Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations or suspension of the marketing authorisations, as applicable, taking into consideration the approved indications for each product

Scientific conclusions

Overall summary of the scientific evaluation of dihydroergotamine containing medicinal products (see Annex I)

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authorisations for ergot derivatives containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications: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

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

The marketing authorisation holders (MAHs) submitted all available efficacy data from clinical trials and observational studies, including data that became available since the granting of the initial marketing authorisation. The MAHs also 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.

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

Clinical efficacy

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 evidence for 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 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.

Clinical safety

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 noted 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.

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 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).

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.

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. However, a total of 134 cases of ergostim or symptoms potentially related to ergotism have been reported by the MAHs.

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 vasonconstrictive 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 (sequelae, need for surgery, amputation), the young age of the patients with symptoms of ergotism and the short time to onset of the reaction, the safety profile of dihydroergotamine is highly questionable.

The CHMP considered the MAHs' 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.

Benefit –risk balance

The Committee concluded that the benefit-risk balance of dihydroergotamine containing products for oral use is not favourable pursuant to Article 116 of Directive 2001/83/EC for prophylaxis of migraine, for orthostatic hypotension and for symptomatic treatment of veno-lymphatic insufficiency.

Grounds for the suspension / variation to the terms of the marketing authorisations

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for ergot derivatives containing medicinal products in the concerned indications.
- The Committee considered the overall submitted data provided by the MAHs 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 oral 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.