Annex II

Scientific conclusions and grounds for the suspension of the marketing authorisations presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of meprobamate-containing medicinal products for oral use (see Annex I)

Meprobamate is a carbamate derivative, acting as a central nervous system depressant with anxiety-relieving, sedative and muscle relaxant activity. Meprobamate is considered to have a relatively narrow therapeutic index, with a steep dose-response curve, resulting in an increased risk of unintentional 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, with pharmacological effects similar to those of alcohol and barbiturates, including within the normal dosage and treatment duration, due to the nature of the product. 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. A number of indications are approved across Europe, including 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. Meprobamate 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.

Following a number of French national safety and efficacy reviews and pharmacovigilance analyses of meprobamate, the French National Competent Authority (Afssaps) implemented risk minimisation measures to reduce the identified risks of meprobamate and initiated national pharmacovigilance analyses to assess the impact of these measures. Two recent pharmacovigilance analyses of data from spontaneous reports, conducted by the Lille CRPV (*Centre régional de pharmacovigilance*) and finalised in 2011, 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. In addition, Afssaps was particularly concerned by adverse events in elderly patients. Afssaps therefore considered the benefit-risk of meprobamate-containing products to be unfavourable and notified the European Medicines Agency (EMA) and the Committee for Medicinal Products for Human Use (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.

Discussion on safety

The CHMP reviewed the available data submitted by the MAHs but considered that this limited data was insufficient to conclude on the safety of meprobamate and the predictability of any associated risks. 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 reviewed the data from the two pharmacovigilance analyses of safety data on meprobamate conducted by the Lille CRPV, which were the basis of the Afssaps decision to suspend the marketing authorisations for the products concerned. The first 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 a DHPC) on their risk profile. The study period was defined as covering the period July 2009 to March 2011 and the resulting data was compared to data from the May 2006 to July 2009 period. The second analysis reviewed a combination product containing meprobamate together with acepromet azine, indicated in the treatment of occasional insomnia, with a treatment duration of 2 to 5 days. This analysis assessed the impact of the implementation of risk minimisation measures (restriction of the indication and the posology as well as a reduction of the pack size) on its risk profile. The study period was defined as 1 October 2005 to 30 September 2010.

Regarding meprobamate-only products, the first Lille CPRV analysis identified 119 medically confirmed cases following the implementation of the risk minimisation measures, which was similar to the data for the period prior to the implementation, despite an assumed reduction in patient exposure, based on sales data. During the study period, the main adverse events reported generally occurred in the

System Organ Classes (SOCs) nervous system disorders (29%) and procedure-related lesions/intoxications and complications (12%). Other frequent SOCs were psychiatric disorders, skin and subcutaneous tissue disorders, and haematologic and lymphatic disorders (6-9% each). The most frequently encountered serious adverse events were comas (11 cases), consciousness disorders (16 cases), 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. 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). 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 fatalities associated with meprobamate were reported during the study period (including 2 due to overdoses). This is comparable to the 15 fatalities (including 7 due to overdoses) recorded during the May 2006 to July 2009 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/acepromethazine combination products, the second Lille CPRV analysis identified 365 medically confirmed cases during the study period, of which 277 (76%) were recorded as serious (corresponding to 894 adverse events) while 88 were recorded as non-serious (corresponding to 153 adverse events). By comparison, 308 serious and non-serious reports were recorded during the 2001 to 2006 period. The analysis concluded that the reporting rate for meprobamate/acepromethazine did not decrease following the implementation of the risk minimisation measures. During the study period, the main 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). 30 fatal cases were recorded during the study period, of which 27 were associated with the use of psychotropic drugs and 20 were recorded as overdoses. Seven comas had a fatal outcome. An association with the use of meprobamate/acepromethazine was considered as possible in all cases. 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. The overall 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.

In summary, the CHMP noted the 52 fatal cases identified (including 30 cases of overdoses) in the two French pharmacovigilance analyses, for which an association with meprobamate was considered possible. The CHMP also 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.

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. Finally, the CHMP also noted a clinical epidemiological study by Kovacs et al, 2002, which reported 25 cases of accidental overdoses with meprobamate.

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.

The CHMP also noted the pharmacovigilance analyses of the impact of the risk minimisation measures for meprobamate and meprobamate/acepromet azine implemented in France, which did not result in a significant nor sufficient reduction of the incidence of adverse reactions associated with meprobamate, including in cases of 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. In conclusion, the CHMP was of the opinion 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.

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 disorder, alcohol withdrawal and migraine do not recommend meprobamate.

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.

Grounds for the suspension of the Marketing Authorisations

Whereas

- The Committee 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.

- The Committee raised concerns regarding the considerable proportion of elderly patients and regarding use in this population, especially considering the increased risk of adverse events due to interactions with concomitant medication.

- The Committee noted that meprobamate has a relatively narrow therapeutic index and therefore considered that accidental overdoses, which are often serious and can be fatal, are a serious risk with meprobamate.

- The CHMP 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.

- 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.

- The CHMP considered, based on the assessment of the impact of the risk minimisation measures implemented in France and of the limited additional risk minimisation measures proposed by the MAHs, 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.

- 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 suspension to be lifted, the Marketing Authorisation Holders should provide convincing data to identify a patient population in which the benefits of meprobamate clearly outweigh its identified risks (see Annex III of the Opinion).