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Assessment report for meprobamate-containing medicinal products for oral use

Procedure number: EMEA/H/A-107/1316

Procedure under Article 107 of Directive 2001/83/EC, as amended

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 25 July 2011, France informed the European Medicines Agency (EMA) of its intention to suspend the Marketing Authorisations of meprobamate-containing medicinal products for oral use in its Member State. A procedure under Article 107 of Directive 2001/83/EC, as amended was automatically initiated for meprobamate-containing medicinal products for oral use.

2. Scientific discussion

2.1. Introduction

Meprobamate is a carbamate derivative, acting as a central nervous system depressant with anxiety-relieving, sedative and muscle relaxant activity. Meprobamate is generally considered to be more of a sedative than an anxiolytic. Although differing in structure, the pharmacological effects of meprobamate resemble those of barbiturates. It inhibits several areas of the central nervous system including the thalamus, hypothalamus, limbic system, the reticular formation and polysynaptic reflexes of the spinal cord (Rho et al, 1997). It also inhibits adenosine uptake (Philips and Delong, 1987; Delong et al, 1985).

Meprobamate is considered to have a relatively narrow therapeutic index, with a steep dose-response curve, resulting in an increased risk of accidental overdoses with serious and potentially fatal adverse events, including coma, profound hypotension, hypothermia, respiratory arrest and cardiogenic shock. Meprobamate can cause physical and psychological dependence and a potentially life-threatening abstinence syndrome with delirium on abrupt withdrawal, in particular after prolonged use, similar to that of alcohol and barbiturates, including within the normal dosage and treatment duration, due to the nature of the product. Although it has some anticonvulsant effect in absence seizures, it may induce generalized tonic-clonic attacks in the predisposed which may be a drawback during alcohol withdrawal, a condition characterized by an increased susceptibility to convulsions.

Oral formulations of meprobamate have been authorised in the EU as prescription-only products. It is available as a single product or as fixed combinations with other substances, including:
- in combination with acepromet azine
- in combination with ergotamine, caffeine and chlorcyclizine
- in combination with quinine
- in combination with magnesium oxide, magnesium sulphate, kaolin and sterculia gum

It was noted that some of these substances (e.g. ergotamine and quinine) also possess a narrow safety margin.

In February 2006, following a safety and efficacy review of all medicines containing meprobamate as only active substance, the French National Competent Authority (Afssaps) identified a risk of pharmacodependence and withdrawal symptoms and confusion states, generally in elderly. The indication of meprobamate tablets 250mg and 400mg, was therefore restricted to "*withdrawal aid for alcohol-dependent subjects when the benefit/risk ratio of benzodiazepines does not appear to be favourable*" and the prescription duration was limited to a maximum of 12 weeks. These measures were implemented in 2006. In addition, following a French survey carried out in 2004 by the Poison and Toxicovigilance Centres of the potential life-threatening risk of meprobamate overdose, the Afssaps requested an update of the overdose section and a reduction of the pack sizes, from 30 to 20 tablets per box for meprobamate 250mg (total of 5g per box) and to 10 tablets per box for meprobamate 400 mg (total of 4g per box). These changes were implemented in July 2009 and an information letter (DHPC) was sent to healthcare professionals. Subsequently, Afssaps initiated a national pharmacovigilance follow-up of the safety risks associated with meprobamate, in order to assess the impact of the implemented measures.

Two pharmacovigilance analyses of data from spontaneous reports were conducted by the Lille CRPV (*Centre régional de pharmacovigilance*) and finalised in 2011. The analyses did not identify any significant impact of the implemented risk minimisation measures and noted the lack of clinical data on the benefit of these products. The number of spontaneous reports notified for meprobamate-containing products for oral use remained stable, in particular the number of deaths due to overdose, despite

packaging changes. In addition, the Afssaps was particularly concerned by adverse events in elderly patients. The lack of convincing efficacy data was also noted and the Afssaps therefore considered the benefit-risk of meprobamate-containing products to be unfavourable and notified the EMA and the CHMP on 25 July 2011 of its intention to suspend the French marketing authorisations of oral medicines containing meprobamate, effective as of January 2012. As a result, a procedure under article 107 of Directive 2011/83/EC was automatically initiated at European level for meprobamate-containing medicinal products for oral use.

The documentation relevant to the procedure was sent to all MAHs across the European Union (EU). In its assessment, the CHMP considered all available data, including the responses received from nine MAHs involved in the procedure. The MAH of the originator product (Sanofi-Aventis) informed the CHMP of its intention to suspend the marketing and to withdraw the marketing authorisations of their meprobamate-containing products in all concerned member states. Consequently, Sanofi-Aventis did not submit any responses. Nonetheless, post-marketing data from this MAH, reviewed in the context of French national evaluations, was included in the CHMP assessment.

The CHMP acknowledged the significant differences in approved indications of meprobamate between the various member states in which it is marketed, which translate into divergences in the medical use of the products, especially between products containing only meprobamate and products containing meprobamate in combination with other substances. The indications include:
- *aid for alcohol withdrawal,*
- *treatment of anxiety states,*
- *treatment of muscle tension, cramps or spastic state of voluntary muscles*
- *symptomatic treatment of digestive functional disorders*
- *treatment of migraine attacks and*
- *treatment of occasional insomnia*

Other divergences in the approved product information texts, in particular with regard to dosage and treatment duration as well as with regard to contra-indications and warnings, were also noted. Regarding precautions of use in the elderly population, recommendations of dose reduction (half the normal adult dose or less may be sufficient for a therapeutic response in elderly) or caution for use is present for the majority of products. The CHMP noted that for a number of products, duration of use was restricted due to concerns of pharmacodependence.

2.2. Discussion on safety

2.2.1. Non-clinical data

A reproductive toxicity study was conducted by one MAH, in rats and chick embryos. No teratogenicity or harmful effect on the number or weight of the foetuses was observed. However, as literature data is inconsistent regarding the potential teratogenicity of meprobamate, the MAH contraindicated pregnancy and lactation in the SPC of its meprobamate-containing product.

2.2.2. Clinical safety

2.2.2.1. Clinical studies

Only one of the MAHs provided data from conducted clinical trials with meprobamate. The MAH stated that the trials were conducted between 1958 and 1987 after which the MAH stopped its clinical trial program. The studies included a total of 1352 patients and although they were performed according to the existing requirements at the time, they do not meet the current requirements. Study descriptions are usually incomplete and contain only subjective observations. In some trials, safety data was not collected. A detailed subgroup analysis on the predictability of risks with meprobamate according to age, time to onset, concomitant medications and illnesses can therefore not be made. However, a number of adverse events were recorded. In trial No. 2, one case of muscle weakness became more severe with up-titration of meprobamate up to 3000-4000 mg daily, causing gait and walk disturbances. Tremor became more pronounced with higher doses but no therapy cessation was necessary. In trial No. 11, one overdose case (3000 mg meprobamate ingested in one dose) was recorded in a male patient. The patient flushed and became somnolent, although pulse, tension and respiration did not change. Long-term complications did not occur. 8 fatalities occurred among the 1352 patients participating in the clinical trial program. Four of these fatalities were caused by delirium tremens due to alcohol withdrawal. 4 patients

died because of other reasons. Causal relationship between the use of meprobamate and the death of these patients was not confirmed by the investigators.

The CHMP considered the trials to be based on subjective observations and to be poorly documented. Some completely lack collection of safety data, and in others, no comparison was performed between the adverse events induced by meprobamate and the placebo or the comparator. The CHMP concluded that the available safety data from clinical trials is insufficient to draw any conclusions on the safety of meprobamate and the predictability of any associated risks.

2.2.2.2. Published literature

Some MAHs carried out literature searches for clinical data relevant to the risks associated with medicinal products containing meprobamate and submitted a number of publications of interest. A published study on the potential teratogenic effect of meprobamate (G Timmermann, N Acs, F Bánhidy and AE Czeizel*, A study of teratogenic and foetotoxic effects of large doses of meprobamate used for a suicide attempt by 42 pregnant women*. Toxicology and Industrial Health 2008; 24:97-107) did not identify any teratogenic or foetotoxic (including neurotoxic) effects on foetal development. A clinical epidemiological study (Kovács T. Páll D, Abafalvi Zs., Karányi Zs., *Acute toxicological cases examined during a 10-year period in our clinic*, Orvosi Hetilap (Medical Weekly) 2002, 143;2:71-76) showed that after benzodiazepines, meprobamate was the medicine most frequently used for suicide attempts and complete suicides in a high suicide-frequency region of Hungary. However, 25 cases of accidental overdoses were also noted. A publication by Fathallah et al, 2011 (Fathallah N, Zamy M, Slim R, Fain O, Hmouda H, Bouraoui K, Ben Salem C, Biour M, *Acute Pancreatitis in the Course of Meprobamate Poisoning*, JOP. J Pancreas 2011; 12(4):404-406) described a case of massive poisoning with meprobamate leading to acute pancreatitis. Even if very rare, this complication should be considered, according to the authors, as an additional possible manifestation of meprobamate poisoning, in addition to the cardiovascular and central nervous symptoms. Finally, a safety study by Buire et al, 2009, evaluated the relationship between the Glasgow Coma Scale (GCS) and meprobamate plasma concentrations in meprobamate poisoning to determine the relevance of plasma level measurements. The authors commented that conscious patients with a high meprobamate concentration are probably addicted to the drug, while patients with low meprobamate concentrations and low GCSs had likely taken other sedating medications and alcohol in addition to meprobamate.

The CHMP considered that the available literature supports the toxicity of meprobamate, which is often severe and may be life-threatening. The CHMP also noted the 25 cases of accidental overdoses with meprobamate, identified byKovacs et al, 2002 and concluded that accidental overdoses are a serious risk with meprobamate.

2.2.2.3. Post-marketing data

The CHMP noted the limited number of spontaneous reports submitted in the MAH responses and that the reporting periods differed from product to product. The CHMP noted that some of the products have never been marketed. In total, 36 cases were submitted as part of the MAH responses. Considering the inherent issues of underreporting and the limited period of safety data analysed for some of the products, the CHMP was of the view that this dataset does not give a complete overview of the spontaneous reporting for meprobamate products. The CHMP considered the provided data on treatment duration and on off-label use to be too limited to conduct a specific analysis for the elderly population.

Therefore, in order to assess the safety profile of meprobamate, mainly neurological and psychiatric adverse events, including pharmacodependence and serious withdrawal symptoms under normal conditions of use, particularly in the elderly, the CHMP also reviewed the data from two pharmacovigilance analyses of safety data on meprobamate and meprobamate/acepromet azine, conducted nationally in France by the Lille CRPV), to assess the impact of the national implementation of risk minimisation measures.

Lille CRPV analysis of meprobamate-only products

The first Lille CRPV analysis reviewed meprobamate-only products, indicated as withdrawal aid for alcohol-dependent subjects, with a treatment duration of 1 to 3 weeks, with a maximum of 12 weeks. This analysis assessed the impact of the implementation of the 2009 risk minimisation measures (restriction of the indications, reduction of pack size and circulation of the DHPC). The safety data analysed included the national six-monthly monitoring submitted by the MAH covering three periods: 1

May 2009 to 31 October 2009 (only case reports from 20 July 2009, the date on which the pack sizes of oral meprobamate were modified and onwards were analysed), 1 November 2009 to 30 April 2010 and 1 May 2010 to 31 October 2010. Cases reported to regional pharmacovigilance centres for the period 1 July 2009 to 27 March 2011 were also included, after removal of duplicate case reports. These data were compared to those from the MAH report covering the period 1 May 2006 to 20 July 2009. The study period was defined as covering the period July 2009 to March 2011.

Exposure to meprobamate was based on data from GERS (Groupement pour l'Elaboration et la Réalisation de Statistiques), private practices and hospitals for the period July 2009 to October 2010. By estimating the average monthly number of units sold during this period and comparing it to the data from the May 2006 to July 2009 period, it was estimated that the implemented measures resulted in a reduction in units sold per month (which may have been due either to a decrease in the treatment period or a decrease of the number of patients treated) of 10% for the 250 mg strength and 27% for the 400 mg strength.

During the study period, 119 medically confirmed spontaneous case reports were reported. 86 were recorded during the period July 2009 to October 2010. 55 were reported as serious, corresponding to 226 adverse events, while 31 were reported as non-serious, corresponding to 60 adverse events. The reporting rate for this period was estimated to be 5.7 case reports per month. Over the period November 2010 to March 2011, 33 additional cases (27 serious) were reported, resulting in an estimated reporting rate of 6.6 reports per month. In comparison, the period May 2006 to July 2009 recorded 206 adverse events (133 serious and 73 non-serious), resulting in a reporting rate of 5.4 reports per month for this period. The analysis therefore noted that despite the reduction of sales and the resulting assumed decrease in patient exposure, the number of spontaneous case reports did not decrease following the implementation of the risk minimisation measures.

Information on treatment duration was only recorded in 40 of the 119 cases (34%) and in the majority of these cases (75%), the duration was in accordance with that approved (1 to 3 weeks with a maximum of 12 weeks). The 79 cases in which the treatment period was not specified included 9 cases of addiction, suggestion that the duration of use was longer than that authorised. The MAH provided data suggesting an average treatment duration of 36.8 days. Regarding the indications, these were rarely specified in the case reports.

Looking at the reported adverse events over the study period July 2009 to March 2011, the main primary adverse events generally occurred in the System Organ Classes (SOCs) nervous system disorders (30%) and procedure-related lesions/intoxications and complications (16%). Other frequent SOCs were psychiatric disorders, skin and subcutaneous tissue disorders, and haematologic and lymphatic disorders (6-9% each). The results were similar to the ones of the May 2006 to July 2009 period. During the study period, the most frequently encountered serious adverse events were comas (11 cases), consciousness disorders (16 cases, 8 of drowsiness, 5 of impaired consciousness and 3 of loss of consciousness), confusion states (15 cases) and intoxications (33 cases, including deliberate, accidental or non-specified). 6 cases of inhalation pneumopathy and 3 cases of addiction/withdrawal were reported. One non-fatal case of coma was reported, following serious liver failure, in a cirrhotic patient. Two non-fatal cases of falls were also reported, one associated with chronic alcoholism and the other with drowsiness. The most frequently reported non-serious adverse events were overdose (10 cases), drowsiness (6 cases) and addiction and withdrawal (6 cases). The analysis concluded that the distribution of adverse events during the July 2009 to March 2011 period was similar to that of the May 2006 to July 2009 period although it noted that the number of overdoses was approximately twice as high during the current study period.

Seven fatalities were reported over the period July 2009 to March 2011, all of which occurred in patients who also used psychotropic drugs (benzodiazepines, neuroleptics and/or antidepressants) of which three were recorded as overdoses. The relationship with oral meprobamate was recorded as possible in all 7 cases. Over the May 2006 to July 2009 period, 15 fatalities were recorded (including 7 due to overdose). The analysis concluded that there was no decrease in the number of deaths over the July 2009 to March 2011 period and that the impact of the pack size change appears to be low.

Regarding elderly patients, the patient age was specified in 94% of cases for the July 2009 to March 2011 period. 41% of patients were over 65 years of age while 32% were 75 years of age or older. Overall, elderly patients are at higher risk of adverse events such as falls, drowsiness, consciousness disorders and confusion, as well as inhalation pneumopathies and arterial hypotension. In comparison, approximately 50% (102 out of 206) patients were over 65 years of age during the May 2006 to July

2009 period, with the same pattern of neurological and psychiatric SOC adverse events. The issue of co-medication was noted as a confounding factor, especially in elderly patients.

Lille CRPV analysis of meprobamate / acepromethazine combination products

The second Lille CRPV analysis reviewed a combination product containing meprobamate together with acepromethazine (a phenothiazine structure H1 anti-histamine), indicated in the treatment of occasional insomnia, with a treatment duration of 2 to 5 days. This analysis assessed the effectiveness of risk minimisation measures implemented in October 2010 and the first quarter of 2011, including a restriction of the indication and the posology as well as a reduction of the pack size. Data from the latest Periodic Safety Update Report (PSUR) provided by the MAH of the originator product (Sanofi-Aventis) covering the period 1 October 2005 to 30 September 2010 was assessed, together with cases reported to Afssaps during the period 1 October 2005 to 27 March 2011, after elimination of duplicate case reports. The study period was defined as 1 October 2005 to 27 March 2011.

The analysis identified 365 medically confirmed spontaneous case reports associated with meprobamate/acepromethazine during the period October 2005 to March 2011. Of these, 277 (76%) were recorded as serious (corresponding to 894 adverse events) while 88 were recorded as non-serious (corresponding to 153 adverse events). This equates to an estimated 5.5 reports per month. By comparison, 308 serious and non-serious reports were recorded during the 2001 to 2006 period. The analysis concluded that the average reporting rate for meprobamate/acepromethazine did not decrease for the 2005 to 2011 period.

Regarding elderly patients, 80 (22%) patients were aged over 65 years and amongst these, 49 (13%) were aged 75 years or above. 89% of patients aged over 65 years presented a serious adverse event and elderly patients represent 64% of cases of falls and 60% of cases of confusion and disorientation. By comparison, 27% of notifications during the 2001 to 2006 period involved patients aged over 65 years.

Regarding treatment duration, duration was specified in 92 out of 365 cases (25%). It was noted that, amongst cases for which treatment duration was not specified, 15 cases of addiction were observed. According to EGB (Echantillon Généraliste des Bénéficiaires, the French National Insurance Healthcare database), data extracted for the period 2006 to 2010 showed that the average annual number of boxes dispensed per patient increases with age, in particular for patients over 60 years of age. Treatment duration exceeded 30 days in more than 75% of patients over the age of 40. The analysis concluded that treatment duration remains a problem with this medicinal product.

The main primary adverse events occurred generally in the SOCs nervous system disorders (34%), procedure-related lesions/intoxications and complications (8%) and general disorders (8%). The most frequently encountered serious adverse events were comas (75 cases). There were also reports of consciousness disorders (36 cases), falls (30 cases), hypotension (26 cases) and confusion and disorientation (20 cases). Inhalation pneumopathy was reported in 13 cases. The most frequently encountered non-serious adverse events were falls (9 cases) and overdoses (11 cases). By comparison, the most frequently reported events during the 2001 to 2006 period involved overdoses (100 cases), comas (77 cases), falls (18 cases), hypotension (19 cases), confusion (18 cases) and drowsiness (18 cases). Due to the combination of meprobamate and acepromethazine (phenothiazine structure with neuroleptic properties), extrapyramidal disorders were also reported, with 25 cases recorded as serious and 9 as non-serious. These cases mainly involved confusion, extrapyramidal syndromes and urinary retention. The analysis also recorded 17 cases of addiction/withdrawal (13 serious and 4 non-serious).

30 fatal cases were recorded during the study period, 11 of which in the general disorders SOC and 6 in the nervous system SOC. 27 of the fatal cases involved patients who were also taking associated psychotropic drugs (benzodiazepines, neuroleptics and/or antidepressants). 20 cases recorded overdoses while the others occurred in the context of heart disorders (2 cases), fulminant hepatitis (1 case), in utero exposure with foetal malformations (1 case), pulmonary oedema (1 case), haematoma (1 case) and psychiatric or neurological disorders (2 cases). In 2 cases, no details were provided. Seven comas had a fatal outcome. An association with the use of meprobamate/acepromethazine was considered as possible in all cases.

Regarding overdoses, 134 cases were reported during the study period, i.e. 37% of all adverse events observed during this period, which was a slightly higher proportion than during the 2001 to 2006 period. Regarding falls, 39 cases were reported during the study period (30 serious and 9 non-serious). Twenty five patients (64%) were aged over 65 years, 13 of whom were aged over 75 years. No

associated deaths were reported. Regarding drug interactions, co-medication was noted as a confounding factor. In the majority of cases, patients were co-medicated, in particular with psychotropic drugs (benzodiazepines, neuroleptics and/or antidepressants in particular), whose effects may have contributed to the observed neurological and psychiatric disorders.

CHMP conclusion on Lille CRPV analyses

Regarding meprobamate-only products, the CHMP noted the 119 medically confirmed cases reported following the implementation of the risk minimisation measures, which was similar to the data for the period prior to the implementation, despite the assumed reduction in patient exposure, based on sales data. In addition, the CHMP noted that despite the 10% decrease in the proportion of elderly patient during the current study period, elderly patients remained the main affected age group (40% of patients over 65 years of age and 32% of patients over 75 years of age) and that the elderly were affected in the majority of cases of falls and confusion. The CHMP was therefore not reassured regarding the use of meprobamate in elderly patients. Cases of accidental overdose (higher doses than recommended during several days) occurred in 9% of patients. The CHMP considered that the data identified a risk of pharmacodependence, based on utilization data issued from a claims database showing prolonged use of meprobamate. This was confirmed by the analysis, which identified 9 cases of addiction/withdrawal during the study period (3 serious cases and 6 non-serious cases). 7 fatal cases were also reported during the study period. Finally, the CHMP noted a non-fatal case of coma, following severe liver failure, in a cirrhotic patient. The CHMP was of the opinion that patients who are being treated for alcohol withdrawal are at risk of serious adverse reactions, given that liver function is likely to be affected in most patients with chronic alcohol problems.

Regarding the meprobamate/aceprometazine combination products, the CHMP noted the 365 medically confirmed cases reported. The reports involved patients over the age of 65 in 22% of cases and patients aged 75 and over in 13% of cases. While the CHMP noted the minor decrease in the number of elderly patients, it raised concerns over the high proportion of elderly patients using the product. The CHMP was of the opinion that the identified risks persist, despite the implemented risk minimisation measures, particularly in patients over the age of 65, who are at high risk of falls and confusion. The CHMP was concerned by the identified risk of pharmacodependence, including in cases under normal conditions of use, as suggested by the 17 reported cases of pharmacodependence and withdrawal symptoms (13 serious and 4 non-serious). The risks of serious withdrawal symptoms were also acknowledged by the MAH during the oral explanation.

Overall, looking at the results of both analyses, the CHMP concluded that the number of reported adverse events did not decrease following the 2009 (single product) and 2010 (combination product) implementation of the risk minimisation measures and that use in elderly is still of concern. 52 fatal cases were identified (including 30 cases of overdoses) for which an association with meprobamate was considered possible. Serious concerns regarding pharmacodependence were also identified, with the associated risk of serious withdrawal symptoms. The CHMP acknowledged the potential confounding effect of co-medication as patients were co-medicated in almost all cases, particularly with psychotropic drugs. However, the CHMP was of the opinion that this may have increased the risks of adverse events with meprobamate due to interactions and therefore it cannot be excluded that meprobamate may have had a contributory role. This is of particular concern in the elderly population.

Other data

The CHMP also reviewed spontaneous case reports submitted to the Eudravigilance database and identified 18 cases of accidental overdoses, of which 17 were fatal. Noting that meprobamate has a relatively narrow therapeutic index, with a steep dose-response curve, the CHMP therefore concluded that accidental overdoses are a serious risk with meprobamate. Based on the same Eudravigilance dataset, the CHMP also noted 11 cases of withdrawal symptoms, of which one was fatal. The CHMP therefore concluded that meprobamate has a potential for pharmacodependence after prolonged use, leading to a risk of withdrawal symptoms which are serious and can be fatal.

2.2.2.4. Overall conclusions on clinical safety

In summary, having assessed the totality of the available data, including responses submitted by the MAHs in writing and during an oral explanation, as well as the nationally-conducted French pharmacovigilance assessments, the CHMP concluded that a number of serious neurological (coma and loss of consciousness) and psychiatric (pharmacodependence and withdrawal symptoms) adverse

events, which can be serious and potentially fatal, have been reported with the use of meprobamate, including under normal conditions of use. Elderly patients constitute a considerable proportion of patients and the use in this population is of concern, especially considering the increased risk of adverse events due to interactions with concomitant medication. The CHMP noted that meprobamate has a relatively narrow therapeutic index, with a steep dose-response curve, as supported by the available data which identified a number of accidental overdoses which were often serious, including fatalities. The CHMP therefore concluded that accidental overdoses are a serious risk with meprobamate. The CHMP also considered that meprobamate has a potential for pharmacodependence after prolonged use, leading to a risk of withdrawal symptoms which are serious and can be fatal. Finally, the CHMP noted a case of non-fatal coma, following severe liver failure, in a cirrhotic patient and was therefore of the opinion that patients treated for alcohol withdrawal are at risk of potential serious adverse reactions due to liver impairment.

2.2.3. Risk minimisation measures

The CHMP noted that the majority of MAHs responded that they considered the benefit-risk of their products to be positive and that routine pharmacovigilance activities were sufficient to address the identified safety concerns. As a consequence, they considered additional risk minimisation measures to be unnecessary. Some MAHs nonetheless proposed minor amendments to the product information, in particular with regard to treatment duration. One MAH suggested that further to the treatment duration restriction already implemented in France, the only way to reduce the number of voluntary overdose cases would be to restrict the use of the product to hospital-use only. One MAH considered the benefit-risk of meprobamate to be negative in the alcohol withdrawal indication and proposed to remove the indication where authorised. The CHMP reviewed the MAH proposals but considered them insufficient to reduce the identified risk of meprobamate. In particular, restriction to hospital-use only was not considered practical, given the nature of the indications and the duration of treatment.

Having reviewed the pharmacovigilance analyses of the impact of the risk minimisation measures for meprobamate and meprobamate/acepromethazine implemented in France, the CHMP concluded that these did not result in a significant nor sufficient reduction of the incidence of adverse reactions associated with meprobamate, including in cases under normal conditions of use. Particularly, the use in the elderly remained considerable. The measures were also inadequate to address the risk of pharmacodependence and of serious withdrawal symptoms. Having also reviewed the limited additional risk minimisation measures proposed by the MAHs, the CHMP concluded that no risk minimisations measures could be identified that would adequately reduce the identified risks associated with the use of meprobamate to a clinically acceptable level within normal conditions of use.

2.3. Discussion on efficacy

The CHMP noted that the available data on the efficacy of meprobamate is limited in some indications and non-existent in others. Any existing data is old and does not meet the current methodology requirements. In conclusion, while the efficacy remains largely unchanged since the granting of the initial marketing authorisation, the CHMP was of the opinion that the available data showed only very limited clinical efficacy of meprobamate in its approved indications. The CHMP also noted that the available medical practice guidelines for anxiety disorders (D. Baldwin et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology; J. of Psychopharmacology; 19(6)2005:567-596, The NICE guideline on management in primary, secondary and community care; 2011, www.nice.org.uk), alcohol withdrawal (Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence, NICE guideline Draft for consultation, June 2010, www.nice.org.uk; M.F. Mayo-Smith et al. Management of Alcohol withdrawal delirium, an evidence-based practice guideline, Arch. Intern. Med. 2004 ;164 :1405-1412) or migraine (S. Evers, EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force, European Journal of Neurology 2009, 16:968-981; S.D. Silberstein, Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review), American Academy of Neurology, 2000) do not recommend meprobamate.

2.4. Overall benefit-risk assessment

In summary, the CHMP assessed the totality of the available data, including responses submitted by the MAHs in writing and during an oral explanation, as well as the nationally-conducted French pharmacovigilance assessments.

With regards to safety, the CHMP considered that a number of serious neurological (coma, loss of consciousness) and psychiatric (pharmacodependence and withdrawal symptoms) adverse events, which can be serious and potentially fatal, have been reported with the use of meprobamate, including under normal conditions of use. Elderly patients constitute a considerable proportion of patients and use in this population is of concern, especially considering the increased risk of adverse events due to interactions with concomitant medication. The CHMP noted that meprobamate has a relatively narrow therapeutic index, with a steep dose-response curve, as supported by the available data which identified a number of accidental overdoses which were often serious, including fatalities. The CHMP therefore concluded that accidental overdoses are a serious risk with meprobamate. The CHMP also considered that meprobamate has a potential for pharmacodependence after prolonged use, leading to a risk of withdrawal symptoms which are serious and can be fatal. Finally, the CHMP was of the opinion that patients treated for alcohol withdrawal are at risk of potential serious adverse reactions due to impaired liver function.

With regard to risk minimisation measures, the CHMP reviewed the pharmacovigilance analyses of the impact of the risk minimisation measures for meprobamate and meprobamate/acepromet azine implemented in France and the limited additional risk minimisation measures proposed by the MAHs. The CHMP concluded that no risk minimisations measures could be identified that would adequately reduce the identified risks associated with the use of meprobamate to a clinically acceptable level, especially with regard to elderly patients and the risk of pharmacodependence.

In addition, while the efficacy remains largely unchanged since the granting of the initial marketing authorisation, the CHMP was of the opinion that the available data showed only very limited clinical efficacy of meprobamate in its approved indications.

In conclusion, taking into account the serious neurological and psychiatric adverse events associated with the use of meprobamate, including under normal conditions of use, the risk of accidental overdoses and of pharmacodependence associated with withdrawal symptoms, the very limited clinical evidence of meprobamate and the lack of effectiveness of the implemented and proposed risk minimisation measures, the CHMP was of the opinion that the risk-benefit balance of meprobamate-containing medicinal products for oral use is not positive under normal conditions of use. Giving due consideration to the serious risk of withdrawal symptoms, the CHMP recommended that the withdrawal of meprobamate from the market should be implemented over a 15 month period, in order to ensure the safe termination of treatment or switching of patients already being treated with meprobamate. During this period no new patients should be initiated on treatment with meprobamate.

3. Overall conclusion

The CHMP considered that a number of neurological and psychiatric adverse events, which can be serious and potentially fatal, have been reported with the use of meprobamate, including under normal conditions of use. Elderly patients constitute a considerable proportion of patients and use in this population is of concern, especially considering the increased risk of adverse events due to interactions with concomitant medication.

Meprobamate has a relatively narrow therapeutic index and the CHMP therefore considered that accidental overdoses, which are often serious and can be fatal, are a serious risk with meprobamate.

The CHMP also considered that meprobamate has a potential for pharmacodependence under normal conditions of use and that as a consequence, meprobamate is also associated with a risk of serious withdrawal symptoms.

Finally, the CHMP is of the opinion that patients treated for alcohol withdrawal are at risk of potential serious adverse reactions due to impaired liver function.

With regard to risk minimisation measures, the CHMP assessed the impact of the risk minimisation implemented in France and the limited additional risk minimisation measures proposed by the MAHs. The CHMP concluded that no risk minimisations measures could be identified that would adequately reduce the identified risks associated with the use of meprobamate to a clinically acceptable level.

In addition, the CHMP considered that the available data showed only very limited clinical efficacy of meprobamate in its approved indications.

The CHMP therefore concluded that the risk-benefit balance of meprobamate-containing medicinal products for oral use is not positive under normal conditions of use. Consequently, the CHMP recommended to the European Commission the suspension of the Marketing Authorisations of meprobamate-containing medicinal products listed in Annex I of the Opinion in all concerned EU Member States, to be effective within 15 months of the adoption of the European Commission Decision, in order to ensure the safe termination of treatment or switching of patients already being treated with meprobamate. During this period no new patients should be initiated on treatment with meprobamate.

For the lifting of the suspension, the MAHs should provide convincing data to identify a population in which the benefits of meprobamate clearly outweigh its identified risks (see Annex III of the Opinion).