11 February 2021
EMA/PRAC/51715/2021

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for amfepramone-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1501

INN/active substance: amfepramone

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Questions

The marketing authorisation holders MAH(s) are requested to address the following questions:

Information on marketing authorisations

Question 1. Concerning your amfepramone-containing medicinal product(s), please provide in the annexed table:

a) Information on type of marketing authorisation and marketing status of each strength and package size. Where marketing authorisations have been rejected or withdrawn in any member state (MS), please state the reason.

b) Information on the legal status (e.g., OTC, POM, distribution restrictions) and whether the product is included in the list of narcotic/psychotropic drugs (as applicable in a given MS). If any limitations or specifications related to dispensing process exist (e.g. age limit control or maximum number of packages on a single prescription), please further specify within the footnote below the annexed table.

c) Information on the prescribing limitations. Please clearly indicate which specific limitations (including legal and professional restrictions) in the prescribing process exist (by indication, by prescriber specialty and other, if applicable).

d) Figures on yearly sales and patient exposure (patient-treatment years and defined daily dose; if applicable) since first marketing authorisation by product, including pharmaceutical form, and by MS.

e) Information included in section 4.1, 4.2, 4.3, 4.6, 5.1, 5.2, 5.3 as well as, in relation to pulmonary, cardiac, cerebrovascular and neuropsychiatric events, abuse and dependence, in 4.4 and 4.8 of the summary of product characteristics (SmPC) and corresponding sections of the package leaflet (PL). The English translation of the national wording should be provided and the main differences between the product information (PI) in the different EU MS should be highlighted.

Non-Clinical

Question 2. Please provide and discuss available non-clinical studies of amfepramone in relation to:

a) Cardiac safety: including safety pharmacology studies, including those conducted according to the guidelines ICH S7A and B, as well as data from repeat dose toxicity studies.

b) Drug dependence and drug tolerance

c) Genotoxicity: a complete overview of genotoxic studies being reported in the literature (e.g. Silva Nunes et al. 2013[1]) as well as those conducted by the MAHs with amfepramone

d) Reproductive toxicity

A discussion of the clinical relevance of these data, comparing non-clinical and clinical exposure and considering available toxicokinetic data should be included.

[1] da Silva Nunes MF, da Silva Nunes R, et al (2013) Use of Buccal Micronucleus Assay to Determine Mutagenicity Induced by Amfepramone in Humans and the Protective Effects of Vitamin C, Journal of Toxicology and Environmental Health, Part A, 76:19, 1121-1128

Safety

Question 3. For each of the following topics, information described in 3.1. and 3.2. should be provided:

a) **Pulmonary** (SOC Respiratory, thoracic and mediastinal disorders)

b) **Cardiac** (SOC Cardiac disorders)

c) **Cerebrovascular** (SOC Vascular disorders)

d) **Neuropsychiatric** (SOC Psychiatric disorders and SOC Nervous system disorders)

e) **Off-label use, misuse, abuse** (HLGT Off label uses and intentional product misuses/use issues)

f) **Drug dependence** (HLGT Psychiatric disorders NEC (HLT Substance related and addictive disorders))

3.1. Cumulative reviews of all spontaneous and solicited case reports (serious and non-serious), since the first commercialisation of amfepramone products, based on the search, in the MAHs' own safety database and other available databases (e.g. EudraVigilance), of all the MedDRA Preferred Terms (PTs) within the specified SOC or HLGT where amfepramone-containing medicinal product(s) is a suspected or interacting medicinal product. These reviews should include analyses by age and sex of patient, indication for use, TTO, dosing regimen, duration of amfepramone use, outcome, seriousness, concomitant medications and illnesses, relevant medical history or other important information. Causality assessment should be performed for the serious cases using the WHO-UMC scoring system and possible risk factors should be discussed. Where contraindications/restrictions may not have been adhered to, this should be specified.

3.2. All relevant clinical trial data (including both MAH sponsored and non-sponsored studies), data from pharmaco-epidemiological studies and published literature should also be provided and discussed.

Question 4. Provide a cumulative review of all cases of use of amfepramone reported in **pregnant women**, including detailed information on respective trimester of exposure, duration of exposure, and pregnancy outcome (e.g. induced abortion, spontaneous abortion, malformation or other adverse pregnancy outcomes) as well as whether risk minimisation measures recommended in the product information were adhered to.

Question 5. Please provide the **total number of all serious and non-serious reported adverse drug reactions** with amfepramone since initial marketing authorisation and provide a cumulative review of **all fatal and life-threatening cases**.

Mechanism of action

Question 6. Based on the pharmacodynamics and pharmacokinetics of amfepramone, provide a discussion on its **mechanism of action in obesity** and the **mechanism(s) potentially leading to pulmonary, cardiac, cerebrovascular and neuropsychiatric serious adverse reactions as well as to dependence**.

Efficacy

Question 7. Please provide **all efficacy data** available for amfepramone-containing medicinal products in their approved indication for short-term use in the EU. This should include data on maintenance of effect after discontinuation of treatment.

A critical discussion of this data should be provided. Specifically, a thorough discussion is awaited on the long-term clinical benefit of amfepramone on body weight and within an anti-obesity program, considering the restricted treatment duration with amfepramone-containing medicinal products (i.e. <3 months).

A summary of clinical guidelines on current approach to management of obesity in relation to amfepramone use and supportive publications, should also be provided and discussed.

Benefit-Risk balance and risk minimisation measures

Question 8. Please provide details of any specific measure(s) that have already been taken (in addition to those listed in answer to question 1) in order to minimise the above-mentioned safety issues in patients treated with amfepramone-containing medicinal product(s) and comment on the effectiveness of such measure(s).

Question 9. Please provide a thorough **benefit-risk balance** assessment of amfepramone-containing medicinal product(s).

Question 10. Based on the provided safety information, please discuss the need for further **risk minimisation measures** (including changes to the SmPC/PL and/or additional risk minimisation measures) which may improve the benefit-risk balance of your amfepramone-containing medicinal products. Provide proposals for any measures as and if appropriate as well as how their effectiveness would be monitored.

Annex - Question 1

a, b, c and d)

Product name	Type of marketing authorisation[1]	Marketing status[1]	Legal status and inclusion on list of narcotic/psychotropic drugs[2]	Pharmaceutical forms and strengths	Prescribing limitations[3]	Sales figures[4]	Estimated patient exposure[4]

[1]. Information should be provided for each strength and package size. Where marketing authorisations have been rejected or withdrawn in any MS, please state the reason.
[2]. Limitation or specifics of dispensing to be provided as footnote.
[3]. To be presented by indication, specialty and other as applicable.
[4]. Expressed in patient-years and stratified by year and by Member State, by product and pharmaceutical form and by age (<12 and 12-18). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

e)

PI	SmPC[1]	PL[1]	Main differences in SmPCs/PLs between the different EU Member States
Indication			
Posology (incl. max. daily dose)			
Contraindications			
Pulmonary warnings and precautions and undesirable effects			
Cardiac warnings and precautions and undesirable effects			
Cerebrovascular warnings and precautions and undesirable effects			
Neuropsychiatric events warnings and precautions and undesirable effects			
Abuse and dependence warnings and precautions and undesirable effects			

PI	SmPC[1]	PL[1]	Main differences in SmPCs/PLs between the different EU Member States
Pregnancy			
Pharmacodynamic properties			
Pharmacokinetic properties			
Preclinical safety data			

[1]. Information should be provided for each MS separately in order to then highlight the main differences in the last column.