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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 31 of Directive 2001/83/EC

Methysergide containing medicinal products

International non-proprietary name: methysergide

Procedure No. EMEA/H/A-31/1335

Note

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



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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 16 May 2012, France triggered a referral under Article 31 of Directive 2001/83/EC for methysergide containing medicinal products. Following a national pharmacovigilance review held in 2011, new spontaneous notifications reported with those products pointed out serious cases of valvulopathy, pulmonary, pleural and retroperitoneal fibrosis and France considered that the risk is not outweighed by the limited evidence of efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for methysergide containing medicinal products should be maintained, varied, suspended or withdrawn in relation to the below mentioned indications (specific wording of the indication may vary from product to product):

- Prophylaxis of migraine headache;
- Cluster headache;
- Treatment of diarrhoea caused by carcinoid syndrome.

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

2. Scientific discussion

2.1. Introduction

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_{2B} 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_{2B} 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.

2.2. Clinical efficacy

The CHMP considered all available data submitted by the MAH from several clinical trials in support of the efficacy of Methysergide in its approved indications.

2.2.1. Results

Prophylaxis of migraine

In support of the indication “prophylaxis of migraine”, the MAH referred to 15 controlled or partially-controlled clinical trials.

Four randomised, double-blind placebo-controlled studies have been identified as suggesting superior efficacy of methysergide compared to placebo in the reduction of headache frequency. These four studies are summarised below.

Lance, 1963¹ evaluated methysergide in the prevention of migraine and other vascular headaches in a single-centre, placebo-controlled study of 90 migraine patients (36 classical and 54 common migraines) and 31 tension/vascular headache patients who experienced severe and frequent attacks. Twenty-six (26) of the migraine patients were male and 64 were female and, of the vascular/tension headache patients, 17 were male and 14 were female. The patients ranged in age from 9 to 75 years-old and the duration of their illness ranged from 1 to 55 years. Patients took either two placebo or two methysergide (1 mg) tablets three times a day for one month in a treatment-blinded fashion. Patients were then re-assessed and classified as “headache-free”, “substantially improved”, “not improved” or “worse”. The assessor was also blinded to which treatment the patient had taken. The authors noted that patients included in this trial had suffered attacks for a long period of time and had been treated previously by many different methods, and so their response at each monthly assessment was usually out-spoken and unequivocal making assessment of the treatment response easy. At re-assessment following one month of treatment, 38/56 (67%) migraine patients taking 1 mg methysergide tablets were either “headache-free” (16/56, 28%) or “substantially improved” (22/56, 39%) compared with only 1/34 (2.9%) of those who took placebo who were “headache-free” and 6/34 (17.6%) showing a substantial improvement. However, of the 31 patients with vascular/tension headaches, only 5/17 (29%) patients receiving methysergide were “substantially improved” compared with 4/14 (29%) patients receiving placebo. None of the patients with vascular/tension headaches were “headache-free” on either treatment.

Pedersen, 1966² In this placebo-controlled, patient- and assessor-blinded, randomised, single-centre study, 102 migraine patients took either 3 mg “prolonged action” methysergide tablets or matching placebo at a daily-dose of two tablets for adults or one tablet for children. The study was a cross-over design with each period being six weeks in duration with a one week intervening period during which time adult patients took one methysergide and one placebo tablet daily to eliminate a possible carry-over effect of methysergide in the subsequent placebo period and, if the methysergide response should be short-lived, to avoid an increased frequency of attacks brought on by the sudden withdrawal of active drug. Half of the patients received methysergide and half received placebo during each period. Patients recorded the severity of their attacks and, in cases of severe attack, ergotamine tartrate could be used. Of the 102 patients enrolled in this study, 60 completed the study satisfactorily. The investigators found that the effect of methysergide did carry-over to the placebo period and so they restricted comparison of treatments to 3-week periods instead of the initially planned 6-week periods. One patient was excluded from the analysis because they had an unusually good response (i.e. no headaches at all whilst on methysergide and very frequent attacks whilst taking placebo). The total number of migraine attacks in the remaining 59 patients was 160 in the 3-week placebo periods and 120 in the 3-week methysergide periods representing a 25% statistically-significant reduction in frequency of headaches with methysergide treatment, although no details of the statistical testing

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

² Pedersen E, Møller CE. Methysergide in migraine prophylaxis. Clin Pharmacol Ther 1966;7(4):520-526.

were provided. The total number of attacks in the 6-week periods was 361 with placebo treatment and 256 during methysergide treatment, a 29% reduction. Furthermore, when the frequency of attacks during methysergide treatment was compared with the pre-study frequency, 57% of patients experienced at least 50% fewer attacks. The corresponding figure for placebo was 27%.

Ryan, 1968³ The investigators conducted a double-blind, cross-over study in 62 migraine patients aged 21 to 65 years where patients received one of three medications (2 mg methysergide, 2 mg pizotifen or placebo) at each of three 4-week periods. Patients took one capsule of their assigned treatment on day 1 and then one capsule twice daily for days 2 to 28 of the 4-week period. Following this period, patients repeated this 4-week cycle until they had taken all three medications. During the 4-week treatment periods, patients recorded the severity of their headache and any other medications used to treat the attack. The mean number of headaches across all three periods was 6.2 with methysergide and 8.9 with placebo. Furthermore, the mean headache index (calculated by multiplying the number of severe headaches by three, the number of moderate headaches by two and the number of mild headaches by one) was reduced from 17 with placebo treatment to 11.3 with methysergide treatment.

Shekelle, 1964⁴ Methysergide was evaluated in a double-blind, placebo-controlled cross-over study in 17 patients with migraine (and one patient with cluster headache) aged 22 to 46 years. Patients took either 2 mg methysergide or placebo three times daily for five weeks and then switched treatments for the second 5-week period. The order of medications was randomised and both the patient and assessors were blinded to treatments. Patients recorded the number of days on which headache occurred. The prophylactic effects of methysergide and placebo were compared by subtracting the number of headache days reported by each patient during the last four weeks of methysergide treatment from the number reported during the last four weeks of placebo treatment. The first week of each treatment period was ignored to allow time for the treatments to establish their effect and to accommodate for any carry-over effect. Thirteen (13) of the 18 patients completed the two treatment periods. Nine of the 13 patients reported a decrease, usually moderate, in both the frequency and severity of headaches whilst taking methysergide and three patients showed no improvement. Only one patient reported no headache whilst taking methysergide but two headaches whilst taking placebo. The authors employed Rushton's sequential t-test on the 13 patients who completed both treatments and determined that the logarithm of the likelihood ratio exceeded 2.94, the critical value for the right-handed inequality, and, therefore, the null hypothesis (that methysergide is equal in effectiveness to placebo) was rejected.

In addition to the above four randomised, double-blind, placebo-controlled study, further 11 methysergide trials versus placebo or comparator were submitted and are summarised below.

Curran and Lance, 1964⁵ A total of 320 patients with migraine participated in a clinical trial of methysergide which included 240 female and 80 male patients. Patients were initially prescribed 6 mg of methysergide daily, and this was gradually reduced in improved patients to the minimal dose which maintained improvement. Sixty-three (63) patients (20%) became virtually headache-free and a further 117 (36%) were substantially improved over a follow-up period of 18 months. The drug was discontinued in 43 patients (13%), 11 patients (3%) having relapsed on therapy and 32 (10%) had severe side-effects. Eighty-eight (88) of the improved patients had been followed for periods of seven months or more. The 11 patients who relapsed after some months on methysergide therapy had never been completely free of headache, i.e., no patient who became headache-free during the first month of

³ Ryan RE. Double-blind crossover comparison of BC-105, methysergide, and placebo in the prophylaxis of migraine headache. *Headache* 1968;8(3):118-126.

⁴ Shekelle RB, Ostfeld AM. Methysergide in the migraine syndrome. *Clin Pharmacol Ther* 1964;5:201-204.

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

methysergide therapy relapsed. The improvement rate in male patients (69%) was higher than that observed in females (52%). Thirty-one (31) female patients (13%) discontinued methysergide compared to one male patient (1.3%). Methysergide was less effective in patients with one or two attacks each month, only 42% responding to treatment compared to 75% of patients experiencing more than eight headaches per month who were improved. The site of the headache, whether unilateral or bilateral, did not alter the response to methysergide. Side-effects were experienced by 45% of migrainous subjects. The responses to placebo and methysergide over a 6-month period were compared with the responses to cyproheptadine and Bellergal (belladonna, ergotamine, phenobarbital) over a similar period. The 64% improvement obtained with methysergide in the first six months was significantly greater than the 46% of patients responding to cyproheptadine ($p < 0.01$), the 34% responding to Bellergal ($p < 0.001$), and the 20% response to placebo ($p < 0.001$).

Southwell, 1964⁶ reported a double-blind, cross-over trial of methysergide in 53 patients with severe intractable migraine. The trial lasted 12 weeks, each patient taking methysergide for six weeks and placebo for six weeks. The dosage of methysergide was initially 6 mg daily, but was reduced to 3 mg daily in some patients because of side-effects. Of the 53 patients starting the trial, 34 completed it. Seventeen (17) withdrew because of side-effects, and two had to be excluded from analysis because of incomplete data. A total of 141 "severe" headaches were recorded by 34 patients while on placebo compared to 103 while on methysergide. The reduction of severe headaches by 30% was statistically significant ($p < 0.05$). The total number of headaches (including mild headaches) was 415 on placebo and 358 on methysergide. The reduction of 14% for all headaches was not significant, and it was speculated that some of these might have been tension headaches, which had previously been shown not to respond to methysergide. Furthermore, a statistically significant decrease was noted only in the group in which methysergide was taken second, indicating a carry-over effect. Side effects leading to withdrawal in 14 methysergide patients included feeling drunk, giddiness, nausea and pain or aching limbs.

Lance JW, 1970⁷ reported further experience of methysergide in an open study for up to three years comparing methysergide (3-6 mg/day) to four other active treatments and to placebo. A total of 96 out of 151 patients who took methysergide improved, and at 64% this response was statistically significantly better than placebo with 31% improved ($p < 0.001$). Methysergide was reported as the most effective agent of those tested with 20% of patients becoming headache-free and a further 44% of the remainder being "more than half improved". Ten percent (10%) of patients taking methysergide withdrew due to side effects; the most common being nausea and muscle spasms.

Presthus, 1971⁸ compared pizotifen to methysergide (1 mg three times per day) in migraine prophylaxis in a randomised sequence, double-blind, crossover trial with 19 patients. Patients were treated for five weeks with each treatment with a one week washout between treatments. No statistically significant difference in the effect of the two drugs could be shown with regard to pain intensity, attack frequency or duration. One patient developed what was believed to be an allergic reaction (exanthema) after five weeks of methysergide treatment, which resolved when the medication was stopped.

Forssman, 1972⁹ compared pizotifen to methysergide in migraine prevention in a randomised, double-blind, crossover study. The drugs were each given for 10 weeks following a 6-week run-in period. In order to avoid carry-over effects, only the last six weeks of each treatment period were

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

⁷ Lance JW, Anthony M. A comparative trial of serotonin antagonists in the management of migraine. *Proc Aust Assoc Neurol* 1970; 7:31-5.

⁸ Presthus J. BC 105 and methysergide (Deseril) in migraine prophylaxis. *Acta Neurol Scand* 1971; 47(4):514-8.

⁹ Forssman B, Henriksson KG, Kihlstrand S. A comparison between BC 105 and methysergide in the prophylaxis of migraine. *Acta Neurol Scand* 1972; 48(2):204-12.

analysed. The results during the treatment periods were compared to the 6-week run-in period during which no drugs were given. Sixteen (16) patients with classic or common migraine and one patient with cluster headache were evaluated. Pizotifen and methysergide both significantly decreased headache frequency, with no significant difference between them. No serious adverse events were noted. The most commonly encountered adverse events in patients taking methysergide were drowsiness, nausea, increased appetite, weight gain and depression. No symptoms or signs of vasoconstriction were recorded.

Andersson, 1973¹⁰ compared in a double-blind trial pizotifen (0.5 mg bid) to methysergide (1 mg qid) in 73 patients with classic or common migraine. Each treatment period was three months. Treatment was stopped in 13 patients because of adverse events, whereas 11 were dropped for other reasons. Attack frequency decreased from 5.9 attacks a month to 3.5 with pizotifen and to 4.1 with methysergide. The average reduction in attacks per month was 39% for pizotifen and 26% for methysergide. The attack frequency fell by more than 50% in 37% of the patients on pizotifen and in 31% of the patients on methysergide. The principal adverse events were weight gain (with pizotifen) and muscle pain (with methysergide).

Herrmann, 1977¹¹ in a controlled double-blind study compared lisuride (25 mg tid) to methysergide (2 mg tid) in 253 patients. The study lasted three months. The frequency, intensity, and duration of attacks that occurred in the preceding month and the accompanying symptoms were analysed. There were no important differences between the 130 patients who were treated with lisuride and the 123 treated with methysergide. A 50% or greater reduction in attack frequency occurred in 53% of patients treated with lisuride and in 51% of those treated with methysergide (not significant). Thirty-nine percent of the methysergide group and 17% of the lisuride group discontinued the medications because of adverse events. The most common adverse events in patients on methysergide which led to withdrawal were nausea, vomiting, dizziness and gastrointestinal disturbances.

Behan and Reid, 1980¹² carried out a double-blind, crossover study comparing propranolol with methysergide in a group of 56 patients with chronic common (44) or classic (12) migraine with at least two severe attacks a month. Each patient was treated with either methysergide (1 mg tid) or propranolol (40 mg tid) for three months. Following a washout period of 1 month, the alternative drug was given for three months. Twenty patients did not complete the trial. Both drugs significantly reduced both frequency and severity of the migraine attacks.

Steardo, 1986¹³ compared flunarizine to methysergide in a double-blind, randomised, parallel group controlled trial that lasted six months, one month baseline assessment followed by five months treatment. A total of 104 patients were enrolled, 53 receiving flunarizine (10 mg twice per day) and 51 methysergide (2 mg twice per day). Efficacy was assessed from questionnaires that recorded the frequency, severity, and duration of the headaches. Dropouts due to lack of efficacy were similar between groups, and five patients withdrew from methysergide due to adverse events (gastric events and circulatory disorders). Patients in both groups had a highly significant reduction in the number and duration of migraine attacks compared to baseline ($p < 0.001$).

Whewell, 1966¹⁴ reported a randomised double-blind cross-over study of methysergide (1 mg qid) and placebo given to 74 patients in general practice with a diagnosis of migraine. The duration of dosing was for three months following a 1-month placebo run-in, and patients were switched to the

¹⁰ Andersson PG. BC-105 and Deseril in migraine prophylaxis. (A double blind study). *Headache* 1973;13(2):68-73

¹¹ Herrmann WM, Horowski R, Dannehl K. Clinical effectiveness of lisuride hydrogen maleate: a double blind trial versus methysergide. *Headache* 1977;17(2):54-60.

¹² Behan PO, Reid M. Propranolol in the treatment of migraine. *Practitioner* 1980; 224(1340):201-4.

¹³ Steardo L, Marano E, Barone P. Prophylaxis of migraine attacks with a calcium-channel blocker: Flunarizine versus methysergide. *J Clin Pharmacol* 1986; 26(7):524-8.

¹⁴ Whewell J. Methysergide in prophylaxis of migraine: a clinical trial in general practice. *Br Med J* 1966; 2(5510):394-5.

alternate therapy for a further three months. Fifty patients completed the study, and overall there was a 19% reduction in severe headache frequency, and a 25% reduction in the duration of severe attacks (mean reduction 10.6 h, $p < 0.05$). It was notable that only severe headaches were improved. One patient taking methysergide withdrew due to nausea, otherwise side effects were reported as not troublesome.

Titus, 1986¹⁵ reported a controlled study comparing 124 migrainous patients aged 12 to 56 years who were randomly assigned to treatment with either 5-hydroxytryptophan (600 mg/day) or methysergide (3 mg/day) for six months. The two groups were homogeneous with respect to age, sex, contraceptive pill use, type of migraine and frequency of attacks before entry. Thirty-one percent (31%) were lost to follow-up and five subjects from the methysergide group withdrew due to severe side effects (not specified), compared to four in the 5-hydroxytryptophan group. A significant improvement (defined as >50% reduction in migraine frequency or a reduction in severe attacks) was observed in 75% of the patients treated with methysergide and in 71% of the cases treated with 5-hydroxytryptophan, which was not a significant difference. Side effects were reported in 25% of methysergide patients (including nausea, leg pain, insomnia, weight gain, impotence and drowsiness) compared to 28% randomised to 5-hydroxytryptophan).

Cluster headache

In support of the indication “cluster headache”, the MAH referred to a review made by Kudrow L. (1980)¹⁶ which suggested the prophylactic efficacy of methysergide, particularly for the “episodic form” of cluster headache.

Kudrow, 1980 reported that 53% of patients (out of a series of 77 patients with cluster headache) experienced a 75% or greater improvement in symptoms with methysergide (8 mg/day for 21 days), compared to 88% who exhibited a similar improvement following 21 days of prednisolone (40 mg/day reducing to zero). By contrast, 80% of “chronic” cluster headache patients receiving methysergide were considered treatment failures.

The only other substantive study reported at that time was performed by Lovshin LL et al. (1963)¹⁷ in 159 cluster headache patients, where 69% were reported to have good to excellent results.

A number of smaller studies were performed and the results are summarised in the Table 1, which has been reproduced from Kudrow’s 1980 review.

Table 1: Results of methysergide maintenance therapy in cluster headache

Author(s)	Year	Patient Numbers	Good to Excellent Result (%)
Sicuteri	1959	2	100
Heyck	1960	8	100
Freidman	1960	3	67
Graham	1960	20	80
Bergouignan & Seilhean	1960	3	100
Freidman & Losin	1961	21	71
Harris	1961	5	100
Hale & Reid	1962	8	38
Lovshin	1963	159	69
Kudrow	1978	77	65

†Adapted from Kudrow⁽²⁾

¹⁵ Titus F, Davalos A, Alom J, Codina A. 5-Hydroxytryptophan versus methysergide in the prophylaxis of migraine. Randomized clinical trial. *Eur Neurol* 1986; 25(5):327-9.

¹⁶ Kudrow L. Cluster Headache Mechanisms and management. 1 ed. Oxford: Oxford University Press; 1980

¹⁷ Lovshin LL. Use of methysergide in the treatment of extracranial vascular headache. *The Journal of Head and Face Pain* 1963; 3(3): 107-11.

The majority of studies included in the table 1 involved small numbers of patients, and some of the earlier ones did not differentiate between the different forms of cluster headache.

Krabbe, 1989¹⁸ reported less convincing evidence of effectiveness in two studies, one observational and one prospective. In the observational study, involving retrospective assessment of 164 cases of cluster headache, satisfactory outcome was reported in 26% of patients. A subsequent prospective study of 42 patients with primary, secondary or episodic cluster headache, with a dose escalation regime ranging from 3-12 mg methysergide per day, revealed that 26% of patients experienced a good or excellent outcome with good tolerability to the drug. In contrast to other studies, the response to methysergide reported in these patients was not influenced by the type of cluster headache and was similar between episodic, primary and secondary chronic forms.

In a review by Pradalier et al (2001)¹⁹, verapamil and methysergide were cited as the most useful treatments of the episodic form of cluster headache. They noted that due to the episodic nature of the condition, double-blind placebo controlled studies were often lacking since they are difficult to perform due to spontaneous and variable duration of the headache remission.

In a recent survey of 85 patients with cluster headache conducted in Belgium by Van Alboom et al (2009)²⁰, 80% were of the episodic form, and the prescribed medications that patients had received at any time following diagnosis were verapamil (82%), lithium (35%), methysergide (31%) and topiramate (22%).

Treatment of diarrhoea caused by carcinoid disease

No information was submitted by the MAHs in support of this indication.

2.2.2. Discussion

Prophylaxis of migraine

The efficacy of methysergide in prophylaxis of migraine was supported by four randomised, double-blind, placebo-controlled studies. The results of these studies suggested the efficacy of methysergide compared to placebo in the above mentioned indication. From the eleven methysergide trials presented above, three clinical trials (Curran and Lance, 1964; Southwell, 1964; Whewell J, 1966) have shown efficacy of methysergide compared to placebo in prophylaxis of migraine. Three trials comparing methysergide to pizotifen (Presthus, 1971; Forssman, 1972; Andersson, 1973) have shown no statistically significant differences between the two treatments. One trial comparing methysergide and propranolol (Behan and Reid, 1980) failed to demonstrate any statistically significant differences between these treatments. The trials comparing methysergide to lisuride (Herrman, 1977) to flunarizine (Steardo, 1986) and to 5-hydroxytryptophan (Titus, 1986) suggested no clinically significant difference in response.

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. The number of patients included was small, the duration of treatment was short (4-6 weeks) and the clinical efficacy parameters used

¹⁸ Krabbe A. Limited efficacy of methysergide in cluster headache. A clinical experience. Cephalalgia 1989;9 (SUPPL. 10): 404-5.

¹⁹ Pradalier A, Baudesson G, Vincent D, Imberty-Campinos C. Treatment of the cluster headache. Rev Med Interne 2001; 22(2): 151-62.

²⁰ Van Alboom E, Louis P, Van Zanducke M et al. Diagnostic and therapeutic trajectory of cluster headache patients in Flanders. ACTA NEUROL BELG 2009;109(1):10-7.

are not in line with the European Guidelines on clinical investigation of medicinal products for the treatment of migraine²¹.

The CHMP also noted that methysergide is included in the latest recommendations of migraine preventive treatments of the European Federation of Neurological Societies (EFNS) 2009²², as drug of third choice for migraine prophylaxis for short-term use only (maximum 6 months per treatment period) (Level C: only probable efficacy). In the latest French recommendations of 2013, methysergide is included as Grade B or C (probably effective) medicine for migraine prophylaxis²³. 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.

Cluster headache

The clinical trials evidence of the efficacy of methysergide as a prophylactic treatment for cluster headache is less robust compared to the evidence for migraine prophylaxis. The majority of studies involved small numbers of patients, and did not differentiate between the different forms of cluster headache. Randomised controlled trials are lacking, and the methodologies of trials that have been conducted are not in line with the current requirements.

The CHMP also noted that methysergide is included as second choice treatment (Level B: probably effective) in the latest recommendations of cluster headache preventive treatments of the EFNS (2006)²⁴. Methysergide is recommended as an alternative treatment for episodic cluster headaches, particularly of the episodic form in which it appeared to have the greatest efficacy, based on a review of open-label studies. Other recently published guidelines also include methysergide in the list of preventive therapies for cluster headache. The UK guidelines²⁵ recommend the use of methysergide when other treatments have failed. The Danish and Italian guidelines^{26,27}, published in 2012, mentioned methysergide in a list of other preventive therapies after verapamil, prednisolone and lithium.

The CHMP noted that methysergide is recommended by experts as a rescue treatment, reserved for patients in whom other treatments have failed.

Treatment of diarrhoea caused by carcinoid disease

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*".

Scientific Advisory Group (SAG)

In addition, 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,

²¹ Guideline on clinical investigation of medicinal products for the treatment of migraine. CPMP/EWP/788/01 Rev. 1 (2007)

²² 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.

²³ 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.

²⁴ 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.

²⁵ 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)).

²⁶ Sarchielli P. XI Congress of the International headache society. *Expert Opin Pharmacother* 2004; 5(4):959-75.

²⁷ 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.

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 SAG considered that treatment with methysergide should be limited to patients with intractable headache, i.e. who are pharmacologically refractory to standard treatment and who are disabled by their condition. The SAG also considered that treatment with methysergide should be initiated and supervised by specialised physicians (usually a neurologist) with experience in the treatment of migraine and cluster headache.

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.

2.3. Clinical safety

In order to evaluate the safety of methysergide, the CHMP considered data from literature and safety database including spontaneous and literature reports. Estimates from a more recent period (2004-2012) for the main identified fibrotic risks were also assessed.

The total patient exposure to methysergide for the period between January 2004 to May 2012 was estimated to be 12,331 patient treatment years.

2.3.1. Results

Literature review

Only few recent publications considering the incidence of fibrosis in patients receiving methysergide are available, with most recent articles on the subject referring to rate quotes in a review article published by Silberstein in 1998²⁸. This review itself refers to incidence rates based on much earlier work^{29,30}. In their responses, the MAH provided the incidence rates for methysergide-induced fibrosis (valvular, retroperitoneal and pleuropulmonary) from a review of the available literature which was compared to the incidence and prevalence figures (where available) for the general population.

Valvular heart disease

Bana et al (1974) observed 1000 patients taking methysergide over a 7-year period and reported an overall incidence of 3.6% for the development of cardiac murmurs, as detected by auscultation. This equates to an incidence rate of around five patients per 10,000 patient years. This rate is probably lower than the true rate as cardiac auscultation would not be expected to be as sensitive as cardiac ultrasound in detecting valvular abnormalities. Nonetheless, auscultation by a cardiologist at that time would be expected to detect moderate and severe degrees of valve dysfunction. Notwithstanding the limitations of this estimate, it is noted to be similar to the estimates for the general population (symptomatic valvular regurgitation in non-drug exposed subjects estimated as 5.5/10,000 patient

²⁸ Silberstein SD. Methysergide. Cephalalgia 1998;18(7):421-35.

²⁹ 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.

³⁰ Bana DS, MacNeal PS, LeCompte PM. Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974;88(5):640-55.

years, and rate of 4.2/10,000 for the general population published recently by Steffensen et al (2012)³¹).

Retroperitoneal Fibrosis (RPF)

In a 10-year prospective Dutch study which assessed the incidence and clinico-radiological characteristics of idiopathic RPF in the normal population (van Bommel, 2009³²), 53 patients were found to have a diagnosis of idiopathic RPF. The estimated annual incidence of RPF was 0.13/10,000 individuals. The mean age of these subjects was 64 years and the male-female ratio was 3.3:1.0.

In a series of 1000 methysergide-treated patients observed over five years (Graham, 1966) there were 10 identified cases of retroperitoneal fibrosis. This equates to an annual incidence of 20 per 10,000 patient years. The author attributed the relatively high incidence of RPF in these patients to the fact that they were patients with unusually severe headaches and likely to be taking higher than recommended doses of methysergide.

In a prospective study of patients receiving methysergide, intravenous pyelograms (IVP) revealed evidence of fibrosis in 2.5% of patients who were asymptomatic, which regressed on discontinuation of treatment (Elkind, 1968³³).

Pleural/Pulmonary Fibrosis

The background prevalence of idiopathic pulmonary fibrosis in US adults population observed on a 5-year period is estimated between 1.4-4.3 per 10,000 individuals, with annual incidence rates of 0.7 – 1.6 per 10,000 people (Raghu, 2006³⁴). Set against these background rates, the incidence of pleural fibrosis following methysergide is quoted by Silberstein SD (1998) as 1:5000 (i.e. 2 per 10,000) which is just above the upper limit of the background rate estimate.

Other adverse events

The MAH reported that the most common adverse events associated with methysergide (occurring in ≥ 5% of patients) are dizziness, nausea and/or vomiting, epigastric pain, psychic reactions, peripheral arterial insufficiency and peripheral oedema. According to the review by Silberstein in 1998, approximately 10% of patients gain weight whilst on treatment and approximately 40% of patients experiencing peripheral arterial insufficiency developed symptoms only when the methysergide dose exceeded 8 mg/day. In addition, in the study by Curran and Lance (1964), which included 320 patients, 45% had adverse events of which the most troublesome were caused by vasoconstriction. However, these symptoms could be relieved in some instances by the addition of a vasodilator drug without removing the headache benefit.

In an anecdotal report by McNeal in 1965³⁵, eight patients developed cardiac murmurs whilst receiving 2-12 mg daily methysergide for periods varying from a few months to over two years but the murmurs lessened or disappeared when methysergide was discontinued.

Safety database review

The results of the expanded search in the safety database conducted over a 43-year period are summarised below.

³¹ Steffensen C, Maegbaek ML, Laurberg P 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.

³² 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.

³³ Elkind AH, Friedman AP, Bachman A et al. Silent retroperitoneal fibrosis associated with methysergide therapy. *JAMA : the Journal of the American Medical Association* 1968; 206(5): 1041-4.

³⁴ Raghu G, Weycker D, Edelsberg J et al. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006; 174(7): 810-6.

³⁵ MacNeal PS. Quoted in "Headache Rounds", Faulkner Hospital, Boston, January 13, 1965.

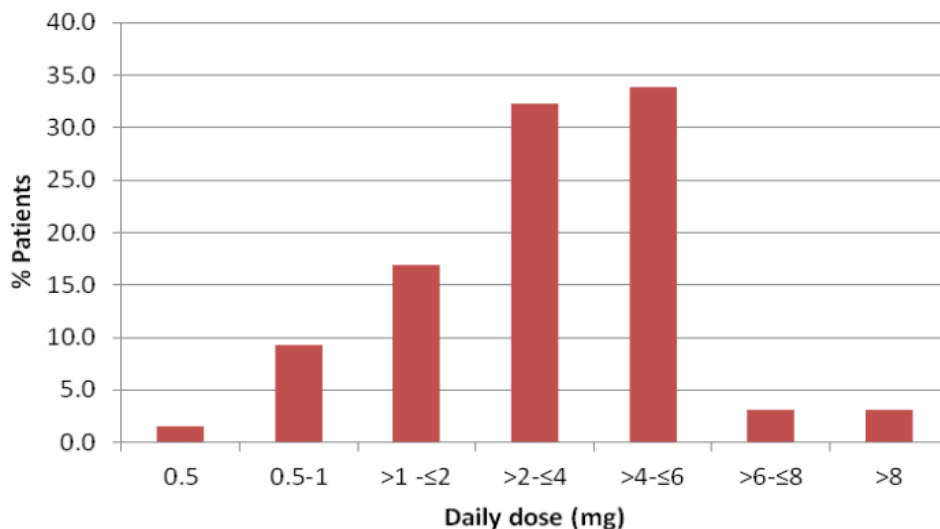
The safety database identified 351 of 1 047 methysergide treated patients with events indicative of fibrosis. In these 351 cases identified, 157 (44.7 %) were related to retroperitoneal fibrosis, 104 (29.6%) to pleural/pulmonary fibrosis, 66 (18.8 %) to cardiac fibrosis and 24 (7.1 %) to other types of fibrosis.

The age distribution of the fibrosis cases was analysed. The analysis showed that fibrosis development does not appear to be related to patient age. Most of cases reported occurred in patients between 40 and 70 years of age.

The relationship between duration of treatment and fibrosis events was also analysed. Of the 135 patients among 351 for whom exposure duration was recorded (excluding non-assessable cases), daily exposure to methysergide was less than or equal to six months in 14.8% of the cases and between 6 months to 1 year for 31.1%. The remaining patients (54.1%) were treated longer than one year. Even with less than one year exposure, fibrosis has been reported for around 46% cases.

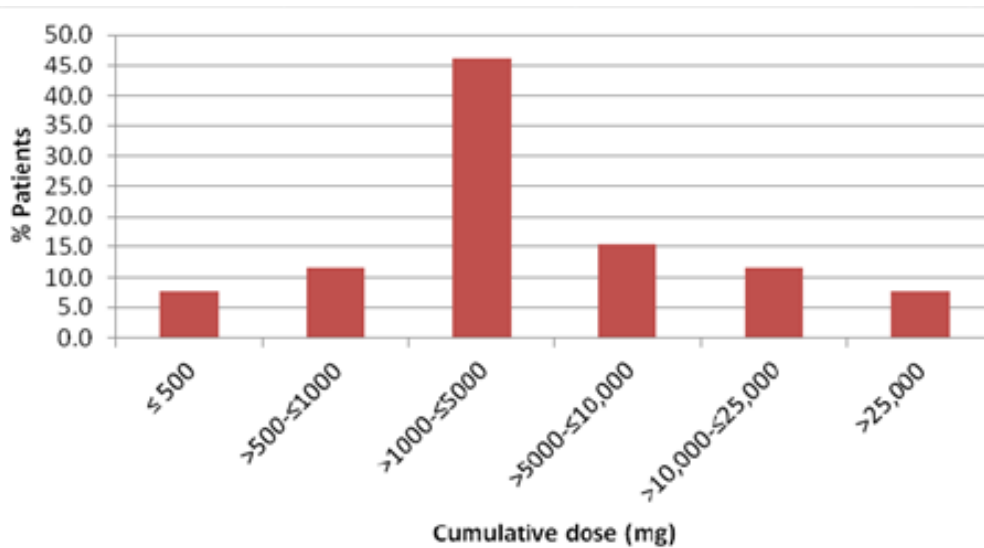
The relationship between daily dose of methysergide and fibrosis events was analysed. The daily dose of methysergide was reported for 66 patients and ranged from 0.5-12 mg. Of these 66 patients, 21 received a daily dose ≤ 2 mg, 40 received a daily dose between to 2-6 mg and 5 received more than 6 mg daily. Fibrosis reaction was shown in 92.4% of patients (n=61) receiving ≤ 6 mg daily and in 7.6% patients receiving > 6 mg daily (n=5). The proportion of patients reporting fibrosis appears to increase with increasing daily dose. The MAH claimed that no correlation between daily dose and proportion of patients was seen when all doses were included but a strong correlation was seen with daily doses up to 6 mg (figure 1).

Figure 1: Distribution of patients with fibrosis by daily dose of methysergide



With regard to the relationship between cumulative dose of methysergide and fibrosis events, it appears that the majority (80.8%) of patients with fibrosis received a cumulative dose of methysergide of more than 1g (figure 2).

Figure 2: Distribution of patients with fibrosis by cumulative dose of methysergide



Estimated rate of fibrotic reactions (2004-2012)

In order to estimate the reporting rate of fibrotic reactions, the MAH identified all fibrosis cases that occurred between January 2004 and October 2011. Twenty (20) cases were identified during this period. The MAH also retrieved additional reported events that occurred from November 2011 to May 2012. Seven cases were reported during this period but only one case was identified with a fibrotic event (retroperitoneal fibrosis); no other events were related to fibrosis. The MAH estimated the annual incidence in the patient population using the 21 cases identified above. The annual incidence of fibrotic events estimated by the MAH is 17.0-20.3 per 10 000 patient population treated with methysergide. Retroperitoneal fibrosis and cardiac fibrosis accounted for most of these cases with 8.9-11.4 cases and 5.7 cases per 10,000 patients, respectively. These figures should be interpreted with caution due to likely underreporting and difficulties in estimating exposure.

2.3.2. Discussion

Literature review

The incidence rates of valvular and pulmonary fibrosis in patients treated with methysergide is shown to be similar to those of the general population. However, these results should be taken 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).

Other adverse events have been reported from the literature, with the most common (occurring in ≥ 5% of patients) being dizziness, nausea and/or vomiting, epigastric pain, psychic reactions, peripheral arterial insufficiency and peripheral oedema.

Safety database review

A significant proportion of events reported with methysergide (351 out of 1047 in the database) relate to fibrotic reactions. Furthermore, significant under reporting of fibrosis cases by health care

professionals is to be expected (difficulties and delays in diagnosis, adverse drug reactions with a substance marketed for a long time and which are mentioned in currently approved Summary of Product Characteristics (SmPC) are generally less reported, off-label use etc.).

The analysis showed that fibrosis development does not appear to be related to patient age.

The results of the analysis by treatment duration showed that the majority of the patients with potential fibrosis had methysergide therapy for at least 1 year (54.1%), and some between 6 months and 1 year (31.1%). Although the number of fibrotic events is lower with methysergide intake for up to six months (14.8%), occurrence of fibrosis cannot be excluded with short-term treatment.

The correlation between fibrosis events and methysergide daily doses up to 6 mg is of concern. The majority of patients (92.4%) who developed fibrosis received ≤ 6 mg daily of methysergide, which is within the recommended posology.

Taking into account the number of fibrosis reported and the probable under reporting, the risk of fibrotic reactions associated with methysergide cannot be excluded. The CHMP noted that some of the retroperitoneal fibrotic reactions reported are very severe (ureter fibrosis, bilateral uretic stenting, bilateral nephrostomy etc.) and this is a matter of concern especially when methysergide is used in the long term.

Discussion on the mechanism of action of methysergide and possible relation with fibrosis reactions

Many authors have suggested that agonist activity of drugs at the 5-HT_{2B} receptor may be capable of inducing fibrosis, in particular heart valve fibrosis^{36,37,38,39}. Agonism to 5-HT_{2B} receptors induces a proliferative response and mitogenicity of the cells expressing this receptor leading to fibrogenesis. 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_{2B} receptor, long-term treatment with methysergide will expose patients to the potential for tissue fibrosis mediated by its principal active metabolite, methylergometrine.

2.4. Risk minimisation activities

The CHMP recommended amendments to the product information (see section 2.7) and communication to healthcare professionals through a direct healthcare professional communication (DHPC – see section 2.6). In addition, the CHMP recommended the following additional risk minimisation activities:

Information and awareness of Healthcare professionals and patients

Education measures are necessary in order to clearly inform prescribers and patients on the risk of fibrosis associated with methysergide and on the measures necessary to minimise the risk.

- Physician and patient's guide

³⁶ Rothman RB et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000; 102(23): 2836-2841.

³⁷ Zanettini R et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; 356(1): 39-46.

³⁸ Bhattacharyya S, Schapira AH, Mikhailidis DP, Davar J. Drug-induced fibrotic valvular heart disease. *Lancet* 2009; 374(9689): 577-85.

³⁹ Hofmann C et al. Lisuride, a dopamine receptor agonist with 5-HT_{2B} receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role for 5-HT_{2B} receptor agonism in cardiac valvular fibrosis. *Clin Neuropharmacol* 2006; 29(2): 80-86

The CHMP recommended that educational information should be provided to physician and patient, such as 'guides'. These could be provided online for download by prescribers and patients.

The physician's guide should include the following information:

- Revised indications;
- Investigations to be performed prior to treatment and every six months;
- Warnings on the risk of fibrosis and the ongoing need for assessment of the risk and benefit treatment.

The patient's guide should include the following information:

- A summary of the risks and benefits of the treatment;
- Details of the symptoms of fibrosis;
- An explanation for the need for six monthly monitoring with information on the types of investigations to be performed;
- Guidance on how to keep a diary to monitor migraines attacks.
 - Information card for patients

The CHMP recommended a small information card as additional risk minimisation activity to provide concise information on the important signs and symptoms of fibrosis and when to seek medical attention.

The card should include the following information:

- Summary of the risk and the benefit of the treatment;
- Need for six monthly monitoring and types of investigations;
- Guidance on how to keep a diary to monitor migraine attacks;
- Guidance on signs and symptoms that may be suggestive of fibrosis.

2.5. Overall benefit/risk assessment

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. The results of these studies are suggestive of 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.

While the clinical trial evidence of efficacy has its limitation, when taken together with the clinical guidelines and the input from the SAG, it was considered by the Committee to be suggestive of a clinically significant effect of methysergide in the prophylaxis of migraine.

With regard to the indication "*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. But again when taken together with the feedback from the SAG and current clinical guidelines, the data is suggestive of a clinically significant benefit of methysergide in cluster headache.

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*".

For the assessment of safety, 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. However, these results should be taken 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).

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 (≤ 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 uretic 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_{2B} 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 submitted data provided by the MAH in writing, the CHMP concluded that the benefit-risk balance of methysergide is favourable in:

- 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.

2.6. Communication plan

As part of this referral procedure, the MAH and the CHMP agreed on the wording of a direct healthcare professional communication (DHPC) designed to inform prescribers on the measures taken for the safe use of these medicinal products. The core elements of this DHPC were agreed by the CHMP, together with the communication plan (see attachments to this report).

The MAHs should agree on the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to the current prescribers and specialised physicians to inform them of the changes for methysergide therapy immediately prior to the product returning to the market.

2.7. Changes to the product information

The CHMP recommended changes to the product information in line with the above conclusions. Detailed changes can be found in Annex III of the opinion.

3. Overall conclusion

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.