standing position. The treatment dose of dihydroergotamine, however, was adapted according to individual treatment needs resulting in different doses in different patients. Together with intransparent statistics (only means are given) as well as inadequately defined inclusion criteria, this study does not provide solid evidence for a treatment efficacy of dihydroergotamine in orthostatic hypotension.

The Krüger study is double-blinded and addresses patients with non-drug induced orthostatic hypotension. In this study the dihydroergotamine dose was adjusted to individual therapeutic response (reduction to 2.5 mg/d or increase up to 12.5 mg/d). As no individual measurements are provided, the statistical results cannot be verified. Subjective symptoms at baseline differ massively between treatment and placebo group. In conclusion, the CHMP commented that the study does not provide relevant scientific evidence of efficacy.

The CHMP also noted the position of several MAHs that there is not enough evidence to support an indication of oral dihydroergotamine in orthostatic hypotension.

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 treatment of orthostatic hypotension. Based on the clinical experience the group considered that dihydroergotamine has only been used rarely for the treatment of orthostatic hypotension with no clear benefit to the patients. In addition, it was the IV formulation of the product that was used and not the oral formulation that is in the scope of this referral procedure. Therefore, the group was of the opinion that based on the available evidence there is no need for this substance as there is no clear subset of patients that would benefit from it.

Symptomatic treatment of veno-lymphatic insufficiency

The open label study (Wenzel-E et al, 1989) discusses the use of dihydroergotamine in venous insufficiency. Twelve (12) patients suffering from peripheral venous insufficiency were treated first with intravenous dihydroergotamine followed by oral dihydroergotamine administration for one week. Although significant reduction in venous capacity, capillary flow of erythrocytes and peak flow of reactive hyperemia were demonstrated, due to a very small study group, the uncontrolled design and other methodological limitations, the CHMP could not draw any conclusion on the efficacy of dihydroergotamine from the data presented.

In the small placebo controlled study (Bjerle et al. 1979), the effect of oral treatment with 10mg dihydroergotamine was evaluated during a 4 week double blinded study on 18 patients with primary varicouse veins. Although venous pooling and venous reflux were significantly reduced in the dihydroergotamine group, the CHMP considered that the small study population, the lack of a primary endpoint, the soft inclusion criteria and a not entirely traceable statistical analysis limit the interpretation of the results.

The CHMP also noted the position of several MAHs that there is not enough evidence to support an indication of oral dihydroergotamine in the symptomatic treatment of veno-lymphatic insufficiency.

Overall, very few studies have been conducted in patients with veno-lymphatic insufficiency. These studies are old and of poor methodological quality: uncontrolled, open designed, with a low number of patients (n=12 in Wenzel, 1989, the most recent study). Some of them were conducted with the intravenous administration which is not in the scope of this referral procedure for dihydroergotamine. The patients disease is not well defined, nor the efficacy endpoints. The relevance of clinical endpoints is questionable. The CHMP was of the opinion that no scientific conclusion can be drawn regarding the efficacy of dihydroergotamine based on these study results.

2.3. Clinical safety

The MAHs submitted their own overviews and critical summaries of all spontaneous reports of fibrotic reactions (cardiac with or without pulmonary arterial hypertension, pulmonary, pleural, peritoneal, retroperitoneal, etc) and ergotism with their ergot derivatives-containing medicinal products. A review of all other available data (i.e. literature data, pre-clinical data, and other clinical data including epidemiological studies) that were relevant to evaluate the risk of fibrosis was provided where possible.

2.3.1. Results

Risk of fibrosis

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

A total of 83 cases of fibrosis have been reported; 5 cases were duplicates and 3 cases reported by one of the MAHs were not fibrotic events, leading to a total of 75 cases.

The localisation of the fibrosis reported was as follows: 19 cardiac (including 3 reported with pulmonary hypertension), 3 mediastinal, 13 pleural (including 1 with an associated retroperitoneal localisation), 9 pulmonary, 24 retroperitoneal (including 1 with mediastinal localisation, 1 with cardiac localisation, and 3 with pleural localisation). Moreover, 5 cases have been reported with an isolated pulmonary hypertension and 2 as suspected fibrosis.

Considering the 75 cases reported, 19 have been considered as not assessable or no conclusion could be drawn on the basis of the data provided, causality of dihydroergotamine has been excluded in 5 cases, one case of potential pulmonary fibrosis and cardiac malformation was described in a newborn exposed in utero. This leads to a total of 50 cases where relationship between dihydroergotamine and fibrosis reported cannot be excluded.

With regard to these 50 cases of fibrotic reactions:

- 18 cases were clearly described, with long duration of treatment (mean 12.3 years; extremes ranged from 2 to 30 years), no concomitant suspected drug. Treatment was discontinued in 12 cases and the outcome was reported as improving or recovered in 7 of these 12 cases.
- 8 cases were reported with concomitant use of a drug well known to induce fibrosis (benfluorex, dexflenfuramine, pergolide), 9 were reported with a beta-blocker or fenofibrate, and 8 were overexposed to ergotamine derivative drug. One case of pleural fibrosis was also confounded by exposition to asbestos and in one case of retroperitoneal fibrosis the patient had a relevant medical history (radiation therapy, meningioma, leukaemia). However, duration of treatment was long in these cases (mean duration: 6.4 years - extremes ranged from 3 months to 18 years), treatment was discontinued in most of the cases (17/26) and the outcome was reported as improving or recovered in 9 of these 17 cases.
- In 6 cases information was lacking on concomitant drugs and medical history.

An overall evaluation of these 50 cases where causality of dihydroergotamine cannot be excluded is presented below.

Age of the patients (not reported for 2 patients)

- Range: from 31 to 86 years old
- Mean : 58.9 years old

Gender of the patients
- 30% male
- 70% female

Seriousness of the cases
- 37/40 cases were reported as serious (seriousness not reported for 10 cases)

Indication of treatment (not reported in 13 cases)
- Migraine: 27 cases (including 2 patients with an additional indication: hypotension)
- Headache: 4 cases
- Hypotension: 6 cases (including orthostatic hypotension in 2 cases)

Duration of treatment (not reported in 9 cases, and unclear for 5 cases: “few months”, “long time”, “several years”)
- Range: 3 months to 30 years
- Mean: 9.1 years

Time to onset (not reported for 20 cases, unclear for 1 case: “few months”)
- Range: 3 months to 30 years
- Mean 7.1 years

Dosage (not reported for 28 patients)
- Range: 1 mg per day to 10 mg per day
- For 10 patients dosage was 9-10 mg/day (upper limit)

Discontinuation of dihydroergotamine after the reaction (not reported in 16 cases)
- Yes: 31 patients
- No: 3 patients

Dechallenge (not reported for 31 cases)
- Positive: 11 cases
- Negative: 8 cases

Outcome (not reported in 13 cases)
- Patients recovered: 11 cases (including 7 cases of retroperitoneal fibrosis)
- Patients improving: 11 cases (including 1 with sequeale)
- Patients not recovered: 13 cases (including 5 cases of cardiac fibrosis and 5 of retroperitoneal fibrosis)
- Death: 2 patients (related to pulmonary fibrosis in one case)

A French pharmacovigilance survey was performed in 2011 on dihydroergotamine and some complementary information can be found below.

Eight additional cases of potential fibrosis have been reported in the frame of the French survey on dihydroergotamine including 5 serious cases. Retroperitoneal fibrosis was reported in 3 cases and cardiac reaction was reported in the 5 remaining cases. One was reported as mitral insufficiency, 3 were reported as valvulopathy or aortic / mitral insufficiencies and one case was reported with an unknown brand name of dihydroergotamine.
A co-suspected drug was reported in 5 cases (beta blocker in one case, with benfluorex in 3 cases, and methysergide in 1 case). Duration of treatment was not reported in 3 cases and extremes ranged from 1 to 7 years for the remaining cases.
For 3 cases, causality of dihydroergotamine is doubtful given a long time treatment with a concomitant suspected drug (benfluorex, ergotamine) and an unknown or short (6 month) duration of treatment with dihydroergotamine.
Causality of dihydroergotamine cannot be excluded in 4 cases including one case where it was reported a long time treatment, a negative etiologic assessment, no concomitant suspected drugs and a positive dechallenge after dihydroergotamine discontinuation and treatment with corticosteroids.

Ergotism
A total of 134 cases of ergotism or symptoms potentially related to ergotism (e.g. ischemic colitis, peripheral ischemia, paraesthesia, pain in extremities, vasospasm, etc) have been reported by the MAHs.

Among these 134 cases, 21 cases have been excluded as they were not considered as ergotism, were too poorly documented to allow for an assessment, or causality of dihydroergotamine was excluded. For the 113 remaining cases causality of dihydroergotamine cannot be excluded, including 56 cases that have been considered as strongly related to treatment with dihydroergotamine. Of these 56 cases, 24 cases occurred in a context of overdose or interaction with a contraindicated CYP3A inhibitor or vasoconstrictive agent whereas for the 32 remaining cases dihydroergotamine was used as recommended.

Considering those 32 cases, the mean age of patients was 41 years-old (extremes ranged from 4 to 73 years), time to onset of the reaction ranged from 20 min to 2 months (mean: 9 days) after dihydroergotamine initiation, dechallenge was positive for 17 cases (not reported for 11 cases) and 65% of the cases were serious. Of them, in 5 cases patients recovered with sequelea, 3 did not recover and 3 patients underwent a surgery (one was amputated, 1 had a colon resection, and 1 had a resection of the small bowel).

2.3.2. Discussion

Risk of fibrosis
On the safety side, the CHMP commented on the problem of under-reporting for this product considering the period that it is on the market. Under-notification can be suspected given that:

- Adverse drug reactions with a substance marketed for a long time are generally less reported
- Fibrosis is mentioned in several current European Summaries of Product Characteristics (SmPCs) and expected reactions are often less under-reported
- Fibrosis is also an insidious reaction that occurs after a long period of treatment and thus with often a delayed diagnosis.

Moreover, safety data provided by some MAHs are incomplete (gap between reviewing period and marketing period of the product) and it cannot be excluded that cases reported with their products are lacking.

Overall, 8 cases of fibrotic adverse reactions from a French survey conducted in 2011 and 50 cases among the 75 cases reported by the MAHs have been considered as potentially related to dihydroergotamine including 24 with no confounding factor. One case was confounded by medical history and in 25 cases co-suspected drugs were reported: benfluorex (4 cases), dexflenfuramine (4 cases), pergolide (1 case), beta blockers (9 cases), fenofibrate (2 cases) and ergot derivative drug (8 cases). These co-suspected drugs are known to induce fibrosis. However the CHMP noted that beta blockers are not widely recognised as a cause of fibrosis. In some published literature, they are considered as an aetiology of retroperitoneal fibrosis (*P. Meier et al, La fibrose rétropéritonéale, une maladie inflammatoire méconnue. Observations cliniques et revue de la littérature. Néphrologie Vol. 24 n° 4 2003, pp. 173-180*).

In the reported cases, dihydroergotamine is mostly indicated for migraine or headache (30 patients) and used with the recommended daily dosage. As expected, fibrosis occurred mostly in female patients (68%) after long time of treatment with dihydroergotamine (9.1 years on average) and the most frequent type of fibrosis reaction reported was retroperitoneal (36%), followed by cardiac (30%) and pleural (18%).

Almost all cases were serious (93% of the cases where seriousness was reported) and treatment with dihydroergotamine was discontinued in 91% of the cases (for which information is available) and in 57% of these cases, the outcome has been reported as improved or recovered. However, the CHMP noted that for most of these patients an improvement or recovering had been observed after corticosteroid treatment or surgery (valve replacement), and in most cases the improvement is stated based on clinical symptoms (no scan).

Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis. The relationship between fibrosis and serotoninergic receptor activation, particularly 5-HT_{2B} receptors by ergot derivatives is extensively described in the literature. Agonism to 5-HT_{2B} receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. Overall, the varying affinity for serotoninergic receptors with the different ergot derivatives and the therapeutic doses used may explain the differences observed for notification rates for the fibrotic reactions. Therefore, even if it is highly pharmacologically plausible that ergot derivatives acting as 5-

HT_{2B} receptor agonists may induce "serotonergic" valve disease similar to that induced by carcinoid tumours or fibrotic lesions of other tissues, it must be remembered that some ergot derivatives are not 5-HT_{2B} receptor agonists. Therefore, other mechanisms inducing fibrosis cannot be excluded, which suggests a causal link between fibrosis and agonism of 5-HT_{2A} and 5-HT_{1B} receptors and also plausible effect on serotonin transporter.

To conclude, given the cases reported for a reaction difficult to diagnose early (delayed symptoms) and probably under reported, the use of the drug at an approved dosage, added to a plausible pharmacological profile, dihydroergotamine is considered to be strongly associated with a risk of fibrotic reactions. In addition, given that fibrosis is a serious life threatening reaction, observed after long duration of treatment with dihydroergotamine(a drug used in indications requiring long duration of treatment) this has an impact on the benefit-risk balance of the products. Moreover, the 8 new spontaneous notifications reported during the French survey conducted in 2011 show that the risk minimisation measures that are currently in place are not sufficient to prevent the risk of fibrotic reactions.

Ergotism

With regard to the risk of ergotism, the review of cases provided by the MAHs was not exhaustive and the methodology used to retrieve cases of ergotism was unclear for most of the MAHs. Some symptoms related to ergotism may be confounded with migraine symptoms and thus not reported as an adverse drug reaction.

Ergotism is a serious reaction, which leads in rare cases reported to important sequelae following amputation or colon resection for example. This reaction occurred in young patients (mean age among cases reported: 41 years-old), with a short time to onset after dihydroergotamine initiation (less than 2 months, mean: 2 days). The severity of such adverse effects and their possible fatal outcome is underlined.

Symptoms of ergotism are listed in the sections 4.8, 4.9 of all the SmPCs and ergotism is identified in section 4.4 as a consequence of a prolonged use of dihydroergotamine or high dosage. For all products the concomitant use of CYP3A inhibitors is contraindicated with dihydroergotamine (section 4.5) and for others the concomitant use of vasoconstrictive agent is also contraindicated. However, more than half of the cases of ergotism reported have been described out of a context of overdose or without the use of a contraindicated drug. Moreover, the number of cases reported with a contraindicated concomitant drug reveals that information in the SmPC is not sufficient to avoid an exposition of the patient to the serious risk of ergotism.

To conclude, ergotism is an adverse reaction of ergot derivative drugs well-known to occur in a context of overdose or interaction. However, given the number of cases reported with dihydroergotamine, with symptoms related to ergotism (despite probable lacking cases) even when dihydroergotamine is used as recommended (no overdosage, no contraindicated drug, and short time treatment), the high pharmacological plausibility and a suggestive chronology in most of the cases, it is considered that patients are exposed to a high risk of ergotism when treated with dihydroergotamine. Moreover, given the seriousness of ergotism and its consequences (sequelea, need for surgery, amputation), the young age of the patients with symptoms of ergotism and the short time to onset of the reaction, this has an impact on the benefit-risk balance of the products.

2.4. Overall benefit/risk assessment

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

On the efficacy side for the indication "*prophylaxis of migraine headache*" data derive from a few randomised, double-blind, placebo-controlled studies or double-blind non placebo-controlled and open-label studies, the majority of which was conducted after the granting of the initial marketing authorisation.

The double-blind, randomised, placebo-controlled studies were old and generally not carried out with the current up-to-date methodology. The number of patients included was small and the duration of treatment was too short and the clinical efficacy parameters used are not in line with the European Guidelines on clinical investigation of medicinal products for the treatment of migraine.

In the only recent, large study with appropriate design (double-blind, placebo-controlled, 5-month treatment study (PROMISE study) that became available after the granting of the initial marketing authorisation, the efficacy of dihydroergotamine in the prevention of migraine has not been demonstrated as there was no statistically significant difference between dihydroergotamine and placebo. A total of 363 subjects were treated with dihydroergotamine or placebo during 4 months after 1 month of placebo "run-in". The frequency of attacks of migraine (the primary efficacy criteria) was not statistically significant (dihydroergotamine group (-1.84 ± 1.55) vs. placebo group (-1.67 ± 1.49) (p=0.220)). For the percentage of responders (61.1% in the dihydroergotamine group vs. 55.9% in the placebo group) the difference was not statistically significant.

A post-hoc analysis was performed in the sub-group of patients (n=288) with functional handicap and quality of life (QOL) decrease (defined by Migraine Specific Quality of Life, MSQ<80). After 4 months of treatment, the attack frequency decreased by 2.0 ± 1.6 (–60.0%) with dihydroergotamine versus 1.7 ± 1.5 (–48.8%) with placebo (p = 0.014 for the relative variations). No significant improvement over placebo was observed in the subset of patients with unaffected QOL. The evidence for efficacy of dihydroergotamine in the prevention of migraine in this study has not been demonstrated taking into account that there was no statistically significant difference between dihydroergotamine and placebo with respect to the reduction of the frequency of migraine attacks (the primary efficacy criterion) in the overall population.

The literature data indicate a possible efficacy of oral dihydroergotamine in migraine prophylaxis, but definite scientific proof remains weak. There is little evidence from double-blind, placebo-controlled clinical trials and no uniform picture of the efficacy of oral ergotamine compared to placebo or other substances in the prevention of migraine emerges from these studies since studies reported both positive and negative results.

In conclusion, the studies provided by the MAHs were not carried out with up-to-date methodology. The number of patients included was small and the duration of treatment was too short. In the only recent, large study with appropriate design (PROMISE study) there was no statistically significant difference between dihydroergotamine and placebo with respect to the reduction of the frequency of migraine attacks (the primary efficacy criterion) in the overall population.

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.

For the indication "*orthostatic hypotension*" the submitted studies were considered by the CHMP of poor methodological quality: they were mainly uncontrolled trials with only 1 double-blind study but with low number of patients. Some of them assessed the injection route or doses higher than recommended (up to 42mg daily, instead of 10mg daily). Patient population was heterogeneous, or patients with hypotension induced by treatment with psychotropic drugs. In these studies, dihydroergotamine seems to have some efficacy only by injection route or at doses higher than the authorised dose. The authorised oral doses seem to have weak or null efficacy due to the low bioavailability of the drug.

Only one study, Thulesius (1986), demonstrated a significant decrease of immediate drop in blood pressure after standing up with 10mg per day dihydroergotamine compared to placebo, in patients with hypotension induced by treatment with psychotropic drugs and it became available after the initial marketing authorisation was granted. The design of this study was considered acceptable by the CHMP (i.e. controlled, randomised, double-blind) but the size of the study was considered small (n=58). In addition, patients were included if they displayed a reduction of systolic blood pressure of more than 10 mmHg, which does not comply with the established definition of orthostatic hypotension (at least 20 mm Hg below baseline). Systolic blood pressure of the placebo and the dihydroergotamine group differed already at baseline. Efficacy was assessed by comparing absolute blood pressure measurements after treatment rather than comparing the differences between supine and standing position which was not considered acceptable. The CHMP also stated that the study population, consisting only of drug induced orthostatic hypotension patients, is not representative to conclude on the efficacy of dihydroergotamine in the total population of orthostatic hypotension patients.

The CHMP also noted the position of several MAHs that there is not enough evidence to support an indication of oral dihydroergotamine in orthostatic hypotension.

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 treatment of orthostatic hypotension. Based on the clinical experience the group considered that dihydroergotamine has only been used rarely for the treatment of orthostatic hypotension with no clear benefit to the patients. In addition, it was the IV formulation of the product that was used and not the oral formulation that is in the scope of this referral procedure. Therefore, the group was of the opinion that based on the available evidence there is no need for this substance as there is no clear subset of patients that would benefit from it.

For the indication "*symptomatic treatment of veno-lymphatic insufficiency*" very few studies have been conducted. The open label study (Wenzel-E et al, 1989) that became available after the granting of the initial marketing authorisation discusses the use of dihydroergotamine in venous insufficiency. Twelve patients suffering from peripheral venous insufficiency were treated first with intravenous dihydroergotamine followed by oral dihydroergotamine administration for one week. Although significant reduction in venous capacity, capillary flow of erythrocytes and peak flow of reactive hyperemia were demonstrated, due to a very small study group, the uncontrolled design and other methodological limitations, the CHMP could not draw any conclusion on the efficacy of dihydroergotamine.

The studies presented are old and of poor methodological quality: uncontrolled, open designed, with a low number of patients (n=12 in Wenzel, 1989, the most recent study). Some of them were conducted with the intravenous administration which is not in the scope of this referral procedure for dihydroergotamine. The patients disease is not well defined, nor the efficacy endpoints. The relevance of clinical endpoints is questionable. The CHMP noted the position of several MAHs that there is not enough evidence to support an indication of oral dihydroergotamine in the symptomatic treatment of veno-lymphatic insufficiency and was of the opinion that no scientific conclusion can be drawn regarding the efficacy of dihydroergotamine based on these study results.

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.

With regard to the reported cases, the CHMP commented on the problem of under-reporting for this product considering the period that it is on the market. Under-notification can be suspected given that:

- Adverse drug reactions with a substance marketed for a long time are generally less reported
- Fibrosis is mentioned in several current European Summaries of Product Characteristics (SmPCs) and expected reactions are often under-reported
- Fibrosis is also an insidious reaction that occurs after a long period of treatment and thus with often a delayed diagnosis.

Moreover, safety data provided by some MAHs are incomplete (gap between reviewing period and marketing period of the product) and it cannot be excluded that cases reported with their products are lacking.

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blockers are not widely recognized as a cause of fibrosis. In some published literature, they are considered as an aetiology of retroperitoneal fibrosis (*P. Meier et al, La fibrose rétropéritonéale, une maladie inflammatoire méconnue. Observations cliniques et revue de la littérature. Néphrologie Vol. 24 n° 4 2003, pp. 173-180*).

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To conclude, given the cases reported for a reaction difficult to diagnose early (delayed symptoms) and probably under reported, the use of the drug at an approved dosage, added to a plausible pharmacological profile, dihydroergotamine is considered to be strongly associated with a risk of fibrotic reactions. In addition, given that fibrosis is a serious life threatening reaction, observed after long duration of treatment with dihydroergotamine(a drug used in indications requiring long duration of treatment) this has an impact on the benefit-risk balance of the products. Moreover, the 8 new spontaneous notifications reported during the French survey conducted in 2011 show that the risk minimisation measures that are currently in place are not sufficient to prevent the risk of fibrotic reactions.

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Ergotism is an adverse reaction of ergot derivative drugs well-known to occur in a context of overdose or interaction. However, given the number of cases reported with dihydroergotamine, with symptoms related to ergotism (despite probable lacking cases) even when dihydroergotamine is used as recommended (no overdosage, no contraindicated drug, and short time treatment), the high pharmacological plausibility and a suggestive chronology in most of the cases, it is considered that patients are exposed to a high risk of ergotism when treated with dihydroergotamine. Moreover, given the seriousness of ergotism and its consequences (sequelea, need for surgery, amputation), the young age of the patients with symptoms of ergotism and the short time to onset of the reaction, this has an impact on the benefit-risk balance of the products.
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The CHMP considered the MAH's proposals for risk minimisation measures. These included restricting the therapeutic indications, recommending close monitoring of patients and the issuing of a DHPC. Although some of the proposed measures could help the early identification of patients with fibrosis, it may be too late as these reactions are sometimes irreversible. The Committee therefore pointed out that the proposed measures 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 dihydroergotamine-containing medicinal products/ suspension where applicable
- Risk of fibrotic reactions and ergotism
- Limited evidence of efficacy in the indications reviewed
- Benefits of dihydroergotamine-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).

- Prophylaxis of migraine headache
- Orthostatic hypotension
- Symptomatic treatment of veno-lymphatic insufficiency

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 oral dihydroergotamine 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 oral dihydroergotamine in the currently assessed indications is very limited, and therefore the potential benefit for patients in these indications is outweighed by the above identified risk.
- The Committee considered that the benefit-risk balance of dihydroergotamine containing products:
  - Is not favourable for prophylaxis of migraine headache.
  - Is not favourable for orthostatic hypotension.
  - Is not favourable for symptomatic treatment of veno-lymphatic insufficiency.

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

- The variation to the terms of the marketing authorisation for dihydroergotamine 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:
  - Prophylaxis of migraine headache.
  - Orthostatic hypotension.
  - Symptomatic treatment of veno-lymphatic insufficiency.

- The suspension of the marketing authorisation for dihydroergotamine 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.

Appendix I

Divergent Position(s)

Article 31 referral of Directive 2001/83/EC

Procedure No: EMEA/H/A-31/1325

Ergot derivatives containing medicinal products - dihydroergotamine

Divergent statement

The undersigned member of CHMP did not agree with the Committee's opinion.

The reasons for divergent opinion were the following:

There is a long-standing experience from treatment with dihydroergotamine which has rather well characterised pharmacodynamic profile. In severe orthostatic hypotension, where treatment alternatives are few, there is in our opinion a place for dihydroergotamine as supportive treatment in some patients where the benefit is considered to outweigh the risk. Thus we do not support the deletion of the indication for treatment in orthostatic hypotension.

CHMP member(s) expressing a divergent opinion:

Kristina Dunder (SE)	27 June 2013	Signature: ……