

## **Annex II**

### **Scientific conclusions and grounds for the variation of the marketing authorisations**

## Scientific conclusions

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

Methysergide is an ergot alkaloid, first described in clinical practice in 1959. Methysergide binds with varying affinities to a range of serotonergic receptors (5-HT receptors). In particular, it binds to and is an antagonist of the 5HT<sub>2B</sub> receptor. There are a number of pharmacological pathways by which methysergide may be effective in preventing migraine, for instance some data support the role of antagonism of the 5-HT<sub>2B</sub> receptor in the prophylaxis of migraine.

Methysergide is currently indicated in the prophylaxis of migraine headache, cluster headache and also in the treatment of diarrhoea caused by carcinoid disease (specific wording of the indication may vary from product to product).

Methysergide containing products are currently authorised in the following EU countries: Belgium, France, the Netherlands and the United Kingdom.

In 2011, a French national pharmacovigilance review reported serious cases of valvulopathy, pulmonary, pleural and retroperitoneal fibrosis associated with methysergide containing medicinal products. Based on this, France considered that the benefit risk balance of methysergide containing products should be reviewed and triggered a referral under Article 31 of Directive 2001/83/EC.

### Efficacy

The CHMP has considered the totality of the available data on the safety and efficacy of methysergide. For the indication "*prophylaxis of migraine*", data were submitted from randomised, double-blind, placebo-controlled studies<sup>1,2,3,4</sup>. The results of these studies are suggestive of the efficacy of methysergide compared to placebo in the prophylaxis of migraine. In addition, further trials comparing methysergide with placebo or comparators were also presented, some of which also showed efficacy of methysergide compared to placebo in this indication<sup>5,6,7</sup>. The CHMP highlighted that these results should be taken with caution as these studies are old and generally not carried out with the current up-to-date methodology<sup>8</sup>.

The CHMP also noted that methysergide is included in the latest recommendations of migraine preventive treatments of the European Federation of Neurological Societies (EFNS; 2009)<sup>9</sup> as drug of third choice for migraine prophylaxis for short-term use only, and in the latest French recommendations of 2013 as Grade B or C (probably effective) for migraine prophylaxis<sup>10</sup>.

Considering the overall data available, the CHMP is of the opinion that there is some evidence of clinically significant efficacy of methysergide in the prophylactic treatment of severe and debilitating migraine.

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<sup>1</sup> Lance JW *et al.* An evaluation of methysergide in the prevention of migraine and other vascular headaches. *Med J Aust* 1963; 814-818.

<sup>2</sup> Pedersen E, Møller CE. Methysergide in migraine prophylaxis. *Clin Pharmacol Ther* 19667(4):520-526

<sup>3</sup> Ryan RE. Double-blind crossover comparison of BC-105, methysergide, and placebo in the prophylaxis of migraine headache. *Headache* 19688(3):118-126.

<sup>4</sup> Shekelle RB, Ostfeld AM. Methysergide in the migraine syndrome. *Clin Pharmacol Ther* 19645:201-204

<sup>5</sup> Curran DA, Lance JW. Clinical trial of methysergide and other preparations in the management of migraine. *J Neurol Neurosurg Psychiatry* 1964; 27:463-9.

<sup>6</sup> Southwell N, Williams J, Mackenzie I. Methysergide In The Prophylaxis Of Migraine. *Lancet* 1964 Jul 3;523-4.

<sup>7</sup> Whewell J. Methysergide in prophylaxis of migraine: a clinical trial in general practice. *Br Med J* 1966; 2(5510):394-5.

<sup>8</sup> Guideline on clinical investigation of medicinal products for the treatment of migraine. CPMP/EWP/788/01 Rev. 1 (2007)

<sup>9</sup> Evers S, Afra J, Frese A *et al.* EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. *Eur J Neurol*. 2009 Sep;16(9):968-81.

<sup>10</sup> Lanteri-Minet M *et al.* Prise en charge diagnostique et thérapeutique de la migraine chez l'adulte et chez l'enfant. *Rev Neurol (Paris)*. 2013 Jan;169(1):14-29. doi: 10.1016/j.neurol.2012.07.022. Epub 2012 Dec 13.

With regard to the indication "*cluster headache*", the applicant referred to a review<sup>11</sup> which suggested the prophylactic efficacy of methysergide, particularly for the episodic form of cluster headache and to a study<sup>12</sup> where 69% of cluster headache patients reported to have good to excellent results. Two studies, one observational and one prospective, reported less convincing evidence<sup>13</sup> where around 26% patients had satisfactory, good or excellent outcomes. In a more recent review<sup>14</sup>, methysergide and verapamil were cited as the most useful treatments of the episodic form of cluster headache. The CHMP noted that the clinical trial evidence for the efficacy of methysergide as a prophylactic treatment for cluster headache is less robust compared to the evidence for migraine prophylaxis and that the majority of studies have a number of limitations.

The CHMP further noted that methysergide is included as second choice treatment in the latest recommendations of cluster headache preventive treatments of the EFNS (2006)<sup>15</sup> and is also included in the list of preventive therapies for cluster headache in recently published guidelines<sup>16,17,18</sup>. In addition, the CHMP noted that methysergide is recommended by experts as a rescue treatment, reserved for patients in whom other treatments have failed.

No data was submitted in support of efficacy of methysergide in the "*treatment of diarrhoea caused by carcinoid disease*", and it is therefore considered that efficacy in this indication has not been demonstrated. In this respect, the CHMP took note of the fact that one of the marketing authorisation holders of the products for which this indication is approved informed the CHMP of their intention to voluntarily withdraw the indication "*diarrhoea caused by carcinoid syndrome*".

The CHMP acknowledged the advice of the Scientific Advisory Group (SAG) which was convened in September 2013 during which the experts discussed, based on their clinical experience, whether it is possible to define a population for which there is a therapeutic need for oral methysergide-containing products when standard treatment for these indications have been ineffective. Based on the clinical experience of headache experts, the SAG considered that there is a small proportion of the populations suffering from migraine and from cluster headache that seems to benefit from treatment with methysergide, when previous treatments have failed.

The CHMP further took note of third party interventions received from patients and healthcare professionals during the assessment, highlighting the importance of maintaining availability of this product to a population that, albeit small, has few or no therapeutic alternatives for a debilitating condition.

## Safety

In order to evaluate the safety of methysergide, the CHMP considered data from literature and safety database including spontaneous and literature reports.

The incidence rates of valvular and pulmonary fibrosis in patients treated with methysergide was shown to be similar to those of the general population<sup>19,20,21,22</sup>. However, these results should be taken

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<sup>11</sup> Kudrow L. Cluster Headache Mechanisms and management. 1 ed. Oxford: Oxford University Press; 1980.

<sup>12</sup> Lovshin LL. Use of methysergide in the treatment of extracranial vascular headache. The Journal of Head and Face Pain 1963; 3(3): 107-11.

<sup>13</sup> Krabbe A. Limited efficacy of methysergide in cluster headache. A clinical experience. Cephalalgia 1989; 9 (SUPPL. 10): 404-5.

<sup>14</sup> Pradalier A, Baudesson G, Vincent D, Imberty-Campinos C. Treatment of the cluster headache. Rev Med Interne 2001; 22(2): 151-62.

<sup>15</sup> May A, Leone M, Afra J et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol. 2006 Oct; 13(10): 1066-77.

<sup>16</sup> MacGregor EA, Steiner TJ, Davies PTG. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache. British Association for the Study of Headache 2010(3rd edition (1st revision)).

<sup>17</sup> Sarchielli P. XI Congress of the International headache society. Expert Opin Pharmacother 2004; 5(4): 959-75.

<sup>18</sup> Bendtsen L, Birk S, Kasch H et al. Reference programme: Diagnosis and treatment of headache disorders and facial pain. Danish Headache Society. J Headache Pain 2012; 13(Suppl 1): S1- S29.

<sup>19</sup> Bana DS, MacNeal PS, LeCompte PM. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. Am Heart J 1974; 88(5): 640-55.

with caution as methods of detection of fibrosis used in these studies are not sensitive enough, in particular for valvular fibrosis. The real incidence rate might be under-estimated and the risk of fibrosis is probably higher. Regarding the risk of retroperitoneal fibrosis, there is evidence of increased risk in patients treated with methysergide (200 versus 1.3 per 100 000 patients)<sup>23,24</sup>.

Existing data seems to show that fibrosis development is not related to patient age. In addition, development of fibrosis appears to be correlated to treatment duration, as most patients developed fibrotic events after long-term therapy (at least one year). However, cases have also been reported with treatment duration up to six months, so occurrence of fibrosis with short-term treatment cannot be excluded. The majority of patients (92.4%) who developed fibrosis received daily doses of methysergide within the currently recommended ( $\leq 6$  mg/day).

Taking into account the number of fibrosis cases reported and the probable under reporting, the risk of fibrotic reactions associated with methysergide cannot be excluded. The CHMP noted that fibrosis can be a life-threatening event and that some of the retroperitoneal fibrotic reactions reported are very severe (ureter fibrosis, bilateral ureteric stenting, bilateral nephrostomy etc.).

The CHMP noted that the mechanistic basis for the fibrosis appears to be well-founded, and fits with the known association between methysergide use and fibrosis, which has been reported with respect of valvular heart disease since the mid-1960s. Since fibrotic reactions are believed to be associated with persistent agonist activation of the 5-HT<sub>2B</sub> receptor, long-term treatment with methysergide will expose patients to the potential for tissue fibrosis mediated by its principal active metabolite, methylergometrine. Therefore, the potential causal association between fibrotic reactions and methysergide cannot be excluded.

The CHMP considered the view of the SAG which recommended some measures to be taken in order to minimise the risk of fibrotic reactions when prescribing methysergide. These included restricted duration of treatment, optimal dose of treatment, specialist supervision and information for prescribing physicians and patients' organisation. The SAG also considered that patients should be monitored at baseline and every six months while on treatment (heart ultrasound, abdominal magnetic resonance imaging (MRI), pulmonary function tests) in order to be able to identify all fibrosis before severe and potentially irreversible reactions have occurred.

Overall, the CHMP considered that methysergide seems to benefit a small patient population of migraine and cluster headache patients. However, in view of the demonstrated risk of fibrosis, adequate risk minimisation measures should be put in place. The indication should be restricted to patients with functional disability in whom other treatments have failed. The CHMP also recommended that methysergide treatment should be initiated and supervised by specialised physicians with experience in the treatment of migraine and cluster headache. Warnings on the risk of fibrosis should be included in the product information, alongside measures to monitor patients for development of fibrosis, and these should also be communicated to prescribers and patients using educational material.

### **Benefit-risk balance**

Having considered the overall data provided by the MAH in writing, the CHMP concluded that the benefit-risk balance of methysergide is favourable in:

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<sup>20</sup> Steffensen C, Maegbaek ML, Laurberg P, Andersen M, Kistorp CMN, Norrelund H, et al. Heart valve disease among patients with hyperprolactinemia: A nationwide population-based cohort study. *Journal of Clinical Endocrinology and Metabolism* 2012; 97(5): 1629-34.

<sup>21</sup> Silberstein SD. Methysergide. *Cephalalgia* 1998; 18(7): 421-35.

<sup>22</sup> Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006; 174(7): 810-6.

<sup>23</sup> Graham JR, Suby HI, LeCompte PR, Sadowsky NL. Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; 274(7): 359-68.

<sup>24</sup> van Bommel EFH, Jansen I, Hendriksz TR, Aarnoudse ALHJ. Idiopathic retroperitoneal fibrosis: Prospective evaluation of incidence and clinicoradiologic presentation. *Medicine (GBR)* 2009; 88(4): 193-201.

- the *prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults.*

*Methysergide is to be used only following unsuccessful treatment with other standard classes of drugs after sufficient treatment duration (at least 4 months) at the maximal tolerated dose. Serious intolerance or contra-indication to a first line drug is regarded as treatment failure. Methysergide is not effective for treating a migraine attack that is already present.*

- the *prophylactic treatment of episodic and chronic cluster headache in adults.*  
*Patients should have failed at least 2 classes of drugs before starting methysergide. The minimal duration of treatment before concluding failure is 2 months.*

This is subject to the agreed warnings, other changes to the product information and additional risk minimisation measures.

Regarding the indication "*treatment of diarrhoea caused by carcinoid disease*", the CHMP concluded that the benefit-risk balance is negative as there is a clearly demonstrated risk of fibrosis but no evidence of benefit.

## Grounds for variation to the terms of the marketing authorisations

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for methysergide containing medicinal products.
- The Committee reviewed all available data on the efficacy and safety of methysergide containing medicinal products, in particular with regard to the risk of fibrotic reactions.
- The Committee considered that a causal association between methysergide and fibrotic reactions is likely based on available data (mainly relating to retroperitoneal fibrosis). Such adverse effects may be serious and in some cases irreversible and potentially fatal.
- The Committee noted that there is no evidence of efficacy of methysergide in the treatment of diarrhoea caused by carcinoid disease, and therefore the potential benefit for patients in this indication is outweighed by the identified risk.
- The Committee considered that there is some evidence for clinically significant efficacy of methysergide in the prophylactic treatment of severe, debilitating migraine and cluster headache for which therapeutic alternatives are limited. In addition, risk minimisation measures can be put in place to minimise the risk of fibrosis.
- Therefore the CHMP was of the opinion that the benefit-risk balance of methysergide containing products:
  - Is favourable for the *prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults*.  
Methysergide *is to be used only following unsuccessful treatment with other standard classes of drugs after sufficient treatment duration (at least 4 months) at the maximal tolerated dose. Serious intolerance or contra-indication to a first line drug is regarded as treatment failure. Methysergide is not effective for treating a migraine attack that is already present.*  
This is provided that the recommended risk minimisation measures are implemented;
  - Is favourable for the *prophylactic treatment of episodic and chronic cluster headache in adults*.  
*Patients should have failed at least 2 classes of drugs before starting methysergide. The minimal duration of treatment before concluding failure is 2 months.*  
This is provided that the recommended risk minimisation measures are implemented;
  - Is not favourable for the *treatment of diarrhoea caused by carcinoid disease*.

Therefore, in accordance with Article 116 of Directive 2001/83/EC, the CHMP recommends the variation to the terms of the marketing authorisation for methysergide containing medicinal products referred to in Annex I.