Annex II

Scientific conclusions

Scientific conclusions

Cases of serious cardiac valve disorders, pulmonary hypertension and off-label use (longer duration and/or higher dose than recommended and use in pregnancy) were reported during the periodic safety update report (PSUR) covering the period 23.12.2005 to 01.06.2020. In light of the known serious safety concerns related to this therapeutic class, those raised serious concerns as to the effectiveness of the risk minimisation measures in place and the Pharmacovigilance Risk Assessment Committee (PRAC) considered that further investigation of all available data for amfepramone-containing products related to both safety and efficacy was warranted. The above serious safety concerns, in the context of uncertainties as to clinical relevance of the modest efficacy of short-term treatment with amfepramone-containing products in treatment of obesity, led the Romanian medicines agency (ANMDMR) to raise concerns about the benefit-risk balance of these medicinal products.

On 25 January 2021 Romania triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of amfepramone-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 27 October 2022 which was revised on 07 November 2022, and then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Amfepramone belongs to the pharmacotherapeutic group "Centrally acting anti-obesity products (ATC code A08AA03)". It is a sympathomimetic agent with indirect action, belonging to the group of anorexigens. In the European Union it is currently authorised in Denmark, Germany and Romania, as adjunctive therapy to diet, in adults and children from 12 or 15 years of age with obesity and a BMI (body mass index - a measure of a person’s weight relative to their height) of 30 kg/m^2 or higher, who have not responded to an appropriate weight reducing regimen alone.

Obesity is a chronic life-long metabolic disease, the treatment of which is based on behavioural changes, diet, and exercise, with or without pharmacotherapy or bariatric surgery, aiming to lose weight and decrease risk factors. The main goals of weight management are to reduce body weight and to maintain a lower body weight in order to obtain cardiovascular (CV), metabolic and general health benefits.

The PRAC considered all available data in relation to the pulmonary, cardiac, cerebrovascular, neuropsychiatric, drug dependence and use in pregnancy safety concerns, as well as regarding the effectiveness of risk minimisation measures in place in the context of the efficacy of amfepramone. This included non-clinical, clinical data, data from spontaneous reporting and from the literature, but results from two studies using respectively primary care data from Germany (performed by EMA) and from Denmark (performed by the data analytical centre of the Danish medicines agency (DAC)). The views of a group of independent experts were also considered (ad-hoc expert group (AHEG)).

The PRAC noted that available efficacy studies show a modest short-term weight reduction (mean difference in loss of initial weight of 3.8%) with amfepramone versus placebo after 12 weeks. However, those studies suffer from serious limitations. The PRAC, supported by the AHEG, considered that data from randomised clinical trials evaluating the effect of a 12-week treatment with amfepramone on weight loss compared to placebo were lacking. It was noted that the data available did not fulfil the current criteria for demonstration of efficacy of medicinal products used in weight management. Further, whilst weight loss may be achieved after a 12-week treatment with amfepramone, the limited data available show weight regain upon treatment cessation and therefore suggest that this may not have any long-term clinical benefit on body weight and within an anti-obesity program. The PRAC and the AHEG considered the clinical relevance of the marginal and

temporary weight loss observed with amfepramone to be questionable in the context of the need for long-term weight loss maintenance for obese patients. They further noted that current treatment guidelines for obesity do not mention amfepramone.

The AHEG acknowledged the need for additional obesity treatments in adults. This led some experts to consider that there may be some situations and conditions in which short-term treatment with amfepramone, in addition to diet, physical activity and lifestyle changes, may provide initial weight loss effects to motivate obese patients to continue with these lifestyle changes or other treatments to maintain reduced weight. However, the AHEG could not define a patient population which may draw special benefit from such treatment or for which amfepramone would satisfy an otherwise unmet need. The experts noted that after amfepramone, several other treatment options had become available, based on data from well-designed clinical trials demonstrating a significant clinically relevant weight loss and an acceptable safety profile. Some of which, also suitable for obese patients with CV risk factors.

In 1996, the Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products (EMEA CPMP, later replaced by the EMA CHMP) concluded as an outcome of a review under Article 12 of Council Directive 75/319/EEC that an epidemiological study had shown that anorectic intake is a risk factor involved in the development of pulmonary artery hypertension and that the use of anorectics is strongly associated with an increased risk for this adverse drug reaction. It was further concluded that prolonged treatment is associated with a risk of pharmacological tolerance, dependence and withdrawal syndrome. Considering those serious safety concerns, the duration of treatment was limited to 4-6 weeks and no longer than three months. The indication was also restricted to adjunctive therapy to diet, in patients with obesity and a BMI $\geq$ 30 kg/m^2 who have not responded to an appropriate weight-reducing regimen alone. Contraindications in case of pulmonary artery hypertension, severe arterial hypertension, CV or cerebrovascular disease, psychiatric disorders including anorexia nervosa and depression, propensity towards drug abuse, known alcoholism were included as well as in combination with other centrally acting anorectic agent (also due to the increased risk of potentially fatal pulmonary artery hypertension).

The PRAC noted the results of the DAC study suggesting a higher risk of pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH), and of heart diseases in patients treated with amfepramone, compared to the control cohort. Further, more patients treated with amfepramone died from heart diseases (myocardial infarction being the main cause of death) compared to subjects in the control group.

It was acknowledged that those results were obtained in groups not matched by BMI. Considering that obesity is a risk factor for some subtypes of pulmonary hypertension and for cardiac diseases a subgroup analysis was performed using ICD codes considered representative of obesity. Of importance, as also noted by the independent experts consulted during the procedure, obesity is however not a known risk factor for PAH. In this analysis, no statistical difference was found in the risks of PH, including PAH, and of heart disease between the two cohorts. A subgroup analysis was also performed in a subset of patients with co-morbidities, in which results varied, with odd ratios tending in different directions but not reaching statistical significance. The PRAC considered that these analyses were limited by the small sample size of the subgroups but also due to the fact that subgroups were likely not representative and may have been otherwise confounded. Particularly for the subgroup of patients with a hospital diagnosis of obesity or co-morbidities data is expected to be incomplete as obesity, hypercholesterolaemia or diabetes are likely to be diagnosed outside the hospital and only coded if relevant for the hospital stay. Therefore, the PRAC considered that caution should be applied when extrapolating these results to the entire cohort of patients treated with amfepramone.

Additionally, cohorts were analysed in a subgroup of patients using other weight loss medication, i.e. ephedrine, orlistat, dexfenfluramine, as a further proxy for obesity. This analysis is not expected to suffer from the same issue in completeness of diagnosis code and, even if only data on prescribed drugs were collected, the PRAC considered it to be the most reliable data set among the subgroup analyses. These analyses do not to support obesity as a great confounder.

In view of the identified limitations and considering that this was not a confirmatory trial, it could not be expected that the study would be able to statistically confirm the risks. However, the majority of point estimates are superior to 1, therefore the PRAC considered the findings unlikely to be attributable to chance. Overall, in the context of the known risk of PAH with anorectics, the PRAC considered that the results further supported the seriousness of this concern for amfepramone and pointed to a persistence of the risk despite the measures implemented in 1996.

In the DAC study, amfepramone use before or during pregnancy was also found to be associated with cardiomyopathy at birth and, when used before pregnancy, with birth defects in general. However, the effect of obesity as confounder in this analysis has not been evaluated.

Despite the expected underreporting, a relevant number of cases have been reported since the implementation of the risk minimisation measures, confirming the known safety concerns of pulmonary, cardiac, cerebrovascular and neuropsychiatric disorders and pointing to the notion that the risks have not been adequately mitigated. This view was also shared by the AHEG. Data that arose since 1996 from the literature has confirmed that the risk of PAH increases with increasing treatment duration, at least for fenfluramine. The PRAC concluded that this data, taken together with data from case reports, the literature and the DAC study, confirmed the relevance of this class effect for sympathomimetic anorectic including amfepramone.

The two studies using primary care data from Denmark and from Germany have shown, despite the acknowledged limitations, an unacceptable level of non-adherence to the risk minimisation measures in place. An unacceptable level of use beyond 3 months was observed in both studies (13.6% and around 12%), whereas this constitutes a critical measure to minimise the risk of PAH, as well as the risk of dependence. In spontaneous reporting, use in combination with other centrally acting anorectic agents as well as in patients having a propensity towards drug abuse, known alcoholism, also respectively putting patients at a greater risk of PAH and dependence was identified. Patients with history or current CV disease or severe arterial hypertension, and psychiatric disorders are at greater risk of developing related adverse events. It is therefore also concerning that the study using data from Germany identified around 4% use in patients with CV diseases, or 26-30% when considering also use in patients with hypertension (severe hypertension is a contraindication), whilst cases were also reported in patients with CV and psychiatric disorders. The study using data from Denmark also found 1.5% use in pregnant women (out of which, after 1997, 9% in the second and third trimesters) and cases were reported in pregnant patients despite the fact that amfepramone must not be used during pregnancy, as a risk to the unborn child cannot be excluded.

In view of the significant level of non-adherence to the risk minimisation measures in place, the PRAC concluded that these were not effective in adequately minimising the risks associated to treatment with amfepramone-containing products.

Taking the views of the AHEG into consideration, PRAC considered the possibility of amendments to the product information, introducing educational material such as a prescriber checklist and a patient card, of removing packs containing tablets for longer treatment than 30 days, of recommending that the possibility of repeat prescriptions and of electronic prescription be prevented at national level, in order to improve awareness of the risks and associated minimisation measures and ensure regular visits for physician to re-assess the suitability of treatment with amfepramone for their patients. However, PRAC considered that the risks associated to treatment with amfepramone as well as the associated risk

minimisation measures are long- and well-known in the medical community, as reflected in the medical and scientific literature. Therefore, PRAC considered that further communication of well-known information would not significantly impact prescribing. Further, the PRAC noted that while the currently available packages allow a maximum treatment duration of 4 months with subsequent prescriptions, the excess of one months did not appear to be the driving force of long-term use considering the observed utilisation patterns. Furthermore, a pack size restriction also would not prevent patients from obtaining prescriptions from multiple physicians, particularly considering the risk of drug dependence. Another likely reason for the observed pattern of use longer than recommended is the chronic nature of obesity necessitating long-term therapy. Therefore, patients and prescribers may seek to extend treatment for longer durations than the authorised 3 months. The potential for dependency and the need for a long-term treatment of obesity are therefore both considered major limiting factors for the effectiveness of additional risk minimisations. The PRAC also discussed the possibility of implementing a controlled access program, as a form of controlled supply system, however some member states raised concerns over the feasibility of implementing such a program considering the diversity of HCPs involved in prescribing and delivery amfepramone. Finally, in view of the modest temporary efficacy of amfepramone, the PRAC considered that the imposition of such a program for this treatment would not be proportionate.

Overall, the PRAC could not identify feasible measures which would ensure effective minimisation of the risks associated to treatment with amfepramone-containing products, in particular the risks of PAH, cardio-/cerebrovascular disease and of dependence, abuse and tolerance.

Therefore, in view of the impossibility to minimise sufficiently the risks associated to treatment with amfepramone-containing products, the PRAC concluded that the risks outweigh the modest temporary benefits of questionable clinical relevance of amfepramone as adjunctive therapy to diet, in patients with obesity and a BMI of 30 kg/m^2 or higher, who have not responded to an appropriate weight reducing regimen alone.

The PRAC also noted the views of the AHEG that long-term (2 years) safety data through the setting up of registries would be beneficial to address CV and PAH safety concerns, and considered whether further studies could provide additional evidence to further characterise the efficacy and safety, of amfepramone. However, in view of the identified safety concerns, in particular in association to use longer than three months, it was not considered feasible to determine conditions to control patients' safety in a long-term clinical trial meeting current standards. Indeed, even under the controlled settings of a clinical trial, where patients can be closely monitored, it is questionable that ADRs associated to amfepramone such as stroke or dependence could be prevented. Whereas in order to exclude the risk of major CV event (MACE), large trials would be required. Further, in view of its rarity, PAH would be unlikely to be detected in clinical trials. In addition, non-interventional safety studies would not enable to generate the necessary data to demonstrate a positive benefit-risk balance, particularly considering the limited availability of further databases and the type of recorded data (e.g. lack of data on BMI). Therefore, the PRAC could not identify conditions which, if fulfilled in the future, would demonstrate a positive benefit-risk balance for these products in a defined patient population.

Consequently, the PRAC recommends the revocation of the marketing authorisations for amfepramone-containing medicinal products.

Re-examination procedure

Following the adoption of the PRAC recommendation in June 2022, the MAHs Artegodan and Temmler Pharma requested a re-examination of the PRAC recommendation on the Article 31 referral for under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for amfepramone-containing products.

The PRAC considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds, which are discussed below:

Safety

Risks of pulmonary hypertension/PAH and valvular heart disorders in the literature and spontaneous reporting

Regarding literature data, the PRAC considered that the SNAP study (the epidemiological study including patients treated with amfepramone, published after 1996, when the risk of PAH was found to be a class effect with anorectics including amfepramone), did not include sufficient number of patients treated with amfepramone (5 or fewer in each group) to detect a risk of PAH specifically with those products (Rich, 2000)[3]. Further, it was already established based on the IPPHS study that the risk of PAH increased in patients treated with anorexic drugs for more than three months. The SNAP study only compared treatment durations of more than 6 months with those of less than 6 months, cumulatively, and found further evidence of the increasing PAH risk with longer anorectic treatment durations. Therefore, this more recent study (SNAP) does not provide reassurance regarding the risk of PAH with amfepramone in general, nor in relation to cumulative use below 6 months. In addition, the published case-report of PAH in a patient with a BMPR2 mutation but no other risk factors was considered to support a possible additive effect of amfepramone in the development of PAH in patients carrying such mutations.

Regarding spontaneous reports, it is acknowledged that a small number of cases of PH and VHD have been reported, however this is not unexpected. Indeed, PAH is a rare condition for which the diagnosis is often delayed due to nonspecific symptoms and signs (e.g. frequently attributed incorrectly to age or to other medical conditions). Further, the possibly long time-to-onset of PAH, taken together with the co-morbidities and other medications (including for weight loss) in that patient population, may hinder the establishment of a link to treatment with amfepramone and thus the absence of cases assessed as certainly related to amfepramone is not unexpected. In this context, the number of identified cases related to pulmonary hypertension (14) involving amfepramone, including those reported since 1996 (12), is noted. Similarly drug-induced VHD is mainly diagnosed by echocardiographic changes, clinical symptoms being delayed, which considering the above mentioned characteristics of the patient population, and the recommended treatment duration, may hinder the identification of suspected drugs. Therefore, whilst evidence available so far does not allow to exclude or confirm a causal link between VHD and amfepramone, the number of identified cases related to VHD (23), most reported after 2000 (18) when this concerned was the subject of a EU review, are noted. Therefore VHD remains a serious potential safety concern.

Moreover, due to the limitation of spontaneously reported data, including underreporting, these data sources are not useful when assessing incidences of adverse reactions and are not adequate to confirm the lack of certain safety concerns.

From a mechanistic perspective, PRAC reiterated its position that whilst ethcathinone is considered unlikely to exert an activity on the 5-HT2B receptor, the clinical relevance of this finding is unclear, as the involvement of other biological pathways remains a possibility, this being evidentiated in the literature. Thus, whilst the knowledge of mechanisms leading to the occurrence of PAH and VHD has increased over the years, the presented non-clinical data are insufficient to exclude a causal association between amfepramone and PH/PAH, or a possible one between amfepramone and VHD.

[3] Rich S, Rubin L, Walker AM, Schneeweiss S, Abenhaim L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. Chest. 2000;117(3):870-4.

The PRAC concurred that the pharmacological action of fenfluramine and amfepramone is not identical and therefore effects seen mainly with fenfluramine use may not be directly extrapolated to amfepramone in terms of a specific pharmacological mechanism. However, considering the accumulated safety data specifically for amfepramone in the context of the concerns associated to this class of medicine, including to other sympathomimetic agent(s) (e.g. phenylpropanolamine), the concerns identified as an outcome of the review in 1996 remain.

Risks of PAH and cardiovascular disorders in the studies in German and Danish databases

The PRAC considered the results from two observational studies performed in German and Danish healthcare databases. Retrospective analyses of data from existing databases such as electronic healthcare databases are important tools when evaluating safety concerns in an observational setting. Nevertheless, a number of limitations and challenges also exist for such analyses. These need to be addressed on a case by case basis, depending on the disease setting, the available data and aim of the study undertaken.

Results of the observational study performed in the German healthcare database did not indicate that patients initiating amfepramone had a higher incidence of the selected CV outcome events compared to patients initiating orlistat, however this was a descriptive study, limited to non-fatal outcomes. Even if some confounding by indication can be reduced by comparing to orlistat, residual confounding may still bias the results due to different patient characteristics, which have not been sufficiently adjusted for. Indeed, these results are referred to as crude event rates, whereas amfepramone is contraindicated in a number of conditions, including those related to underlying CV disease, which is not the case of orlistat therefore patient on orlistat may have been at higher risk for CV events. Patients treated with orlistat were older than those treated with amfepramone (about 6 years mean and median difference) and the level of obesity or other important differences in patient characteristics may exist, which have not been adjusted for. Therefore this analysis appears to have important limitations. The results do not allow refuting CV (or PAH) risks associated with amfepramone.

In the case control study analysing the use of amfepramone in the Danish healthcare database, a higher risk of PH, including PAH, and of heart diseases was observed in the cohort of patients treated with amfepramone, compared to the control cohort who was never prescribed that medicine. In order to inform on possible confounding by BMI, a risk factor for some subtypes of PH and for cardiac diseases but not a known risk factor for PAH, subgroup analyses were performed using available variables considered proxy representative for BMI. These included hospitalisation diagnosis for obesity, certain co-morbidities, and other weight loss medications. Whilst an OR > 1 in the amfepramone group pointing to an increased risk of PH, including PAH, was found in the subgroup analyses with other weight loss medications, though statistical significance was not reached, no increased risks of PH, including PAH and of heart disease was found in the other subgroup analyses. Limitations to these subgroup analyses were however highlighted, including small sample size and possible selection bias of the subsets diagnosed with obesity or associated co-morbidities, the severity or duration of which was also not accounted for. It is questionable that all variables used for the subgroup analyses are (equal) proxy representatives for BMI and hence are appropriate selection of possible confounders. It is further noted that only patients alive during the follow-up period were included in this study. This likely introduced an immortality bias, which is concerning for the interpretation of comparative analyses. In this case, it could underestimate the risks associated with amfepramone. A further limitation with regards to the results for any heart diseases lies with the diagnoses codes used, which unweighted and used jointly, may have been too broad to obtain reliable results.

No significant difference was observed when comparing the risk of the events in association to treatment with amfepramone for less or more than 90 days, except for the risk of heart disease when

considering the full period. However, this comparison should be interpreted carefully considering potential confounders and the conservative definition of the treatment period, which likely underestimated long-term use and may have thus influenced the results. Moreover, cumulative duration of use was not considered.

In view of the identified limitations and considering that this was not a confirmatory trial, it could not be expected that the study would be able to statistically confirm the risks. For the same reasons, it is not possible to reject these risks based on these data. It is common knowledge that the absence of statistical significance in relation to an association tested, does not constitute evidence of absence of an association. This is especially important for safety endpoints. Therefore, the claim that the disappearance of a significant association after stratification should result in the rejection of the suspicion of causality is not agreed. The PRAC maintained its view that the majority of point estimates for PH, including PAH being superior to 1, the findings were unlikely to be attributable to chance. The conclusion was maintained that overall, in the context of the known risk of PAH with anorectics, the results further supported the seriousness of this concern for amfepramone and pointed to a persistence of the risk despite the measures implemented in 1996.

Non-adherence to the product information

The PRAC concurred with the view that cases were identified from spontaneous reporting showing potentially harmful off-label use of amfepramone.

The observational study performed in the German healthcare database suggest a persisting use in non-adherence with the product information, hovering in the last years around 12%. The duration of treatment was estimated from the prescribed daily dose, or where available, the number of tablets in the package for the specific formulation and the number of packages prescribed. It is acknowledged that in this analysis the daily number of tablets was missing in most patients, and for those, the median number of tablets (1 daily tablet) was imputed. Whilst approximately a third of amfepramone formulations sold in Germany since 1998 are 25 mg tablets, to be taken three times daily, in the study this corresponded to less than 3% of the prescriptions, therefore the risk of overestimation of the treatment duration with this imputation was low. Some sensitivity analyses were undertaken with the maximum daily number of tablets recorded in the dataset, whereas the data does not indicate that this may be a commonly used dose and therefore largely underestimate the treatment duration. An analysis of the "continuous treatment duration" allowed a maximum gap of 365 days between prescriptions, for them to be considered part of the same period. Therefore, those results rather informed PRAC on intermittent use over longer periods ; notably 39.5% of patients used amfepramone intermittently several years. Overall, PRAC maintained its view that, whilst limitations are acknowledged, those are not considered to significantly impact the data, which remain valid for the population observed, with the caveat highlighted.

In this study, absolute numbers of patients with prior history of CV conditions treated with amfepramone increased over the examined period. Finally, the technical limitations to patients' follow up in the database might have led to an underestimation of the treatment duration or the presence of prior history of the selected events.

The DAC study, also reports that after the implementation of the 1996 risk minimisation measures, 13.6% of patients were treated with amfepramone for longer than the maximal duration of use, as opposed to 14.9% during the whole study. In this study two redeemed prescriptions were counted as part of the same treatment period with a buffer of one week between the last tablet of a prescription and the next one being redeemed, which was considered an unconventionally conservative approach, likely leading to arbitrary separation of linked treatment episodes and therefore, those figures were considered likely to underestimate the non-adherence to the maximal recommended treatment

duration. The interpretation of repeated treatment periods interrupted by short periods of time, also needs to be considered from a safety perspective. This is illustrated by individuals commonly having more than one treatment episode (mean number of treatments per person: 4.6, median: 2), and the median time between all treatment periods being 39 days.

In this study use in pregnancy was also reported (1.5%, out of which, after 1997, 9% in the second and third trimesters), whereas those products must not be used during pregnancy as a risk to the unborn child cannot be excluded.

It was noted that the analysis was based on number of redeemed prescriptions and did not consider whether the redeemed tablets were taken. This is a common uncertainty in these type of analyses. However, in view of other aspects of the study design such as the conservative treatment period definition used this is considered of limited impact and PRAC maintained its position that the degree of use beyond the recommended treatment duration is if anything underestimated.

The PRAC concurred with the view that the extent of off-label use should always be considered in the context of the risks it may be associated with. The PRAC noted that an evaluation of CV and PH/PAH risks due to use in non-adherence to the product information was not possible in these two observational studies, partly due to important patient characteristics data. Thus, these data can neither further confirm nor refute these risks due to off-label use. However these risks have previously been established, and cases have continued to be reported, including from patients who have used amfepramone for longer treatment durations than authorised.

The incidence of dependence was not investigated in those studies, nevertheless this risk has also previously been established, and the use for longer periods than recommended may also reflect the risk of dependence to amfepramone. Overall, considering the known serious safety concerns of pulmonary, cardio-/cerebrovascular, neuropsychiatric disorders and of dependence, the PRAC maintained its view that the results of these studies, together with information from spontaneous reports (i.e. patients using the product in non-adherence to the risk minimisation measures introduced in the product information in 1996), indicate an unacceptable level of non-adherence to the product information in terms of the treatment duration and conditions for which amfepramone is contraindicated.

In Romania, like in Denmark, amfepramone is included in the list of narcotics. In Romania, those substances are released from pharmacies only using a special prescription, however there is no strict supervision in place to limit the number of prescriptions released for one patient. In Denmark, pharmacies and warehouses must report yearly amounts received, sent and in stock. The PRAC noted that no prescription or utilisation data is available for Romania. As sales data cannot inform on prescription details, adherence to the product information cannot be evaluated based on sales data. Whilst the results of the observational studies cannot directly be extrapolated to Romania, comparable levels of non-adherence may be assumed considering the measures in place in both member states. In conclusion, the PRAC maintained its view that all data taken together with respect to non-adherence to the authorised use, raises concerns on effectiveness of the risk minimisation measures in place.

Efficacy

The PRAC concurred and maintained its view that available studies submitted in support of efficacy show a mean difference of 3.8% between amfepramone and placebo in term of loss of initial weight after 12 weeks. Whilst it is not expected that those studies would have been undertaken in accordance with current standards, it is important to examine the design and conduct of those studies, in order to understand the strengths and uncertainties in relation to the efficacy data. The limitations previously noted by PRAC in relation to those trials remains valid, including small sample size, poor description of

the trials populations and of treatment compliance, pooling of results for heterogenous population (e.g. in terms of BMI and co-morbidities). It is also noted that the AHEG highlighted the lack of sufficiently robust data from randomised clinical trials comparing weight loss with short-term treatment with amfepramone versus placebo.

The PRAC noted that whilst the weight regain observed upon treatment cessation is not unexpected, there is insufficient clinical evidence to support the claims that there are situations where initial treatment with an appetite suppressant for 3 months may be considered beneficial to a patient with obesity, as part of a comprehensive weight-loss programme, or if treatment with another obesity product has to be discontinued due to intolerance, and particularly there are no data to identify patient group(s) who could draw such benefits. The lack of data with regards to the claimed effectiveness of amfepramone in patients with emotional eating, whom would be encouraged by amfepramone to begin and continue a low-calorie diet and to lose weight by behavioural changes was also noted. This view was shared by the AHEG.

Overall the clinical relevance of short-term treatment with amfepramone remains questionable.

Risk minimisation measures

The PRAC noted that the possibility of introducing further risk minimisation measures is generally assessed on a case-by-case basis. In such assessment, the nature of the safety concerns in the context of the risk-benefit balance of the product, the therapeutic need for the product, the target population and the required clinical actions are taken into account, as well as the potential effectiveness, feasibility and proportionality of the measures considered.

The PRAC further reflected on the level of awareness of physicians and prescribers to the risks of amfepramone. Whilst amfepramone-containing products had been reintroduced on the market in some MS after the annulation of the Commission decision of 09.03.2000, medical literature published since has never alleviated the well-known risks of treatment with amfepramone. Further since 1996, regardless of minor discrepancies across product information of these products, the important risks have been described in the product information of all amfepramone-containing products. Therefore, any assumption that the reintroduction on the market would have been perceived as a refutation of the known safety concerns is unfounded. Moreover, any argument that all contraindications would be difficult for physicians to memorise is not sustained, as several of them describe conditions related to the overarching pulmonary, cardiovascular, cerebrovascular and neuropsychiatric safety concerns, which have long been known for this class of products. Furthermore, prescribers are not expected to rely solely on memory when prescribing medicines.

Taking the level of non-adherence observed in Denmark, despite the measures in place, into account, and the need for long-term treatment for obesity, the PRAC maintained its view that the proposed amendments to the PI and further communication of the well-known risks and associated measures through a physician checklist and a DHPC, would not significantly impact prescribing habits and thereby result in sufficient risk minimisation.

The PRAC also concurred that the proposed pack size reduction would not sufficiently contribute to limit the treatment duration as it would neither prevent the prescription of several packs, nor the obtention of prescriptions from multiple physicians, which is a particular concern in light of the established risk of drug dependence. The PRAC also noted the level of non-adherence observed in Germany despite the non-availability of the 120 tablets pack.

The possibility of obtaining prescriptions from multiple physicians, together with the need for long-term treatment of obesity, and the potential for dependency, were also considered to hamper the possible effectiveness of the proposed patient card.

The PRAC had also discussed the possibility of implementing a form of controlled supply system, however considering the modest temporary benefits of amfepramone short-term treatment, it was not considered proportionate. Concerns were also raised regarding the feasibility of implementing such a program.

Overall, the PRAC maintained its view that no feasible measures could be identified which would ensure sufficiently effective minimisation of the risks associated to treatment with amfepramone-containing products, in particular the risks of PAH, cardio-/cerebrovascular disease and of dependence, abuse and tolerance.

In this context, allowing for the further verification of the non-effectiveness of the proposed risk minimisation measures by means of additional studies would continue putting patients at risk of serious adverse reactions, which was not considered acceptable.

Medical need

Whilst it is acknowledged that availability of different treatment options is an advantage in any disease area including for weight management, the PRAC noted that current treatment guidelines for obesity do not mention amfepramone, and that in recent years several pharmacological for weight management have become available in the EU including oral formulations. The PRAC considered that the revocation of the marketing authorisations for amfepramone containing medicinal products, would not result in an unmet medical need.

Conclusion on the benefit-risk balance following the re-examination procedure

In view of the impossibility to minimise sufficiently the risks associated to treatment with amfepramone-containing products, the PRAC maintained its conclusion that the risks outweigh the modest temporary benefits of questionable clinical relevance of amfepramone as adjunctive therapy to diet, in patients with obesity and a BMI of 30 kg/m^2 or higher, who have not responded to an appropriate weight reducing regimen alone.

The PRAC could not identify conditions which, if fulfilled in the future, would demonstrate a positive benefit-risk balance for these products in a defined patient population. Consequently, the PRAC recommends the revocation of the marketing authorisations for amfepramone containing medicinal products.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC, resulting from pharmacovigilance data for amfepramone-containing medicinal products.
- The PRAC reviewed all available data in relation to the safety concerns of pulmonary, cardiac, cerebrovascular, neuropsychiatric diseases, drug dependence and use in pregnancy, as well as the effectiveness of the risk minimisation measures in place in the context of the efficacy of amfepramone in patients with obesity. This included the responses submitted by the marketing authorisation holders (MAHs) in writing and during Oral Explanations, results from two observational studies performed in German and Danish healthcare databases, the views expressed by a group of independent experts, as well as the grounds for the re-examination submitted by the MAHs.
- The PRAC, noted that the studies supporting the weight reduction effect of amfepramone suffered from serious limitations, and considered the clinical relevance of the modest and

temporary weight loss observed with amfepramone to be questionable in the context of the need for long-term weight loss maintenance for patients with obesity.

- The PRAC concluded that the currently available data do not change the risks previously established by CPMP, as an outcome of a review under Article 12 of Council Directive 75/319/EEC, to be associated to treatment with amfepramone.
- The PRAC noted the results of the observational studies and information from spontaneous post-marketing reports showing an unacceptable level of non-adherence to the current measures aimed at minimising the risks of treatment with amfepramone in patients at higher risk of developing adverse drug reactions and the risks known to increase with the treatment duration. The PRAC considered that this raised important public health concerns.
- Therefore, the PRAC concluded that those measures have not been effective in adequately minimising the risks of treatment with amfepramone.
- The PRAC discussed the possibility of implementing further risk minimisation measures and concluded that no feasible and proportionate measures could ensure effective minimisation of the risks associated to treatment with amfepramone-containing products, in particular with respect to the risks of pulmonary arterial hypertension, cardio- and cerebro-vascular diseases and of dependence, abuse and tolerance.
- Therefore, the PRAC concluded that the risks outweigh the modest temporary benefits of amfepramone as adjunctive therapy to diet, in patients with obesity and a BMI of 30 kg/m^2 or higher, who have not responded to an appropriate weight reducing regimen alone.
- Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance for amfepramone-containing medicinal products in a defined patient population.

In view of the above, the PRAC concluded that the benefit-risk balance of amfepramone-containing medicinal products is no longer favourable and, pursuant to Article 116 of Directive 2001/83/EC, should be revoked.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of amfepramone-containing medicinal products is not favourable. Therefore, pursuant to Article 116 of Directive 2001/83/EC, the CMDh recommends the revocation of the marketing authorisations for amfepramone-containing medicinal products.