NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Romania:

Product Name(s) in the Referring Member State	Regenon 25 mg capsule moi
Active substance(s)	amfepramone
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder in the referring Member State	Temmler Pharma GmbH

Background

Amfepramone belongs to the pharmacotherapeutic group "Centrally acting antiobesity products (ATC Code A08AA03)". Amfepramone is a sympathomimetic agent with indirect action, belonging to the group of anorexigens. Substances in this group also act by inhibiting the hunger centre. In the European Union it is currently authorised in Romania, Denmark and Germany as adjunctive therapy to diet, in patients with obesity and a BMI (body mass index) of 30 kg/m2 or higher, who have not responded to an appropriate weight reducing regimen alone.

In 1995 and 1996, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA), reviewed the benefits and risks of centrally acting anorectics, including amfepramone, due to concerns about the risk of primary pulmonary hypertension suspected to be associated to those products. On 9 December 1996, the Decision[1] of the European Commission closing this review [C(96) 3608 final] led to the amendment of the SmPC of those medicinal products (e.g. the duration of treatment was restricted to 4-6 weeks and no more than three months.).

From 1997, further reviews of the benefit/risk balance of anorectic medicinal products were initiated due to concerns about the risk of cardiac valve disorders suspected to be associated to those products and took into consideration the developments concerning the efficacy of anorectic agents. In 1999 as a result, the EMEA CPMP considered the benefit-risk balance negative and recommended the withdrawal of the Marketing Authorisations for medicinal products containing amfepramone, phentermine, clobenzorex, fenbutrazate, fenproporex, mazindol, mefenorex, norpseudoephedrine, phenmetrazine, phendimetrazine, propylhexedrine as well as dexfenfluramine and fenfluramine. The European Commission

[1] COMMISSION DECISION of 9.12.1996 concerning the placing on the market of the medicinal products for human use which contain the following substances: Clobenzorex Norpseudoephedrine Phentermine Fenproporex Mazindol Amfepramone Phendimetrazine

issued the corresponding Commission Decisions[2] on 09 March 2000 that were later annulled by the European Court of Justice.

Issues to be considered

Further to the completion of the first PSUSA procedure for amfepramone-containing products by the PRAC on 14 January 2021 (PSUSA/00000138/202006) covering the period from 23.12.2005 to 01.06.2020, serious concerns were identified, as detailed below.

Cardiac-related ADRs have been reported (42), including aortic valve incompetence (13), mitral valve incompetence (11) and pulmonary arterial hypertension (9). Those cases provided limited information for causality assessment and, as this therapeutic class is well known to be associated with serious cardiac concerns, further investigation of this issue is deemed necessary.

Cases of off-label use were also reported (14) with a duration of use longer than recommended (from 4 to 6 weeks, and not to exceed three months, even in the case weight loss is achieved), some cases reported use of the product up to 20 years, with doses exceeding those recommended in the Product Information (PI). Treatment duration with amfepramone is strictly limited due to the potential for abuse and/or dependence, which is a class effect of centrally acting anorectic substances. Further, cases of prolonged use were co-reported with cardio-vascular events, pulmonary hypertension, abuse and dependence whereas those are known risks associated to long-term use and/or use of higher doses than recommended.
Cases of exposure during pregnancy have also been reported during the reporting period (8). Amfepramone should not be used during pregnancy and the possibility of a pregnancy should be excluded before starting treatment as indicated in the product information.
Therefore, the ANMDMR (Romanian medicines agency) considers that the above cases of off-label use are of significant concern and raise doubts regarding the effectiveness of the risk minimisation measures in place and that off label use should be further investigated.

Further, considering that amfepramone-containing products are indicated for use for a period of 4 to 6 weeks (and should not exceed 3 months), their therapeutic role in a chronic condition is questionable. Of note, according to the current Guideline[3] on evaluation of new medicinal products used in weight management, anti-obesity products should demonstrate statistically significant, placebo-corrected weight loss of at least 5% of baseline weight after 12 months of treatment.

In light of the known serious safety concerns related to this therapeutic class, the cases of serious cardiac valve disorders, pulmonary hypertension and off-label use (longer duration and/or higher dose than recommended and use in pregnancy) reported during the PSUR reporting period, raise serious concerns as to the effectiveness of the risk minimisation measures in place.

In the context of the referenced PSUSA, the PRAC considered that the above-mentioned serious concerns had to be further investigated in an appropriate regulatory procedure that would enable a full assessment of all available data for amfepramone-containing products related to both safety and efficacy and possibly including views from clinical experts.

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[2] COMMISSION DECISION of 09.03.2000 concerning the withdrawal of marketing authorisations of medicinal products for human use which contain the following substances: "Amfepramone";
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2000:095:FULL&from=EN

[3] Guideline on clinical evaluation of medicinal products used in weight management, 23 June 2016 EMA/CHMP/311805/2014 Committee for Medicinal Products for Human Use (CHMP); https://www.ema.europa.eu/en/documents/scientific-

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, leads the ANMDMR to raise concerns about the benefit/risk balance of these medicinal products.

In view of the above and the necessity to take an action at EU level, Romania considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of amfepramone-containing products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

[redacted]

Date 25.01.2021