07 November 2022
EMA/884474/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Amfepramone-containing medicinal products

INN/active substance: amfepramone

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

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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

Table of contents

Table of contents **2**
1. Information on the procedure **3**
2. Scientific discussion **3**
2.1. Introduction 3
2.2. Clinical safety 5
2.2.1. Pulmonary disorders 5
2.2.2. Cardiac disorders 7
2.2.3. Cerebrovascular disorders 8
2.2.4. Neuropsychiatric disorders 9
2.2.5. Drug dependence 10
2.2.6. Use in pregnancy 11
2.2.7. Off-label use, misuse, abuse 11
2.2.8. Non-adherence to the product information 12
2.2.9. Observational studies 12
2.2.10. Discussion on clinical safety 21
2.3. Non-clinical safety 28
2.3.1. Cardiac safety 28
2.3.2. Drug dependence and drug tolerance 28
2.3.3. Genotoxicity 29
2.3.4. Reproductive toxicity 29
2.3.5. Activation of 5-HT2B receptor 29
2.3.6. Discussion on non-clinical safety 30
2.4. Efficacy 30
2.4.1. Discussion on efficacy 32
3. Expert consultation **33**
4. Benefit-risk balance **36**
4.1. Initial benefit-risk balance assessment 36
4.2. Re-examination procedure 39
4.2.1. Detailed grounds for re-examination submitted by the MAHs 39
4.2.2. PRAC discussion on grounds for re-examination 41
4.2.3. Conclusion on the benefit-risk balance following the re-examination procedure 46
5. Summary of new activities and measures **46**
Direct Healthcare Professional Communications and Communication plan 46
6. Grounds for Recommendation following the re-examination procedure **47**
Appendix 1 ..... **48**
Divergent position to PRAC recommendation **48**
Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data 49

1. Information on the procedure

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 therefore 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 issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

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 Denmark, Germany and Romania, as adjunctive therapy to diet, in patients 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. It is authorised in adults and children from 12 years of age (Germany and Romania), or from 15 years of age (Denmark).

Obesity is a chronic metabolic disease characterised by an increase of body fat stores. It is a gateway to ill health, and it has become one of the leading causes of disability and death, affecting not only adults but also children and adolescents worldwide. In 2019, according to Eurostat, slightly more than half (53%) of adults living in the EU were considered as overweight (36% pre-obese and 17% obese) according to their BMI. This population is subject to associated co-morbidities, such as diabetes mellitus type 2, hypertension, coronary heart disease and cancer risk. Treatment of obese and overweight patients is based on behavioural changes, diet, and exercise, with or without pharmacotherapy or bariatric surgery, aiming to lose weight and decrease risk factors.

Amfepramone-containing products are available as 25 mg capsule, to be taken three times a day, and, in Germany only, as 60 mg or 75 mg prolonged-release capsule/tablet. Amfepramone-containing products are available on prescription only. In Denmark it is on the list 'E' of narcotics and pharmacies and warehouses must report the amounts received, sent and in stock once a year. In Romania, it is included in the III-rd list of narcotic and psychotropic drugs and needs to be stored in pharmacies in dedicated areas, a special prescription of an authorised doctor is needed ("green prescription") for dispensing, one prescription may only cover one month and should not be renewed more than twice for a given patient. In Germany no similar restrictions are in place.

It is estimated that approximately 1,874,895 patients were treated with amfepramone containing products in the EU between 2001 and 2020, equivalent to 168,740,570 treatment days or 462,303 treatment years. The use of Amfepramon-Hormosan/Regenon (authorised in the 3 Member States) has been relatively stable over time with a slight decrease, whereas the use of Tenuate retard (authorised only in DE) has steadily increased since its re-introduction on the market in 2003 up to over 30,000 patient years in 2019.

In 1995 and 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), reviewed the benefits and risks of centrally acting anorectics, including amfepramone, due to concerns about the risk of pulmonary arterial hypertension (PAH) suspected to be associated to those products. On 09 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. Key amendments related to the following:

- The therapeutic indication was restricted only to patients with a potentially fatal risk linked with obesity, which was considered to be a BMI of 30kg/m^2 or higher, and as second line therapy in patients who have not responded to an appropriate weight reducing regimen alone.
- The duration of treatment was restricted to 4-6 weeks and 3 months maximum in line with the evidence of efficacy and in consideration with the increased risk of primary pulmonary hypertension (PAH) (and of dependence for the "amphetamine-like" anorectics) beyond three months.
- Treatment was recommended to be conducted under the care of physicians experienced in the treatment of obesity.
- Information on the potentially fatal risk of PAH related with anorectics intake including the required careful compliance with the indication and the duration of treatment, as well as the need to discontinue the treatment of patients presenting with an onset or aggravation of exertional dyspnoea and refer them to a specialist unit for investigation, was included.
- Treatment was contraindicated in patients with specific types of hypertension, cardio-vascular or cerebrovascular disease, psychiatric disorders or drug abuse, and in children below 12 years.
- Adverse reactions related to the central nervous system (tolerance, dependence, withdrawal syndrome, psychosis, depression, nervousness, agitation, sleep disorders, vertigo, convulsions) and cardiovascular (CV) effects (tachycardia, palpitations, hypertension, precordial pain, stroke, angina, myocardial infarction, cardiac failure, cardiac arrest) were included.

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 (MA) for medicinal products containing amfepramone, phentermine, clobenzorex, fenbutrazate, fenproporex, mazindol, mefenorex, norpseudoephedrine, phenmetrazine, phendimetrazine, propylhexedrine as well as dexfenfluramine and fenfluramine. The European

[1] Commission decision of 09.12.1996 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, phenmetrazine, mefenorex

Commission issued the corresponding Commission Decisions[2] on 09 March 2000 that were later annulled by the European Court of Justice[3].

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, reports of cardiac-related adverse drug reactions (ADRs) and/or off-label use (longer duration and/or higher dose than recommended and use in pregnancy), raised significant concerns, including with regards to the effectiveness of the risk minimisation measures in place.

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 obesity, a chronic condition, was considered questionable. Of note, according to the current Guideline[4] 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.

The Romanian medicines agency thus triggered the present review in order for the above-mentioned serious concerns, and their impact on the benefit-risk balance of amfepramone-containing products to be further investigated.

The PRAC considered all available data in relation to the safety concerns highlighted, including non-clinical, clinical data, data from spontaneous reporting and from the literature, but also a rapid data analysis study performed by EMA using primary care data from Germany and an analysis of primary care data from Denmark performed by the analytical centre of the Danish medicines agency (DAC). The views of a group of independent experts were also considered. A summary of the most relevant information is included below.

2.2. Clinical safety

Overall, 145 case reports in which amfepramone was reported as suspected or interacting drug could be retrieved from EudraVigilance (data lock point: 24 May 2021). Following de-duplication a total of 94 cases (with 282 ADRs) were identified in EVDAS and 303 cases (with 399 ADRs) in MAHs' safety databases, including 10 fatal cases.

Cases falling under the safety topics of interest are discussed in detail below.

2.2.1. Pulmonary disorders

A search in EV and in the MAH's safety database retrieved 31 cases including 37 events under the SOC "respiratory, thoracic and mediastinal disorders". The most commonly reported event was pulmonary hypertension (14), followed by dyspnoea (10), dyspnoea exertional (3) and dysphonia (2). The majority of events were considered serious (28 of 37), and one case had a fatal outcome.

The causality was assessed as possible for 9 cases (PT serious: dyspnoea (5), dyspnoea exertional (1), bronchial hyperreactivity (1), pulmonary hypertension (1), throat tightness (1), speech disorder (1), dysphonia (1), asthma (1); PT non-serious: dyspnoea (1), epistaxis (1)), as non-assessable for 13 cases and as unlikely for 9 cases. Time-to-onset (TTO) ranged from days to years.

[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";
[3] Judgements of the European Court of Justice in the cases Artegodan vs the European Commission.
[4] 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)

Treatment duration ranged from 1 day to 20 years, and was longer than 12 weeks/3 months in 9 cases, whilst it is unknown or uncertain in 17 cases. Where the daily dose was reported it did not exceed the maximum daily dose, except for one case of agitation and tachypnoea reported in a women using twice the daily dose.

In the case of pulmonary hypertension assessed as possibly related to treatment, TTO was 10 years and treatment duration 27 days. Of note no information on concomitant treatments was provided.

For the 11 cases where treatment was initiated after the restriction of the treatment duration (after 1996) to a maximum of 3 months, 3 reported longer treatment durations (2 years (2), 5 months(1)) whilst the treatment duration was not mentioned in the remaining 8 cases.

Cases were also reported in patients with conditions where treatment with amfepramone is contraindicated or initial symptoms of such conditions (4 cases of dyspnoea or dyspnoea exertional were reported in 4 patients with history of hypertension (and dyspnoea in one case), 2 patients with history of borderline personality disorder/depression or anxiodepressive syndrome and 4 patients with previous/concurrent use of other anorectics (e.g. benfluorex, fenfluramine, dexfenfluramine and benzphetamine).

In the literature two epidemiological studies, including patients treated with amfepramone, have shown that anorectic intake is a risk factor for pulmonary artery hypertension. The first study, a case-control study in 95 patients with PAH (cases) and 355 controls matched by sex and age, was the main driver for the risk minimisations measures implemented further to the conclusion of the EU review in 1996 (IPPHS study, Abenhaim, 1996)[5]. This study found that the use of anorexic medicines (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension (OR with any anorexic-drug use, 6.3; 95% CI [3.0 - 13.2]). It was further shown that when anorexic drugs were used to a total of more than three months, the odds ratio was 23.1 (95% CI [6.9 to 77.7]), as opposed to 1.8 when used for three months or less (95% CI [0.5 – 5.7]). Specifically for the sub-group of amphetamine-like agents, a non-statistically significant trend for an increased risk was initially observed, however lower adjusted odd-ratio were provided by the authors in an ulterior publication (OR 1.3 ; 95% CI [0.4-4.7]) (Abenhaim, 1999)[6]. Nevertheless, these results are not considered to exclude a risk with amphetamine-like agents, as the study was not adequately powered to detect a risk for those products. In the IPPHS study, 3 patients were treated with amfepramone in each group, and probably for this reason, no statistical analysis was performed for amfepramone. The majority of subjects (90%) were treated with fenfluramine derivatives. A BMI ≥ 30 kg/m^2 was also found to marginally increase the risk of PAH (OR 1.9; 95% CI [1.0 – 3.6]). The odds ratio for anorexic agents was similar whether or not adjusted for high body-mass index. Obesity had not been previously reported as a risk factor for PAH.

In 1996, the CPMP considering preliminary results of the IPPHS study as well as PAH cases reported with other anorectics, concluded that the risk of PAH, increasing with duration of treatment longer than 3 months, was a class effect with those substances, which led to the limitations to the treatment duration. A boxed warning that careful compliance with the indication and the duration of treatment is required and reflecting the findings on this rare but serious risk, as well as the need to discontinue the treatment of patients presenting with an onset or aggravation of exertional dyspnoea and refer them to a specialist unit for investigation, was also included in the product information.

The second study, a cohort study in 205 patients with PAH and 374 controls with other types of pulmonary hypertension, also found a higher risk of PAH in patients treated with fenfluramine for more

[5] Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;335(9):609-616
[6] Abenhaim, reply. Primary pulmonary hypertension and anorectic drugs. N Engl J Med 1999; 340:480-482

than 6 months cumulatively compared to those treated for less than 6 months (OR: 7.5 ; 95% CI [1.7 – 32.4] vs 1.3 ; 95% CI [0.5 - 3.9]) (SNAP study, Rich, 2000)[7].

In the SNAP study, 5 or fewer patients treated with amfepramone were included in each group and no separate results were presented for amfepramone either.

The SNAP study, whilst not designed to detect an increased risk specifically with amfepramone-containing products, constitutes further evidence of the increasing PAH risk with longer anorectics treatment durations.

A further case published in the literature reports on a 27-year-old female treated with amfepramone for 4 weeks and 5 weeks, respectively, 3.5 and 1.5 years before the onset of symptoms of PAH (Abramowicz, 2003)[8]. The patient was heterozygous for a BMPR2 mutation, which is also a risk factor for PAH. However, an additional stressor is necessary for the development of PAH in BMPR2 mutation carriers, such as exposure to fenfluramine and dexfenfluramine (Orcholski, 2018; Humbert, 2002)[9,10]. Therefore, and taking into account the plausible time relationship, and as no other risk factors were identified (such as fenfluramine use), this case is considered to support a possible additive effect of amfepramone in the development of PAH in a patient carrying a BMPR2 mutation. Other published cases were insufficiently documented to conclude on causality.

2.2.2. Cardiac disorders

A search in EV and in the MAH's safety database retrieved 54 cases including 95 events under the SOC "cardiac disorders". The most commonly reported events were those related to heart valve incompetence (36 aortic valve incompetence, mitral valve incompetence and tricuspid valve incompetence), followed by palpitations (14), tachycardia (5) and cardiac failure (4). The majority of events were considered serious (78 out of 95), and one case had a fatal outcome.

The use of other appetite suppressant drugs (known to be associated to cardiac disorders, such as benfluorex, dexfenfluramine or fenfluramine) has been reported in the majority of the serious cases. Cardiac risk factors were also reported in the majority of cases (e.g. arterial hypertension (15), heart valve conditions (13), diabetes or prediabetes (7), tobacco use (6), aortic valve incompetence (4)). The 12 cases which did not report such risk factors were poorly documented.

The causality was assessed as "probable/likely" in 1 case (PT: palpitations), as "probable" in 1 case (PT: tachycardia), "possible" in 30 cases (PT: cardiac failure (3), cardio-respiratory arrest, cardiac arrest, cardiac thrombosis, coronary revascularisation, atrial flutter, tachycardia (5), ventricular tachycardia, palpitations (11), torsade de pointes, ejection fraction decreased, arrhythmia, myocardial infarction, aortic valve incompetence (5), mitral valve incompetence (4), tricuspid valve incompetence, mitral valve stenosis, left atrial enlargement, atrial fibrillation, extrasystoles, cardiac valve disease, heart valve replacement) and as "unlikely" in 7 cases, as "unassessable" in 13 cases, an as "unassessable/unclassifiable" in 2 cases. TTO ranged from a few hours to years for the 33 cases where this information was available.

Treatment duration exceeded 12 weeks/3 months in 14 cases, including 2 cases where treatment was initiated after the restriction of the treatment duration (after 1996).

[7] 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.
[8] Abramowicz MJ, Van Haecke P, Demedts M, Delcroix M. Primary pulmonary hypertension after amfepramone (diethylpropion) with BMPR2 mutation. Eur Respir J. 2003;22(3):560-562
[9] Orcholski ME, Yuan K, Rajasingh C, et al. Drug-induced pulmonary arterial hypertension: a primer for clinicians and scientists. Am J Physiol Lung Cell Mol Physiol. 2018;314(6):L967-L983
[10] Humbert M, Deng Z, Simonneau G, et al. BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. Eur Respir J. 2002;20(3):518-523

Hypertension (1 case post 1996), pulmonary hypertension, cardiac diseases, metabolic diseases (often associated to other cardiovascular risk factors, 2 cases post 1996) and concurrent use with other appetite-suppressants (32, 2 cases post 1996) was reported, which partially overlaps with contra-indications (further to the first EU review the following contraindications were implemented amongst others: severe arterial hypertension, pulmonary artery hypertension, medical history of cardio-vascular diseases or combination therapy with any other centrally acting anorectic).

No pattern could be observed in relation to duration of treatment. Serious cases were reported both in patients treated within and beyond the recommended duration of 3 months.

Out of the 106 clinical trials identified in the literature, involving 7276 patients exposed to amfepramone, CV ADRs were mostly described as mild in nature, and consisted mainly of arrythmias such as palpitations (89 (1.3%)) and tachycardia (82 (1.1%)). Giorelli and colleagues observed similar frequencies (Giorelli, 2008)[11]. A small placebo-controlled study in 57 patients (29 treated with amfepramone, 28 given a placebo), found no significant difference in signs of valvular regurgitation after long-term treatment with amfepramone (i.e. 12 months) compared to (Rottiers, 1999)[12]. Time points at which echography were done was not stated. This efficacy study was not designed to show significance for safety endpoints, therefore its relevance is limited. Many of those studies have evaluated pulse rate (16), blood pressure (27) with contradictory results. Studies (8) investigating electrocardiogram (ECG) have not found any effect of amfepramone on ECG. In one study, the authors did not reveal any adverse effects containing levels of red blood cells and haemoglobin. In addition, no CV signal was identified in studies (4) concerning population with medical history such as angina pectoris, CV disease, diabetes mellitus, coronary artery.

2.2.3. Cerebrovascular disorders

A search in EV and in the MAH's safety database retrieved 17 cases including 18 events under the SOC "cerebrovascular disorders". As well as a further report in the literature describing a serious case of haemorrhagic vasculitis necrotising, which occurred further to overdosing of a non-authorised product containing amfepramone and minor amounts of an unidentified compound with an amine structure (148 mg of amfepramone per day for 4 weeks). This case is not further discussed here as it does not concern an authorised medicinal product and included additional compounds. The most commonly reported event was hypertension (in 7 cases), followed by PT aortic stenosis (in 2 cases). A further 7 cases were reported but are discussed under the section on neuropsychiatric cases (cerebral haemorrhage or infarction reported as cerebral haemorrhage (in 4 cases), cerebral infarction (in 2 cases) and subarachnoid haemorrhage with subdural haematoma (in 1 case)).

The majority of events were considered serious (14 of 17), and one case had a fatal outcome (suicide).

Causality was assessed as "possible" in 5 cases (PT serious: hypertension (1), withdrawal hypertension (1), hypotension (1), systolic hypertension (1); PT non-serious: hypertension (1)), for "unassessable" in 9 cases and as "unlikely" in 3 cases. Information on TTO was largely non-available.

Treatment duration was available in 8 cases and exceeded 3 months in 5 cases (including 3 post 1996 cases where treatment initiation was reported): 5 months (2), 2 years (1).

Conditions corresponding to contraindications were reported in several cases: psychological disorders (5), dependency on medication, drugs or alcohol (5), CV and cerebrovascular diseases (2), concomitant treatment with other centrally stimulating anorectics (6). Further, long treatment

[11] Giorelli P, Ribas-Filho D, Giorelli S, et al. (2008) Efficacy of long-term obesity's treatment with diethylpropion. Rev Nutrolog 1:68-74
[12] Rottiers R. The Trenker Trial, Evaluation of Efficacy of Long-Term Diethylpropionresinate Treatment in Obesity (Gent). Unpublished. 1999.

durations were reported in 5 cases, including 3 cases were therapy was started after the reduction of the maximal treatment duration to a maximum of 3 months (i.e. 5 months (2), 2 years). Start of therapy was not indicated in the remaining two cases.

A short-term study included in a meta-analysis of four anorexigenic medicines acting on the central nervous system (i.e. sibutramine, mazindol, fenproporex and amfepramone) also confirmed the known risk of hypertension associated to amfepramone use (Farah, 1999)[13]. Overall the available studies included in the meta-analysis were not suitable to detect further potential effects of amfepramone on the vascular system. Hypertension was seen in 121 out of 7,292 patients (1.7%) in the intervention group treated with one of those four anorectics compared with 66 out of 5,723 patients (1.2%) in the placebo group (RR: 0,96).

2.2.4. Neuropsychiatric disorders

A search in EV and in the MAH's safety database retrieved 109 cases including 195 events under the SOC "neuropsychiatric disorders". The most commonly reported events were headache (24), dizziness (19), insomnia (9), sleep disorder (9), drug dependence (8), depression (6), drug abuse (6), agitation (6) and restlessness (5).

The majority of events were considered serious (97 of 195), and 3 cases had a fatal outcome.

The causality was assessed as certain in 2 cases (serious: substance abuse (1), drug abuse (1)), possible for 75 case reports (PTs serious (only ≥2): agitation (2), cerebral haemorrhage (3), cerebral infarction (2), confusional state (2), depression (5), dizziness (2), drug abuse/drug dependence (7), hallucination (2), headache (2), irritability (3), psychotic disorder (4), seizure (2), suicide attempt (2), tremor (3)), as probable in 2 cases, probable/likely for 2 case reports, as unlikely in 6 cases and as unassessable in 20 cases. TTO was available in 53 cases corresponding to 91 AEs, around half of which occurred on the day of treatment initiation, a quarter in the following months, and the other quarter up to 10 years later.

In one of the cerebral haemorrhage cases, the patient had underlying hypertension, in which case amfepramone should be used with special caution, or not used at all (in case of severe hypertension).

In the literature, insomnia/wakefulness/sleep disturbance were the most frequently reported AEs, and a study found a statistically significantly higher frequency of insomnia in the amfepramone group than in the placebo group after three months (Cercato, 2009)[14]. It is noted that those PTs are already covered under the listed adverse drug reactions (ADR) "sleep disturbances" and a warning not to take the last tablet less than 4 hours before bedtime due to the risk of insomnia is already included as risk minimisation.

Treatment duration ranged from up to 3 months (34) to up to 30 years (19). Out of the 10 cases where start of treatment was available, the 7 cases where it was initiated after 1997 corresponded to long treatment durations (5 months (1), 1 year (1), 2 years (1), 5 years (3) and 7 years (1)).

Treatment with amfepramone is contraindicated in case of psychiatric disorders (including anorexia nervosa and depression), severe hypertension, propensity towards drug abuse and combination therapy with any other centrally acting anorectic agent, whereas conditions or treatments likely to fall in those categories were reported in several cases (depression (3, including 1 post 1996), hypertension (7 cases, including 1 post 1996), psychosis (1 case; post 1996), the use of 1 or more co-suspect

[13] Farah D, Fonseca MCM. Short-term Evidence in Adults of Anorexigenic Drugs Acting in the Central Nervous System: A Meta-Analysis. Clin Ther. 2019 Sep;41(9):1798-1815.
[14] Cercato C, Roizenblatt VA, Leança CC, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int J Obes (Lond). 2009;33(8):857-865

and/or concomitant centrally acting anorectic agent (34 case reports – 4 of which also reporting drug abuse).

2.2.5. Drug dependence

A search in EV and in the MAH's safety database retrieved 14 cases including 16 events under the HLGT Psychiatric disorders NEC (HLT Substance related and addictive disorders). The most commonly reported events were drug dependence (8) followed by drug abuse (6).

The majority of events were considered serious (12 of 14), and one case had a fatal outcome (confounded by co-suspected drugs, alprazolam and propoxyphene).

The causality was assessed as "certain" (serious cases; serious PTs substance abuse (1), drug abuse (1)) and "possible" (8 serious cases; serious PTs dependence (1), drug abuse (3), drug dependence (4)).

Treatment duration was beyond 3 months in 8 cases and ranged from 2 years to 20 years (including 2 cases post 1996). Three (3) cases were reported in patients dependent on appetite suppressants or stimulants. While another 2 cases were reported in patients off-label or falling under other contraindications (i.e. history of depression and coronary artery disease, or indicated for 'state of exhaustion' in non-obese patient).

A study investigating which anorectic drugs were most frequently prescribed reviewed 527 case records from a clinic over 10 years. In 9% an issue of addiction to amfepramone was identified (Gaind, 1979)[15]. The authors concluded that anorectics were frequently abused. Two more recent long-term randomised placebo-controlled trials (12 months and 24 months) on amfepramone in obese patients could not identify evidence of development of tolerance, dependence or addiction (Giorelli, 2008; Cercato, 2009)[16,17]. However, in these two studies, exclusion criteria included patients with psychiatric conditions and/or history of drug dependence or abuse. Further, interventional trials with a defined dosing scheme and treatment duration are not considered suitable to evaluate dependence or addiction.

Further, a systematic review found amfepramone to exert euphorigenic effects similar to those of amphetamines, although possibly be less intense (Poyatos, 2022)[18]. Pharmacokinetic data showed significant difference between metabolizer phenotype (i.e. approximately threefold variation between the slowest and fastest phenotypes), however it is unknown whether certain patient populations may be more prone to such effects due to differences in the metabolism.

The World Health Organization Expert Committee on Drug Dependency also concluded that whilst little evidence was found on the incidence of dependency on amfepramone, in some patients, tolerance to the anorectic effects of amfepramone may occur within six to twelve weeks[19]. It was further highlighted that amfepramone has been shown to produce euphoria and other mood changes characteristic of drugs of abuse.

[15] Gaind R, Verma S. Abuse of anorectic drugs. Current Medical Research and Opinion. 1979;6(1 SUPPL):149-52
[16] Giorelli PR-F, D.; Giorelli, S.; Giorelli, G. Efficacy of Long-Term Obesity's Treatment with Diethylpropion. Rev Nutrolog. 2008;1(2):68-74
[17] Cercato C, Roizenblatt VA, Leança CC, et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int J Obes (Lond). 2009;33(8):857-865
[18] Poyatos L, Torres A, Papaseit E, et al. Abuse Potential of Cathinones in Humans: A Systematic Review. J Clin Med. 2022 Feb 15;11(4):1004
[19] WHO Expert Committee on Drug Dependence : thirty-third report. 2003.

2.2.6. Use in pregnancy

Pregnancy (and lactation) is currently a contraindication to start treatment with amfepramone, in most products. Where it is not explicitly included as a contraindication, it is specified in the dedicated section that amfepramone should not be used during pregnancy or lactation. In some cases, it is further specified that pregnancy must be excluded before starting treatment and that women of childbearing potential should use a contraceptive method during treatment.

However, reference is also made in the PI of some products to the fact that retrospective studies, involving 1,232 patients who received amfepramone during pregnancy, did not show harmful effects of the drug on pregnancy or the foetus respectively compared to a control group. Moreover, it is stated that abusive consumption of amfepramone during pregnancy may cause withdrawal symptoms in newborns.

Available literature data comes mainly from efficacy studies of amfepramone on weight loss during pregnancy conducted in the 1960´s. A placebo-controlled study evaluating the efficacy of amfepramone in 53 pregnant women showed a higher rate of malformation in amfepramone versus placebo group (Boileau, 1968)[20]. One stillbirth and, further to treatment in the 3rd trimester, two deliveries with malformations were reported. In the remaining efficacy studies, which included 332 pregnant women treated with amfepramone, no adverse effects on newborns were detected (Silverman, 1971; Nulsen, 1960; Jordan, 1961; Sands, 1962)[21,22,23,24]. The retrospective studies involving 1,232 pregnant women could not be identified.

Based on the provided non-clinical data, no genotoxic potential was identified for amfepramone. Studies are limited to rodents only and, in general, do not meet current standards for reproductive toxicity studies. Their relevance for the risk assessment is therefore questionable.

Further, taking into account that the above mentioned studies were conducted 50 to 60 years ago in accordance with the standards in force at the time, their relevance for current recommendations for use during pregnancy is questionable. Although data is scarce, malformation and still birth have been observed therefore a potential risk cannot be ruled out and the product must not be used during pregnancy.

2.2.7. Off-label use, misuse, abuse

A search in EV and in the MAH's safety database retrieved 37 cases including 42 events under the HLGT off label uses and intentional product misuses/use issues. The most commonly reported event was off label use (18), followed by intentional product use issue (11) and intentional product misuse (3). Overall, 8 events were reported after 1996. Most cases were reported in female patients.

Use was reported in several off-label indications i.e. BMI lower than 30 kg/m^2 (8/10 cases for which the information about the BMI was provided), breast enlargement, back pain, food craving, metabolic disorder, performance enhancing product use and depression or depressed mood. Use was also reported for longer periods than authorised (19/24 cases for which the information about treatment duration was provided), including after 1996, out of the 14 where start of treatment was reported, 8 for 6 months to 5 years) or where patients should not be treated with amfepramone due to contraindications (10).

[20] Boileau PA. Control of weight-gain during pregnancy: use of diethylpropion hydrochloride. Appl Ther. 1968;10(11):763-5
[21] Silverman M, Okun R. The use of an appetite suppressant (diethylpropion hydrochloride) during pregnancy. Curr Ther Res Clin Exp. 1971;13(10):648-53
[22] Nulsen RO. Control of excessive weight gain during pregnancy. Curr Ther Res Clin Exp. 1960;2:102-6
[23] Jordan MJ, Bader GM. Use of diethylpropion combined with a supplement for safe and effective weight control in pregnancy. Surg Gynecol Obstet. 1961;112:663-6
[24] Sands RX. Obesity during pregnancy. Treatment with a sustained-release anorexic agent. Southwest Med. 1962;43:422-6.

In the 25 cases were a dosing regimen was reported, higher daily doses than indicated were taken by 7 patients (150 mg (4), 125 mg (1), 300 mg (1) and 750 mg(1)).

A publication also reports on 5 females who developed psychosis while taking amfepramone, of which 4 with paranoid psychosis and 1 with manic psychosis (Carney, 1988)[25]. One of these patients already under treatment for depression, became addicted to use of amphetamines, including amfepramone, which she used for several years.

2.2.8. Non-adherence to the product information

As mentioned in the introduction to this report, a number of restrictions were implemented as risk minimisation measures as an outcome of the EU review finalised in 1996, further amfepramone must not be used in pregnant women. A separate search was performed to retrieve cases since 1996 in which amfepramone has been used in apparent non-adherence to the product information in order to evaluate, independently from the association with co-reported adverse events of interest (which are discussed above), to which extent this occurred. The search in EV and in the MAH's safety database retrieved 72 cases in 69 patients in which amfepramone has been used in apparent non-adherence to the product information after 1996. The following instances were noted (one case can be listed under multiple categories): concomitant appetite suppressant use (12), use in patients with CV conditions (17), use in patients at risk of dependence (4), use in patients with psychiatric disorders (3), use during pregnancy (17), use in patients with a BMI under 30 kg/m^2 (21), use for longer than 3 months (28) and use of doses in excess of those indicated (13).

2.2.9. Observational studies

2.2.9.1.1. EMA study

This study evaluated utilisation trends of amfepramone-containing between 1 January 1998 to 30 June 2020 aiming, among others, to detect any trends related to duration of treatment, further characterise possible long-term usage and provide incidence rates for CV events in patients treated with amfepramone who have no history of such events. This analysis relied on IMS Disease Analyzer Germany, including around 3% of GP practices from the different regions in Germany, which represents a total of 7,204 participants in GP practices pertaining to 24,275 prescriptions. Of these patients, 4825 had an incident prescription. Incident use was defined as the first prescription for amfepramone in a patient with at least 365 days of prior observation.

The protocol and results are published on the EU PAS register[26].

There were only few patients and prescriptions between 2002 and 2003, but there has been a slow but steady increase in the number of patients since 2003. Adjusted to the eligible GP population, the increase in patients with an amfepramone prescription since 2004 was approximately 3-fold reaching around 50 patients per 100,000 population.

2.2.9.1.2. Treatment duration

The duration of treatment was estimated from the prescribed daily dose, where available, the number of tablets in the package and the number of packages prescribed. Of note, packs of 30 and 60 tablets of 25mg capsules or 60 or 75 mg prolonged-release capsule/tablet were available, as well as, before 2001, pack sizes up to 120 tablets of 25mg.

[25] Carney MW. Diethylpropion and psychosis. Clin Neuropharmacol. 1988;11(2):183-8

[26] EUPAS40283

In order to determine if the treatment duration exceeded 90 days, in case of a subsequent prescription for amfepramone within 15 days of the calculated end of the previous amfepramone prescription, the calculated durations were summed even if the subsequent prescription was issued before the end of the previous prescription.

If the number of daily tablets was not available on the incident prescription date but was available in a subsequent prescription, that information was used. If no prescription had a daily number of tablets (86.7% of patients) the median number of tablets (1 tablet) was used with sensitivity analysis including the maximum daily number of tablets recorded in the dataset (6 tablets – this dose is above the 99th percentile of the recorded doses within 90 days after start of treatment in incident users; the 99th percentile is 2 tablets per day and the 1st percentile is 0.5 tablet per day). It was not possible to use the median daily dose individually for the different formulations because of missing data, however, for both formulations, a dose of one tablet per day covers all doses between the 10th and the 90th percentile of doses (i.e. 80% of all recorded doses). Of note, over the whole period a daily dose was more frequently provided in prescriptions for immediate-release formulations (25 mg) (39.4%; 590 out of 1499 prescriptions) than for prolonged-release formulations (60 mg and 75 mg) (10.9%; 2619 out of 24005 prescriptions), however this difference was smaller from 1998 (12.7% for immediate release (96 out of 758) and 9.7% for prolonged-release (2221 out of 22803)). Considering only incident prescriptions from 1998, a daily dose was provided in 10.1% of immediate release prescriptions (45 out of 445) and 9.6% of prolonged-release ones (1462 out of 15156).

Table 1. Yearly number of patients with a prescription, with an incident prescription, and with a calculated treatment duration above 90 days main and sensitivity analysis.

Year	Total amfepramone	Incident amfepramone (% of total)	Incident amfepramone calculated duration >90 days (% of incident)	Incident amfepramone calculated duration >90 days (sensitivity analysis) (% of incident)
1998	122	48 (39.3%)	4 (8.3%)	0 (0.0%)
1999	135	56 (41.5%)	4 (7.1%)	0 (0.0%)
2000	118	39 (33.1%)	2 (5.1%)	0 (0.0%)
2001	137	57 (41.6%)	9 (15.8%)	0 (0.0%)
2002	89	25 (28.1%)	1 (4.0%)	0 (0.0%)
2003	38	14 (36.8%)	4 (28.6%)	0 (0.0%)
2004	159	75 (47.2%)	12 (16.0%)	0 (0.0%)
2005	206	87 (42.2%)	5 (5.7%)	0 (0.0%)
2006	207	68 (32.9%)	5 (7.4%)	0 (0.0%)
2007	199	74 (37.2%)	6 (8.1%)	0 (0.0%)
2008	216	72 (33.3%)	3 (4.2%)	0 (0.0%)
2009	244	75 (30.7%)	9 (12.0%)	0 (0.0%)
2010	390	189 (48.5%)	20 (10.6%)	0 (0.0%)
2011	465	178 (38.3%)	23 (12.9%)	1 (0.6%)
2012	590	249 (42.2%)	27 (10.8%)	3 (1.2%)
2013	731	285 (39.0%)	25 (8.8%)	1 (0.4%)
2014	811	322 (39.7%)	31 (9.6%)	2 (0.6%)
2015	867	360 (41.5%)	34 (9.4%)	3 (0.8%)
2016	1026	394 (38.4%)	47 (11.9%)	4 (1.0%)
2017	1187	422 (35.6%)	48 (11.4%)	3 (0.7%)
2018	1460	624 (42.7%)	97 (15.5%)	1 (0.2%)
2019	1531	565 (36.9%)	68 (12.0%)	1 (0.2%)
2020	398	66 (16.6%)	6 (9.1%)	0 (0.0%)

If the number of daily tablets was not available on the incident prescription date but was available in a subsequent prescription, that information was used. There were a total of 570 patients that had a dose recorded on the start date (499 patients had 1 tablet per day, 36 patients had 0.5 tablets per day, 23

patients had 2 tablets per day, 5 patients had 1.5 tablets per day, 4 patients had 3 tablets per day and 2 patients had either 0.25 tablets, 0.75 tablets or 6 tablets per day), 73 patients had no dose recorded on the start date but had a dose recorded on a later date (63 patients had 1 tablet per day, 7 patients had 2 tablets per day, 2 patients had 0.5 tablets per day and one patient had 1.5 tablets per day), and 4182 patients had no dose recorded on any date.

For the overall period daily dose was available for 40% of immediate-release formulations and the great majority (94%) of prescriptions related to prolonged release formulation, and from 1998 less than 3% of the prescription corresponded to the immediate release formulation. The median number of tablets was used for a large proportion of patients in view of the missing data. A median number of tablets of 1 is in line with the posology for the prolonged-release formulations, whereas the immediate-release 25 mg capsules would normally be expected to be taken 3 times a day. Conversely the sensitivity analysis with 6 tablets a day would correspond to daily doses between two and six-fold above the recommended daily dose, whereas the data does not indicate that this may be common in practice.

2.2.9.1.3. Cardiovascular events

The incidence of selected CV (ICD codes for mitral valve, aortic valve, tricuspid valve, or other heart valve disorder, pulmonary heart disease, cardiomyopathy, heart failure and essential (primary) hypertension) events was calculated in incident users with no prior history of any of the selected events. Calculations were also performed separately for patients with CV conditions except those that only had arterial hypertension. Patients were followed for outcome events for up to 365 days after each prescription. Comparative data were also provided for patients treated with orlistat regardless of whether they had received amfepramone. Orlistat is indicated for weight loss in obese, or overweight patients (BMI > 28 kg/m²) with associated risk factors, and is not known to be associated to CV reactions. These outcome events were limited to non-fatal outcomes due to the nature of the IMS Disease Analyzer Germany database.

There were four outcome events of arterial hypertension that occurred in patients that had received concomitantly both amfepramone and orlistat.

Results do not indicate that patients initiating amfepramone had a higher incidence of selected CV outcome events compared to patients initiating orlistat. However, patients initiating orlistat were older than patients initiating amfepramone, and the analysis did not take account of this age difference.

In addition, an analysis was performed to assess the presence of prior history of any of the selected events. The incidence rates are provided per 100,000 person-years for the periods prior the implementation of related contraindication and warnings, shortly after, and later. Out of a total of 4996 patients that started incident treatment with amfepramone including also years prior to 1998, 1478 patients had a medical history including at least one of the selected CV events ever in their history.

Table 2. Incidence rates of patients with prior history of selected cardiovascular conditions

Amfepramone users	Before 1996	1996-2000	After 2000
Total	91	229	4676
With an history of selected cardiovascular events	19 (20.9%)	59 (25.8%)	1400 (29.9%)
With an history of valvular disorders, pulmonary heart disease, cardiomyopathy or heart failure	5 (5.5%)	9 (3.9%)	173 (3.7%)

Amfepramone users	Before 1996	1996-2000	After 2000
With an history of selected cardiovascular events 365 days prior to start of amfepramone treatment	13 (14.3%)	36 (15.7%)	787 (16.8%)
With an history of valvular disorders, pulmonary heart disease, cardiomyopathy or heart failure 365 days prior to start of amfepramone treatment	2 (2.2%)	3 (1.3%)	66 (1.4%)

2.2.9.1.4. Regular intermittent use

A further analysis calculated the number of patients using amfepramone regularly over extended period of time. In this analysis a maximum gap of 365 days between prescriptions was allowed for prescriptions to be considered part of the same period.

The majority of patients (60.5%) received amfepramone intermittently during a period of up to one year, 23.6 % had at least two prescriptions over one to two years, whilst 15.6% used the product repeatedly over a period longer than two years, with the longest period observed being between 17 and 18 years in one patient (0.1%).

2.2.9.1.5. Generalisability

In IMS Germany, patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as patients can decide which physician to visit and could also visit several physicians concurrently, collected data may be incomplete, and GPs may not record all relevant patients' risk factors. Moreover, the completeness of data on outcomes may depend on the extent to which outcomes are captured in primary care as opposed to secondary care. It can also not be excluded that patients treated with amfepramone visit multiple doctors to receive a prescription, and any such tendencies cannot be studied in the IMS Germany database. Those various factors can lead to an underestimation of the treatment duration or of the presence of prior history of the selected events.

Data from IMS Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases (Becher, 2009; Rathmann, 2018)[27,28]. However, the degree to which results from this study reflect the true overall prescribing of amfepramone in Germany is unknown due to the small sample of GP practices included in the database and the relatively small number of patients prescribed amfepramone in the database. Nonetheless the drug utilisation results of the study remain valid for the population observed, with the caveat highlighted here.

In this study no difference in incidence of selected CV events was observed between patients treated with amfepramone and those treated with orlistat which is indicated for weight loss in obese, or overweight patients (BMI > 28 kg/m²) with associated risk factors, and is not known to be associated to CV reactions. However, it is unlikely that a difference could have been detected in this study, since orlistat users were older and possibly different as regards the BMI level, introducing bias to the analysis. Moreover, fatal events were not included and relevant events could have been missed due to the nature of the database. Additionally, as orlistat is not contraindicated in patients with CV diseases

[27] Becher, H., K. Kostev, and D. Schroder-Bernhardi, Validity and representativeness of the "Disease Analyzer" patient database for use in pharmacoepidemiological and pharmacoeconomic studies. Int J Clin Pharmacol Ther, 2009. 47(10): p. 617-26
[28] Rathmann, W., et al., Basic characteristics and representativeness of the German Disease Analyzer database. Int J Clin Pharmacol Ther, 2018. 56(10): p. 459-466

in contrast to amfepramone, a selection bias is likely. With regard to the described limitations and the fact that this was only a descriptive study, this particular finding is not considered reliable.

2.2.9.2. DAC study

The analytical centre of the Danish medicines agency undertook to perform a case control study to analyse the use of amfepramone in the Danish population.

The data from seven Danish public health registries covering the period from January 1991 to February 2022 provided by the Danish Health Data Authority (DHDA) were used. The cohorts were matched (1:5) by age and gender, comparing individuals having been dispensed amfepramone at least once (n=92,360), with individuals from the general population having never been dispensed amfepramone(n=461,800) at the index date. The cohorts were not matched by BMI, as this could not be performed based on the information available. The majority of subjects were females (79.2 %). The median age of the amfepramone population at first redeemed prescription was 43.0 years.

Analysis were performed for the period 1994-2022, and for the period after 1997, which is when treatment duration was shortened to 4-6 weeks and 3 months maximum in view of the increased risk of PAH (and of dependence for the "amphetamine-like" anorectics) beyond this treatment length.

2.2.9.2.1. Pulmonary hypertension, pulmonary arterial hypertension and any heart disease

Fisher's tests were used to test for significant differences in incidence rates of hospitalisation further to PAH (international classification of diseases (ICD-10) code I270, which included drug-induced PAH), pulmonary hypertension (codes I270 and I272) and heart disease diagnoses in the case population compared to the control cohort. For the case population, only cases who had redeemed an amfepramone prescription prior to receiving a diagnosis were included.

As information on BMI was not available, subgroups analyses were performed with factors correlated to BMI (i.e. hospital diagnosis of obesity (E660, E660B, E660C, E660E, E660F, E660G, E660H, E661, E662), co-morbidities diabetes, hypercholesterolemia, ephedrine, orlistat, dexfenfluramine) in order to inform on how this may have influenced the results. Indeed, BMI is a known risk factor for at least some types of pulmonary hypertension and cardiac diseases. A hospitalisation diagnosis for obesity was identified for a subset of the cohorts (8.3 % (7645/92360) in the amfepramone group vs 0.8 % (3499/461800) in the control group).

2.2.9.2.1.1. Pulmonary hypertension, pulmonary arterial hypertension

Patients in the amfepramone group had a significantly higher risk of developing PH and PAH over both the 1994-2022 and the post-1997 periods. However, after multiple testing corrections, the difference was only statistically significant when considering the whole period (1994-2022). When analysing subgroups, results differed. In the subgroup of patients with a hospital diagnosis for obesity, an increased risk could no longer be found (OR ≤1). For patients with obesity-associated co-morbidities, odds ratio were ≤1 for PAH, and varied, tending to opposite directions for PH, without reaching statistical significance. In the subgroup comparison including patients being treated with anti-obesity drugs, odds ratio were consistently above 1, not reaching statistical significance. An increased risk for treatment duration beyond 3 months, compared to shorter durations, could not be observed in this analysis.

Table 3. Risk of getting diagnosed with pulmonary hypertension after treatment with amfepramone, overall, in subjects with co-morbidities, and in patients treated with other anti-obesity substances.

Subgroups	PH/PAH	Year	OR (CI)	P-value	adj. p-value
-	PAH	1994-2022	1.74 (1.39 - 2.17)	0.00	< 0.05
-	PH	1994-2022	1.76 (1.42 - 2.17)	0.00	< 0.05
-	PAH	1997-2022	1.5 (1.11 - 1.99)	0.01	0.19
-	PH	1997-2022	1.52 (1.14 - 1.99)	0.00	0.1
obesity	PAH	1994-2022	0.56 (0.21 - 1.52)	0.23	1
obesity	PH	1994-2022	0.56 (0.21 - 1.52)	0.23	1
obesity	PAH	1997-2022	0.65 (0.23 - 1.84)	0.35	1
obesity	PH	1997-2022	0.65 (0.23 - 1.84)	0.35	1
hypercholesterolemia	PAH	1994-2022	0.78 (0.08 - 3.9)	1.00	1
hypercholesterolemia	PH	1994-2022	2.8 (1 - 7.68)	0.03	0.94
hypercholesterolemia	PAH	1997-2022	0.68 (0.02 - 5.06)	1.00	1
hypercholesterolemia	PH	1997-2022	2.16 (0.49 - 7.53)	0.26	1
diabetes	PAH	1994-2022	0.81 (0.42 - 1.49)	0.57	1
diabetes	PH	1994-2022	1.11 (0.64 - 1.9)	0.69	1
diabetes	PAH	1997-2022	0.49 (0.15 - 1.24)	0.14	1
diabetes	PH	1997-2022	0.74 (0.3 - 1.6)	0.60	1
orlistat	PAH	1994-2022	3.21 (0.98 - 16.59)	0.05	1
orlistat	PH	1994-2022	1.67 (0.67 - 4.96)	0.32	1
orlistat	PAH	1997-2022	3.2 (0.93 - 17.07)	0.06	1
orlistat	PH	1997-2022	1.7 (0.64 - 5.22)	0.29	1
ephedrine	PAH	1994-2022	1.42 (0.94 - 2.15)	0.08	1
ephedrine	PH	1994-2022	1.49 (1.01 - 2.23)	0.04	1
ephedrine	PAH	1997-2022	1.32 (0.83 - 2.1)	0.25	1
ephedrine	PH	1997-2022	1.35 (0.86 - 2.12)	0.19	1
dexfenfluramine	PAH	1994-2022	1.87 (0.78 - 5.14)	0.19	1
dexfenfluramine	PH	1994-2022	1.7 (0.74 - 4.37)	0.21	1
dexfenfluramine	PAH	1997-2022	2.08 (0.8 - 6.04)	0.13	1
dexfenfluramine	PH	1997-2022	1.82 (0.72 - 4.96)	0.21	1
More than 90 days	PAH	1994-2022	1.13 (0.77 - 1.68)	0.57	1
More than 90 days	PH	1994-2022	1.19 (0.82 - 1.73)	0.36	1
More than 90 days	PAH	1997-2022	1.35 (0.76 - 2.36)	0.26	1
More than 90 days	PH	1997-2022	1.59 (0.95 - 2.62)	0.07	1

Table 4. Number of subjects getting diagnosed with pulmonary hypertension after treatment with amfepramone, overall, in subjects with co-morbidities, and in patients treated with other anti-obesity substances.

Subgroups	PH/PAH	Year	Amfepramone users, % (n)	Controls, % (n)
-	PAH	1994-2022	0.12 (110)	0.07 (316)
-	No PH/PAH	1994-2022	99.85 (92225)	99.92 (461449)
-	PH	1994-2022	0.13 (121)	0.07 (344)
-	PAH	1997-2022	0.06 (58)	0.07 (316)
-	No PH/PAH	1997-2022	61.2 (56524)	99.92 (461449)
-	PH	1997-2022	0.07 (64)	0.07 (344)
obesity	PAH	1994-2022	0.01 (11)	0 (9)
obesity	No PH/PAH	1994-2022	8.83 (8158)	0.8 (3706)
obesity	PH	1994-2022	0.01 (11)	0 (9)
obesity	PAH	1997-2022	0.01 (9)	0 (9)
obesity	No PH/PAH	1997-2022	6.22 (5744)	0.8 (3706)
obesity	PH	1997-2022	0.01 (9)	0 (9)
hypercholesterolemia	PAH	1994-2022	0 (2)	0 (8)
hypercholesterolemia	No PH/PAH	1994-2022	1.55 (1432)	0.96 (4455)
hypercholesterolemia	PH	1994-2022	0.01 (9)	0 (10)
hypercholesterolemia	PAH	1997-2022	0 (1)	0 (8)
hypercholesterolemia	No PH/PAH	1997-2022	0.89 (823)	0.96 (4455)
hypercholesterolemia	PH	1997-2022	0 (4)	0 (10)
diabetes	PAH	1994-2022	0.02 (16)	0.01 (39)
diabetes	No PH/PAH	1994-2022	9.89 (9130)	3.91 (18077)
diabetes	PH	1994-2022	0.02 (23)	0.01 (41)
diabetes	PAH	1997-2022	0.01 (5)	0.01 (39)
diabetes	No PH/PAH	1997-2022	5.16 (4762)	3.91 (18077)
diabetes	PH	1997-2022	0.01 (8)	0.01 (41)
orlistat	PAH	1994-2022	0.03 (25)	0 (3)
orlistat	No PH/PAH	1994-2022	18.48 (17065)	1.42 (6566)
orlistat	PH	1994-2022	0.03 (26)	0 (6)
orlistat	PAH	1997-2022	0.02 (17)	0 (3)

orlistat	No PH/PAH	1997-2022	12.57 (11612)	1.42 (6566)
orlistat	PH	1997-2022	0.02 (18)	0 (6)
ephedrine	PAH	1994-2022	0.07 (67)	0.01 (40)
ephedrine	No PH/PAH	1994-2022	58.02 (53586)	9.81 (45315)
ephedrine	PH	1994-2022	0.08 (74)	0.01 (42)
ephedrine	PAH	1997-2022	0.04 (39)	0.01 (40)
ephedrine	No PH/PAH	1997-2022	36.3 (33527)	9.81 (45315)
ephedrine	PH	1997-2022	0.05 (42)	0.01 (42)
dexfenfluramine	PAH	1994-2022	0.03 (24)	0 (7)
dexfenfluramine	No PH/PAH	1994-2022	13.13 (12129)	1.43 (6607)
dexfenfluramine	PH	1994-2022	0.03 (25)	0 (8)
dexfenfluramine	PAH	1997-2022	0.02 (15)	0 (7)
dexfenfluramine	No PH/PAH	1997-2022	7.36 (6801)	1.43 (6607)
dexfenfluramine	PH	1997-2022	0.02 (15)	0 (8)
More than 90 days	PAH	1994-2022	0.06 (56)	0.01 (54)
More than 90 days	No PH/PAH	1994-2022	47.73 (44083)	10.42 (48142)
More than 90 days	PH	1994-2022	0.07 (63)	0.01 (58)
More than 90 days	PAH	1997-2022	0.02 (23)	0.01 (35)
More than 90 days	No PH/PAH	1997-2022	25.29 (23361)	10.42 (48142)
More than 90 days	PH	1997-2022	0.03 (30)	0.01 (39)

The median period between the first redeemed prescription and the diagnosis of PH/PAH was 16.6 years. No significant difference was found in the mean number of amfepramone tablets taken per year between patients who received a diagnosis of PH/PAH (mean number until diagnosis), and those who did not.

2.2.9.2.1.2. Any heart disease

Patients in the amfepramone group had a higher risk of developing any heart disease over the whole period, but this result was not reproduced when considering only 1997 – 2022. This result could not be confirmed either in the subgroups analysed for diagnosis codes and co-morbidities linked to obesity. An increased risk for treatment duration beyond 3 months, compared to shorter durations, was observed over the whole period but not for 1997 - 2022.

Table 5. Risk of getting diagnosed any heart disease after treatment with amfepramone, overall, in subjects with co-morbidities, and in patients treated with other anti-obesity substances.

Subgroups	Year	OR (CI)	p-value	adj. p-value
-	1994-2022	1.23 (1.21 - 1.25)	0.00	< 0.05
-	1997-2022	0.85 (0.83 - 0.88)	0.00	< 0.05
obesity	1994-2022	0.99 (0.9 - 1.09)	0.85	1
obesity	1997-2022	0.58 (0.52 - 0.65)	0.00	< 0.05
hypercholesterolemia	1994-2022	1.05 (0.92 - 1.19)	0.50	1
hypercholesterolemia	1997-2022	0.8 (0.68 - 0.95)	0.01	0.14
diabetes	1994-2022	0.93 (0.88 - 0.98)	0.00	0.06
diabetes	1997-2022	0.68 (0.63 - 0.73)	0.00	< 0.05
orlistat	1994-2022	0.82 (0.77 - 0.88)	0.00	< 0.05
orlistat	1997-2022	0.59 (0.55 - 0.64)	0.00	< 0.05
ephedrine	1994-2022	1.04 (1.01 - 1.08)	0.01	0.09
ephedrine	1997-2022	0.78 (0.75 - 0.81)	0.00	< 0.05
dexfenfluramine	1994-2022	0.91 (0.85 - 0.98)	0.01	0.13
dexfenfluramine	1997-2022	0.71 (0.66 - 0.77)	0.00	< 0.05
More than 90 days	1994-2022	1.12 (1.08 - 1.15)	0.00	< 0.05
More than 90 days	1997-2022	0.92 (0.88 - 0.97)	0.00	< 0.05

Table 6. Number of subjects getting diagnosed with pulmonary hypertension after treatment with amfepramone, overall, in subjects with co-morbidities, and in patients treated with other anti-obesity substances.

Subgroups	Heart diagnose	Year	Amfepramone users, % (n)	Controls, % (n)
-	Yes	1994-2022	20.82 (19233)	18.7 (86364)
-	No	1994-2022	73.43 (67823)	81.3 (375429)
-	Yes	1997-2022	9.36 (8644)	18.7 (86364)
-	No	1997-2022	47.62 (43980)	81.3 (375429)
obesity	Yes	1994-2022	2.09 (1929)	0.19 (883)
obesity	No	1994-2022	6.76 (6240)	0.61 (2832)
obesity	Yes	1997-2022	0.9 (828)	0.19 (883)

obesity	No	1997-2022	4.94 (4563)	0.61 (2832)
hypercholesterolemia	Yes	1994-2022	0.73 (678)	0.52 (2404)
hypercholesterolemia	No	1994-2022	0.6 (555)	0.45 (2059)
hypercholesterolemia	Yes	1997-2022	0.34 (313)	0.52 (2404)
hypercholesterolemia	No	1997-2022	0.36 (335)	0.45 (2059)
diabetes	Yes	1994-2022	3.79 (3496)	1.76 (8114)
diabetes	No	1994-2022	5.04 (4659)	2.17 (10004)
diabetes	Yes	1997-2022	1.56 (1442)	1.76 (8114)
diabetes	No	1997-2022	2.84 (2619)	2.17 (10004)
orlistat	Yes	1994-2022	3.78 (3490)	0.36 (1666)
orlistat	No	1994-2022	13.52 (12485)	1.06 (4906)
orlistat	Yes	1997-2022	1.94 (1795)	0.36 (1666)
orlistat	No	1997-2022	9.64 (8904)	1.06 (4906)
ephedrine	Yes	1994-2022	12.31 (11368)	2.12 (9794)
ephedrine	No	1994-2022	42.8 (39526)	7.7 (35563)
ephedrine	Yes	1997-2022	6 (5546)	2.12 (9794)
ephedrine	No	1997-2022	28.02 (25880)	7.7 (35563)
dexfenfluramine	Yes	1994-2022	3.29 (3035)	0.41 (1877)
dexfenfluramine	No	1994-2022	9.1 (8401)	1.03 (4738)
dexfenfluramine	Yes	1997-2022	1.5 (1388)	0.41 (1877)
dexfenfluramine	No	1997-2022	5.32 (4915)	1.03 (4738)
More than 90 days	Yes	1994-2022	10.49 (9688)	2.07 (9545)
More than 90 days	No	1994-2022	34.99 (32317)	7.69 (35506)
More than 90 days	Yes	1997-2022	3.74 (3458)	1.12 (5186)
More than 90 days	No	1997-2022	20 (18474)	5.52 (25506)

The median period between the first redeemed prescription and the diagnosis of any heart disease was 10.8 years. No significant difference was found in the mean number of amfepramone tablets taken per year between patients who received a diagnosis of PH/PAH (mean number until diagnosis), and those who did not.

2.2.9.2.2. Cause of death

The median age of death for patients treated with amfepramone was 72.7 years, and 71 years for the control group.

Patients treated with amfepramone were statistically significantly more likely to have died from any cardiac disease diagnosis (12.1 % (2,039) vs 11.5 % (9,383), OR = 1.1) but no difference was observed for death from pulmonary hypertension (0.05% in either group). Amongst subjects who died from any cardiac disease diagnosis, acute myocardial infarction was the most common diagnosis in either group (3.48% in the amfepramone group and 3.07% in the control group).

2.2.9.2.3. Amfepramone treatment duration

For the purpose of calculating treatment duration, consecutively redeemed prescriptions with a buffer of +/- one week between the last tablet of a prescription and the redemption of the next one were considered to constitute the same treatment period. The daily dose use was the recommended daily dose (i.e. 25 mg three times a day). Where prescriptions redeemed more than a week before the last tablet of the previous prescription, patients were considered to use doses above the recommended dose.

Overall, around 15% of patients have been treated with amfepramone for more than 3 months. After 1997, time at which the maximal treatment duration was shortened due to the safety concerns identified in the first EU review, 13.6% of patients were treated with amfepramone for longer than the maximal duration of use.

Table 7. Duration of amfepramone treatment within or beyond the maximal treatment duration and, adhering or exceeding the recommended daily dose.

Amfepramone use	Users, % (n)	Users after 1997, % (n)
All treatment durations ≤ 3 months	85.1 (78620)	86.4 (48893)

Any treatment duration > 3 months	14.9 (13740)	13.6 (7708)
Recommended daily dose or less	98.4 (90870)	98.6 (91041)
Above recommended daily dose	1.6 (1490)	1.4 (1319)

Most treatment periods only lasts 10 days (>200,000) corresponding to 30 tablets. The mean number of treatments per person is 4.6 with a median of 2 with a lower quartile of 1 and an upper quartile of 5. The mean time between all treatments is 207.4 days with a median of 39 days while the mean time between all treatments per patient is 356.8 days with a median of 134.0 days.

Overall, 1.6% of patient exceeded the recommended daily dose, while after 1997, this corresponded to 1.4% of patients.

2.2.9.2.4. Amfepramone during pregnancy

Women from the amfepramone group who had gone through either a pregnancy resulting in birth or had a legally induced abortion were grouped depending on time of use vis-à-vis their pregnancy (i.e. before, during or after the pregnancy). A full pregnancy was estimated to last 10 months, and amfepramone was used for a minimum of 10 days. A fisher's test was used to test for significant differences in the length pregnancy before abortion, as well as numbers of abortions (excluding spontaneous abortion due to lack of data), birth defects and stillbirths between the three groups based on time of use. Summary statistics were also used to show the yearly development in incidence of redeemed prescriptions per woman during pregnancy.

Among the 73,153 female patients treated with amfepramone, 23,172 were pregnant after or during treatment. Over the whole study period 1.5% of women were pregnant while on treatment (1,128), and after 1997, 730 women were pregnant while on treatment. Women treated with amfepramone during their pregnancies underwent significantly more induced abortions and less live birth compared to the control group. Proportionally more still births were also observed, however the difference was not statistically significant. In this group a smaller difference between the proportions of abortions and live birth was noted, compared to the control group. No age effect was observed in this regard.

Table 8. Pregnancy outcomes by time of treatment with amfepramone and in the control group

Pregnancy	Amfepramone before pregnancy, % (n)	Amfepramone during pregnancy, % (n)	Controls, % (n)
Legally induced abortions	22.99% (5042)*	45.49% (565)**	25.54% (57190)
Live birth	76.66% (16811)**	53.70% (667)*	74.12% (165994)
Still birth	0.35% (77)	0.81% (10)	0.35% (773)

*statistically significantly less than in the control group ($p < 0.05$)
**statistically significantly more than in the control group ($p < 0.05$)

Among women who underwent an induced abortion, no apparent difference was observed in length of pregnancy in the three groups.

Statistically significantly more cardiomyopathy (0.51% (87) vs 0.32% (534), OR: 1.6) and birth defects (6.72 % (1,139) vs 5.77% (9,624), OR: 1.2) were observed at births for pregnancies that occurred post-treatment with amfepramone, compared to the control group. This difference was only seen for cardiomyopathy at birth for pregnancies which occurred during treatment with amfepramone (1.03% (7) vs 0.32% (534), OR: 3.3).

Amongst pregnant women treated with amfepramone and who did not undergo an abortion, most only redeemed a prescription in their first month of pregnancy and mostly only once.

Table 9. Numbers of women redeeming prescriptions and of prescription redeemed per pregnancy month, for pregnancies ending in birth

Pregnancy month	0	1	2	3	4	5	6	7	8	9
n redeemed prescriptions	442	305	93	39	18	17	13	13	14	11
n women	402	279	83	33	14	15	10	12	10	11
After 1997										
n redeemed prescriptions	401	280	89	37	18	17	13	13	14	11
n women	366	255	79	31	14	15	10	12	10	11

No significant change was observed in how pregnant women redeemed amfepramone prescriptions throughout the years before and during pregnancy. Less women redeemed prescriptions over time but number of redeemed prescriptions per woman has not changed significantly.

2.2.10. Discussion on clinical safety

Amfepramone is known to be associated to pulmonary, cardiac, cerebrovascular and neuropsychiatric disorders and to a risk of dependence, which is supported by the cases reported post-marketing. Cases of previously identified adverse reactions continued to be reported over the years, despite the risk minimisation measures in place. No new adverse drug reactions were identified based on the data reviewed. Most of the commonly reported adverse events in post-marketing case reports are either already known adverse drug reactions for amfepramone-containing products, and as such listed in the product information, or confounded by other medications known to be associated to those reactions and/or patient's underlying conditions, which however does not exclude a possible contributory role of amfepramone. Given the fact that these adverse drug reactions are known and included in the product information, underreporting of ADRs may be expected.

Pulmonary hypertension and heart diseases in the DAC study

In a case control study analysing the use of amfepramone in the Danish population over the period 1994-2022, a higher risk of pulmonary hypertension, 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.

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 the above results were obtained in the full cohorts, where groups were not matched by BMI. As amfepramone is indicated in obese patients, obesity can be expected to be a preponderant condition in that group. Considering that obesity is a risk factor for some subtypes of pulmonary hypertension and for cardiac diseases (Alpert, 2016; Rosenkranz, 2016; Vachiéry, 2019; Sundström, 2017; McGee, 2005)[29,30,31,32,33], 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 (see also section on experts' consultation), obesity is however not a known risk factor for PAH. It is acknowledged that in 1996, based on the Abenhaim study, a BMI ≥ 30 kg/m^2 was found to marginally increase the risk of PAH, however it is possible that patients with higher BMI are treated with higher doses of anorectics, longer durations of use or a combination of multiple

[29] Alpert M, Omran J, Bostick B (2016) Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Curr Obes Rep 5:424-434
[30] Rosenkranz S, Gibbs JS, Wachter R, et al. (2016) Left ventricular heart failure and pulmonary hypertension. Eur Heart J 37:942-54
[31] Vachiéry J, Tedford R, Rosenkranz S, et al. (2019) Pulmonary hypertension due to left heart disease. Eur Respir J 53:1801897
[32] Sundström J, Bruze G, Ottosson J, et al. (2017) Weight loss and heart failure: A nationwide study of gastric bypass surgery versus intensive lifestyle treatment. Circulation 135:1577-85
[33] McGee DL, and the diverse populations collaboration, 2005: Body Mass Index and Mortality: A Meta-analysis Based on Person-level Data from Twenty-six Observational Studies. Ann Epidemiol 15, 87–97

medicines, which may be an alternative explanation to those results. Further the odds ratio for anorexic agents was similar whether or not adjusted for high body-mass index in that study. According to the guideline of the European Society of Cardiology, obesity is not listed as a risk factor for PAH. PAH affects both the obese and non-obese populations, which is further supported by observations in a cohort of incident patients prospectively enrolled in the French Pulmonary Hypertension Network registry from January 2006 to May 2016 (Weatherald, 2018)[34]. In this cohort study, comparing the characteristics of patients according to the presence or absence of obesity (defined as BMI ≥30 kg/m^2), idiopathic and hereditary PAH was more frequent in the non-obese group (BMI 24.3±3.4) (82.0% vs 65.9%; p<0.001) and (8.8% vs 5.2%; not significant), respectively, while, drug-induced PAH tended to be more frequent in the obese group (BMI 35.4±5.5) (9.2% vs 28.9%; not significant).

The subset of the cohort used for the subgroup analysis with patients with hospital diagnosis of obesity in the DAC study was small: 8.3 % of the amfepramone users and 0.8% of the controls. In this analysis, no statistical difference was found in the risks of pulmonary hypertension, 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. Indeed, the completeness of obesity/overweight diagnosis in the Danish national patient registry has been shown to be very low (only 10.9% among patients recorded with BMI ≥25 kg/m^2, Gribsholt, 2019)[35]. It is not known whether this impacted both groups evenly. 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. Results show constantly an OR > 1 pointing to an increased risk, though statistical significance was not reached. Notably, in the dexfenfluramine subgroup analysis, the point estimate was also above one. If dexfenfluramine was the only responsible drug for the development of PH/PAH in this group with both cohort using the drug, the OR would be expected to be closer to 1.

No significant difference was observed when comparing the risk of those 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, for the group using amfepramone for more than 90 days, this analysis was performed using single treatment courses lasting more than 90 days, and did not take into account the cumulative treatment durations (e.g. multiple treatment cycles with a buffer between redeemed prescriptions > 1 week). Hence, the PRAC considered that this comparison should be interpreted carefully. In particular for PAH, in the two published studies showing that the risk increased with longer anorectic treatment durations, cumulative treatment durations were considered. Therefore, this may have influenced the results as events occurring due to cumulative long-term use may not have been identified as such.

[34] Weatherald J, Huertas A, Boucly A, et al. Association Between BMI and Obesity With Survival in Pulmonary Arterial Hypertension. Chest. 2018;154(4):872-881
[35] Gribsholt SB, Pedersen L, Richelsen B, Thomsen RW. Validity of ICD-10 diagnoses of overweight and obesity in Danish hospitals. Clin Epidemiol. 2019 Sep 11;11:845-854.

The median time from the date of the first redeemed prescription of amfepramone to the date of diagnosis of PAH or any heart disease was 16.6 years (1Q,3Q:10.0,21.2) and 10.8 years (1Q,3Q: 5.7, 17.1), respectively. For PAH, the median time of diagnosis reported for other anorectics varied from 4-5 years (Souza, 2008)[36], to more than 5 years after exposure (Humbert, 2006)[37]. In the latter registry study in France, in around 65 patients exposed to anorexigens the delay between the last intake and the first symptoms of PAH was within 2 years in 24.2% of cases, 2 to 5 years in 32.3% and more than 5 years in 43.5%. Therefore, the PRAC considered that those results were not incompatible with a causal relationship between treatment with amfepramone and the events of interest.

The analysis for the period from 1997 was performed with the same control group as the analysis over the whole period. Although no effect of measures implemented in 1996 for amfepramone is expected on the control group, the involvement of other factors (such as different pattern of use of other anorectics before and after 1997) cannot be excluded. This may therefore have impacted the analysis over this period.

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.

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.

It is acknowledged that PAH has been shown to be associated to the serotonergic effect (5-HT2B receptor agonism) of some anorectics no longer authorised nowadays, whereas amfepramone is a sympathomimetic agent and has a different pharmacological action. However, while the underlying patho-mechanism of drug-induced PAH has not been fully elucidated, it is postulated that sympathomimetic drugs may cause PAH through pulmonary vasoconstriction, fenfluramine-like effects, toxic endothelial injury, vasculitis, and dysregulation of mediators of vascular tone (Humbert, 2012)[38]. It is further noted that another sympathomimetic anorectic agent, phenylpropanolamine, (which is no longer authorised) has also been shown to be associated with PAH based on case reports and an epidemiological study (Barst, 2004)[39].

Amfepramone use before or during pregnancy was also found to be associated with cardiomyopathy at birth (0.51% (87) vs 0.32% (534), OR: 1.6) and, when used before pregnancy, with birth defects in general (1.03% (7) vs 0.32% (534), OR: 3.3). However, the effect of obesity as confounder in this analysis has not been evaluated.

Non-adherence to the product information in the DAC study

The above mentioned DAC study, using data from Danish public health registries, 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 with a

[36] Souza R, et al. 2008. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases European Respiratory Journal 31: 343-348
[37] Humbert M, Sitbon O, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023-30.
[38] Humbert M, Souza R, Simonneau G (eds): Pulmonary Vascular Disorders. Prog Respir Res. Basel, Karger, 2012, vol 41, pp 76–84
[39] Barst RJ, Abenhaim L. Fatal pulmonary arterial hypertension associated with phenylpropanolamine exposure. Heart. 2004;90(7):e42. doi:10.1136/hrt.2004.036491

buffer of one week, which is considered a conservative approach. As the observed long-term treatment is counted in years, treatment interruptions slightly longer than 7 days could be considered negligible in the context of the overall treatment duration. Further, 1.4% exceeded the maximal daily dose. Use in pregnancy was also reported in 1128 women in the full study period (1.5%), including 730 after 1997. Past that date, approximately 9% (72) of the pregnant women treated with amfepramone redeemed amfepramone prescriptions in the second and third trimester, a time at which it is considered unlikely that pregnancy may have not been known, whereas those products must not be used during pregnancy. It should nevertheless be noted that the analysis is based on number of redeemed prescriptions and does not consider whether the redeemed tablets were taken.

Non-adherence to the product information in the EMA study

The observations of the EMA study of data from IMS Disease Analyzer Germany suggest that in a proportionate manner in terms of time (in years), a tendency for off-label use (longer than 90 days) persists, starting at 8.3% in 1998, with a rapid increase to 28.6% of patients in 2003 (after reintroduction of amfepramone containing products to the market following the European Court of Justice decision). In the last years it is hovering around 12%, concretely 11.9% in 2016, 11.4% in 2017, 15.5% in 2018, 12.0% in 2019, and 9.1% for the first half of 2020.

Considering intermittent use, most patients received amfepramone for up to one year (60.5%) or between one and two years (23.6%), with 15.9% of patients receiving amfepramone for longer than 2 years. The longest treatment duration was between 17 and 18 years (0.1%).

It is noted that a few of those percentage values are based on small numbers (e.g. 4 out of 14 incident users in 2003) thus associated with statistical uncertainty, however in the more recent period (from 2010) the number of incident users is consistently above a hundred, with a peak in 2018, where 15.5% use longer than 90 days is noted based on 97 incident users out of 624 and thus associated to a much greater level of certainty. Likewise for the sensitivity analysis, considered to largely underestimate the treatment duration, a peak is seen in 2012, based on 3 incident users out of 249, thus based on a large number of incident user and therefore more certain.

It is also noted that if the number of daily tablets was not available on the incident prescription date but was available in a subsequent prescription, that information was used. This is considered to have led to conservative estimates compared to using the dose on the start dates. Indeed, among the subsequent prescriptions a lower frequency of patients with a dose of 0.5 tablets per day (2.7% vs 6.3%) and a higher frequency of patients with a dose of 2 tablets per day (9.6% vs 4.0%) is observed, therefore it is more likely that a higher number of daily tablets is imputed, leading to a shorter treatment duration calculated. Overall, also considering the small number of patients this corresponded to, this is not expected to have a significant impact on the results. Duration of treatment could have been overestimated in cases where patients initiated treatment with 25 mg daily (immediate release) later switched to the 75 mg prolonged-release formulations. However, most patients received 75 mg prolonged-release formulations, which is intended to be taken once per day, any possible effect is considered to be very limited.

Further, the median number of tablets was used for a large proportion of patients in view of the missing data. A median number of tablets of 1 is in line with the posology for the prolonged-release formulations, whereas the immediate-release 25 mg capsules would normally be expected to be taken 3 times a day. For a given number of capsules prescribed, the lower the assumed daily dose, the longer the calculated treatment duration. Considering that for the overall period daily dose was available for 40% of immediate-release formulations and that the great majority (94%) of prescriptions related to prolonged release formulation, and from 1998 less than 3% of the prescription corresponded to the immediate release formulation, the risk of overestimation of the calculated

treatment duration is low. Conversely the sensitivity analysis with 6 tablets a day is considered to largely underestimate the treatment duration, as it would correspond to daily doses between two and six-fold above the recommended daily dose, whereas the data does not indicate that this may be common in practice.

Therefore, whilst limitations are acknowledged, those are not considered to significantly impact the data and the risk of overestimation of the treatment duration is considered to be low.

Looking at incidence rates of patients with prior history of CV conditions corresponding to contraindications (valvular disorders, pulmonary heart disease, cardiomyopathy or heart failure) or partially overlapping with contraindications (previously mentioned diseases and hypertension, 'severe' hypertension only being a contraindication), those remained stable over the three examined periods (5.5 before 1996 to 3.9% and 3.7% later for the strict contra-indications, and 20.9% before 1996 to 25.8% and 29.9% later for all selected cardiac conditions partially overlapping with contraindications). However, with increasing numbers of amfepramone exposure, absolute numbers of patients with some CV events in their personal history is increasing.

As highlighted in the discussion section to the study, 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 degree to which results from this study reflect the true overall prescribing of amfepramone in Germany is unknown due to the small sample of GP practices included in the database (3%, representing 7,204 participants and to 24,275 prescriptions) and the relatively small number of patients prescribed amfepramone in the database (4,825 had an incident prescription, incident use was defined as the first prescription for amfepramone in a patient with at least 365 days of prior observation). Nonetheless, the results of the study remain valid for the population observed, with the caveat highlighted above. Overall, the results indicate an unacceptable level of non-adherence to the product information in terms of the treatment duration and conditions for which amfepramone is contraindicated.

Non-adherence to the product information in post-marketing reports

Seventy-two (72) cases were identified in which amfepramone has been used in apparent non-adherence to the product information. This represents a significant proportion (18%) of the overall number of cases reported to the MAHs and EudraVigilance. Whilst information on the date is not available in all cases, ≥ 50% of the cases reporting use in patient with CV risks (17/34), use longer than 3 months (28/48), use in patients with a BMI under 30 kg/m^2 (21/24), use of doses above the maximal daily dose (13/19) occurred after 1996. This raises concerns on effectiveness of the risk minimisation measures in place. In addition, under the safety topics reviewed several cases were also reported in patients with underlying conditions representing a contraindication for treatment with amfepramone-containing products.

Further, considering the estimated patient exposure between 2001 and 2020 (1,874,895 patients or 462,303 treatment-years and the observed off label use or use not in adherence to the product information in two database studies, the number of cases reported to the MAHs or EudraVigilance are considered to represent a very significant underreporting.

Effectiveness of the current risk minimisation measures

In 1996, the CPMP 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 ≥ 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) and for children below 12 years.

The most common adverse reactions were noted to be the following: psychotic reactions or psychosis, depression, nervousness, agitation, sleep disorders and vertigo, tachycardia, palpitations, hypertension, precordial pain. Cases of stroke, angina, myocardial infarction, cardiac failure and cardiac arrest were also noted to have been reported, albeit rarely.

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 experts consulted in an ad hoc expert group (AHEG) meeting during the procedure (see also section on expert consultation). In particular, 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 anorectics including amfepramone.

Against this background, the above-mentioned observed off-label use for longer than the maximal duration of use (i.e. 13.6% in Denmark and around 12% in Germany, at least 28 case reports) is considered unacceptable. Such use puts patients at risk of developing PAH or dependence and as such is of great concern and indicates a lack of effectiveness of the risk minimisation measures currently in place. This concern is further supported by the use in combination with other centrally acting anorectic products (12 cases were reported with concomitant treatment with appetite suppressant – less relevant nowadays as) as well as in patients having a propensity towards drug abuse, known alcoholism (7 cases in patients at risk of dependence) respectively exposing patients to the same risks. The off-label use in patients for which treatment with amfepramone is contraindicated (around 4% use in patients with CV diseases in Germany, or 26-30% when considering also use in patients with hypertension (severe hypertension is a contra-indication) and 17 cases in patients with CV conditions, 3 cases in patients with psychiatric disorders, 1.5% use in pregnant women in Denmark (out of which, after 1997, 9% in the second and third trimesters) and 17 cases in pregnant patients) is also of concern. Patients with history or current CV disease, severe arterial hypertension, psychiatric disorders are at greater risks of developing related adverse events. The PRAC noted the view of the cardiologists consulted as part of the AHEG that the risk of CV diseases may be linearly increased for patients with underlying atherosclerosis. According to one European research[40], prevalence of subclinical coronary artery atherosclerosis is 40% in general population, therefore it is expected to be even higher in the obese population. It is also noted that 1.4% patients exceeded the recommended daily dose and 13 cases were reported in patients taking doses in excess of the recommended daily dose, which may also reflect the risk of tolerance to amfepramone. Finally still birth and malformations have been reported and a risk to the unborn child cannot be excluded in case pregnant women take amfepramone. The higher proportion of abortions among women on treatment during pregnancy compared to those on

[40] Bergström G, Persson M, Adiels M, et al. Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. *Circulation*. 2021;144(12):916-929.

treatment before pregnancy, which may indicate that the late detection of pregnancy vis-à-vis interruption of treatment could have a role in this decision, is also of concern.

Overall, the PRAC considered that the presented cases and results of the studies conducted clearly suggest a pattern of non-adherence. In view of the level of non-adherence to the risk minimisation measures in place, PRAC concluded that these were not effective in adequately minimising the risks associated to treatment with amfepramone-containing products.

Additional risk minimisations measures considered

The PRAC considered further risk minimisation measures to adequately minimise the risks associated to treatment with amfepramone, and in particular ensure adherence to the key measures present in the product information.

The PRAC considered making amendments to the product information (PI), however for amfepramone, the cornerstone of risk minimisation resides in the adherence to the measures already described in the product information. No recommendation for specific clinical actions were identified to ensure for example that patients with underlying conditions corresponding to contraindications were not treated. Whilst some discrepancies were noted between the PI of the products and information could be improved, it was considered that this would not have an impact on the adherence to the risk minimisation measures and in turn that it would not have a significant impact on the minimisation of the risks.

The PRAC also considered the possibility of implementing educational material, as discussed by the AHEG, such as a physician checklist that would include a reminder of the indication, aspects related to treatment duration and dosage regimen, contraindication, warnings or precautions, as well as the importance to strictly adhere to the product information. A patient card was also considered to inform patients of the most serious adverse reactions requiring immediate visit to their physician and of the importance of limiting the maximal treatment duration to 3 months. These measures were considered in combination with a DHPC in order to inform on the findings of this review and raise further awareness of the risks and associated measures to adhere to.

However, PRAC was of the view that such measures would not be sufficiently effective. Indeed, 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.

The possibility of removing pack sizes containing more tablets than needed for 30 days of treatment, and to recommend for NCAs to prevent at national level the possibility of repeat prescriptions and of electronic prescription were also considered. This, in order for patients to visit their physician for each new 30-day treatment period and for physician to re-assess the suitability of this treatment following the checklist. However, significant non-adherence has been observed in Germany despite non-availability of the 120 tablets pack. The currently available packages allow a maximum treatment duration of 4 months with subsequent prescriptions, but the excess of one month did not appear to be the driving force of long-term use considering the observed utilisation patterns (use was reported for up to 20 years). 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 considered the suggestion from the AHEG to place amfepramone in the national lists of psychotropic drugs which are regulated and with controlled prescription. However, the PRAC noted that a high level of non-adherence to the maximal treatment duration had been observed in Denmark despite its inclusion on the list 'E' of narcotics and the requirement for pharmacies and warehouses to report the amounts received, sent and in stock once a year, casting serious doubts as to the possible effectiveness of the measures considered.

PRAC also discussed the possibility of implementing a controlled access program, as a form of controlled supply system, in order for example to strictly limit the duration of treatment to a maximum of 3 months for a patient. However, such programs have large implications for all stakeholders, and is normally only considered for product with clearly demonstrated benefits. As obesity is currently a widely spread disease, the treatment is not limited to specialised centres but can be managed by a large number of different physicians, not including only specialists in obesity treatment, but also GPs, internists, gynaecologists and maybe others. Further, any pharmacy can dispense amfepramone. Therefore, some Member States raised concerns over the feasibility of implementing such a program over a widely dispersed system at national level. Finally, in view of the modest temporary efficacy of amfepramone (see also section on efficacy), 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.

2.3. Non-clinical safety

2.3.1. Cardiac safety

Amfepramone was studied in vivo in the dog, rat and cat at i.v. doses ranging mostly from 2.0 – 10 mg/kg. The results appear inconsistent, demonstrating increases in systemic and pulmonary blood pressure and with tachyphylaxis at the second dose at an interval of 30 minutes between the first and the second dose.

A repeat-dose toxicity study has been conducted in rats at the dose levels of 25, 50 and 100 mg/kg for 26 months and in beagle dogs at the dose levels of 0 and 10 mg/kg plus empty-capsule controls Clinical signs of hyperactivity and loss of body weight were recorded at all dose levels in rats and hyperexcitability, random motor activity and vocalising mostly after dosing and marked but inconsistent fluctuation of body weight was observed in dogs. No CV endpoints were included in the studies.

The studies were conducted between 1963 and 1978 and therefore not in accordance with current guidelines concerning CV safety, toxicity testing or GLP.

In vitro hERG assay for measurement of potential blockage of the potassium channel leading to long QT syndrome and cardiac arrest was not conducted.

2.3.2. Drug dependence and drug tolerance

Five non-clinical published studies provide some information on drug dependence and tolerance. In rats, i.p. administered amfepramone induced or maintained self-administration at 10-15 mg/kg dose. However, a clear dose response relation was not demonstrated at higher doses possibly because of

developing stereotyped behaviour. At 2.5-5 mg/kg dose, amfepramone increased motor activity and sensitised rats to the motor activating suggesting psychostimulant and rewarding properties. Further experimental data suggests different mechanism of action of amfepramone in comparison to amphetamine-like drug substances. In a voltametric study amfepramone did not significantly affect basal dopamine efflux in rat nucleus accumbens slices, in contrast to amphetamine that distinctly increased basal efflux by reverse transport. Also, in a microdialysis study locomotor activity remained virtually unaffected after treatment with amfepramone (40 mg/kg) over 15 days.

Primary and secondary pharmacology data are not available for amfepramone and thus direct and off-target effect on CNS receptors occupancy and/or brain penetration with relevance to drug dependence studies are not available. Literature studies on drug dependence and tolerance are considered as supportive only.

2.3.3. Genotoxicity

The MAHs studied the mutagenic potential of amfepramone in vitro using the Ames assay and in vivo using the bone marrow micronucleus test in mice. Both studies were performed compliant to GLP requirements.

No mutagenic effect was observed for amfepramone tested up to cytotoxic concentrations of 3,160 or 5,000 µg/plate in any of the 5 test strains in either experimental setup without and with metabolic activation.

In the micronucleus test amfepramone tested up to the maximum tolerated dose of 30 mg/kg intravenously showed no mutagenic properties.

In mice, slightly reduced motility, slight to moderate ataxia, slight to moderate dyspnoea and tremor were noted at 30 mg amfepramone hydrochloride/kg BW immediately to 5 minutes after administration. The dose levels had been selected based on a preliminary experiment employing two animals per dose (LPT 2005b). Here, no-effect level was observed at 10 mg/kg BW, dose levels of 30 mg/kg BW caused slight to moderate signs of toxicity. The animals treated with 100 mg/kg BW died immediately after administration.

In contrast, a published micronucleus assay showed an increase in the number of micronuclei in AFP users in both basal and differentiated buccal cells compared to controls, suggesting mutagenicity. However, the study displayed several faults, most important the micronucleus assay was not (and is still not) validated for buccal cells. Therefore this study is not considered relevant.

2.3.4. Reproductive toxicity

Two literature references studying the potential for reproductive toxicity (embryo-foetal and perinatal toxicity) in the 1960's were identified. Studies are limited to rodents only and, in general, do not meet current standards for reproductive toxicity studies or GLP. Relevance for the risk assessment is therefore highly questionable. No teratogenic effects were observed.

Nonetheless, bearing in mind, that amfepramone is an old substance with clinical data available, new preclinical studies are not warranted.

2.3.5. Activation of 5-HT2B receptor

In a more recent *in-vitro* study conducted by the MAH ethcathinone, the pharmacologically active main metabolite of amfepramone, displayed no activation or inhibition of human 5-HT2B receptor expressed

in HEK293T cells. This was in line with findings from an *ex-vivo* study in rat gastric fundus, where ethcathinone did not affect 5HT2B receptors at a concentration up to 30 µM (Bibi, 2017)[41].

2.3.6. Discussion on non-clinical safety

Limited non-clinical data is available on the cardiac safety, potential for drug dependence and drug tolerance and for reproductive toxicity of amfepramone.

However, in line with ICH guidelines avoiding of unnecessary use of animals and other resources is preferred and clinical safety data and meta-analyses can supersede lack of adequate non-clinical studies. Considering that clinical data is available for amfepramone, new non-clinical studies would not provide significant added value and further concerns are not pursued from non-clinical point of view.

With regards to the genotoxic potential of amfepramone, whilst in line with the current ICH guideline standard battery of genotoxicological tests should be conducted for prediction of potential human risks, studies performed were conducted in GLP conditions and in accordance with current standards. No genotoxic potential was observed and no further non-clinical genotoxicity tests are warranted.

Activation of 5-HT2B receptors expressed in the heart was shown to account for development of valvular heart disease (VHD) in obese patients receiving other anorectics, i.e. fenfluramine and dexfenfluramine. This receptor is also believed to contribute to development of fenfluramine-related PAH (Launay, 2002; Rothman, 2000; Rothman and Baumann 2009)[42, 43, 44]. Based on the non-clinical data available, ethcathinone is considered unlikely to exert an activity on the 5-HT2B receptor. However, the clinical relevance of this finding is unclear, as the involvement of other biological pathways leading to the occurrence of amfepramone-mediated PH/PAH and VHD (and/or other cardiac events) cannot be excluded. In addition, involvement of other metabolites of amfepramone in the development of PH/PAH/VHD cannot be excluded (Beckett, 1979)[45]. Also, other readouts for 5-HT2B should be considered in order to definitely exclude that amfepramone metabolites can activate the receptor (Papoian, 2017)[46]. Thus, the presented non-clinical data are insufficient to exclude causal associations between amfepramone and VHD (or other cardiac events), and between amfepramone and PAH/PH.

2.4. Efficacy

The MAHs submitted the available data to support the efficacy of their products in their authorised indications. Out of the 103 studies provided (102 published and 1 unpublished MAH-sponsored referred to as Rottiers 1999), 52 were studies of amfepramone (< 75 mg) use for 12 weeks or less – or longer but reporting results in the first 12 weeks. Out of those 35 have assessed the efficacy of amfepramone in adults and adolescents as an anorectic compared to placebo in a randomised, double-blinded design, including 17 randomised, double-blinded, placebo-controlled, parallel group design (i.e. not confounded by effects of crossover trial design). Results of those 17 studies are summarised in the

[41] Bibi U (2017) Investigating the cardiovascular toxicity associated with use of the novel psychoactive substance ethcathinone. Thesis: BSc (Hons) Biomedical Science (2016-2017), St George's University of London, Division of Biomedical Sciences. Supervisor: Dr James Moffatt, pp1-48
[42] Launay L, Herve P, Peoc'H K, et al. (2002) Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. Nat Med 8:1129-35
[43] Rothman R, Baumann M, Savage J, et al. (2000) Evidence for possible involvement of 5-HT2B receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 102:2836-41
[44] Rothman R, Baumann M (2009) Serotonergic drugs and valvular heart disease. Expert Opin Drug Saf 8: 317-29
[45] Beckett AH. A comparative Study of the pharmacokinetics of fenfluramine, ethylamphetamine, diethylpropion and their metabolites. Current Medical Research and Opinion. 1979; 6(1): 107-117
[46] Papoian T, Jagadeesh G, Saulnier M, Simpson N, Ravindran A, Yang B, Laniyonu AA, Khan I, Szarfman A. Regulatory Forum Review*: Utility of in Vitro Secondary Pharmacology Data to Assess Risk of Drug-induced Valvular Heart Disease in Humans: Regulatory Considerations. Toxicol Pathol. 2017 Apr;45(3):381-388

below table. Results of relevant meta-analysis and of a post-marketing surveillance study were also provided.

Table 10. Main characteristics and results of randomised, double-blinded, placebo-controlled, parallel group design studies of amfepramone as a short-term anorectic

Study	Number of evaluated patients A/P	Mean initial weight (kg) A/P	% loss of initial weight (amfepramone/placebo)		
			4 weeks	8 weeks	12 weeks
Russek 1966	19/17	78/77	---/---	4.2/0.1 (6.2/6.6 weeks)	---/---
Andelman et al. 1967	51/46	84.6/82.0	3.2/0.3 (3 weeks)	5.3/0.5 (7 weeks)	5.9/0.5 (11 weeks)
Bolding 1968	18/17	85.6/77.8	6/5	8/6	9/5
Evanselista 1968	24/25	79.7/79.7	---/---	7.6/4.7	---/---
Bose 1969	6/6	96.5/91.5	---/---	---/---	13.9/4.5
Bolding 1974	23/21	81.0/86.9	5.8/3.7	8.1/4.9	8.1/5.1
Allen 1975	41/33	87.3/80.3	---/---	---/---	10.4/5.6
Glazer 1975	20/18	83.1/84.9	2.3/1.4	3.5/2.0	4.7/3.1
McQuarrie 1975	22/18	84.1/74.3	2.8/0.5	4.4/1.3	5.2/2.1
Nolan 1975	21/17	84.3/74.3	4.2/3.9	6.7/4.9	8.1/5.1
Rodin et al. 1975	16/16	89.6/95.6	4.4/3.1	6.5/4.9	7.5/5.9
Albach & Gianoli 1977	36/32	80.1/80.0	5.0/1.8	7.7/2.7	---/---
Allen 1977	33/33	80.9/81.9	5.8/3.4	8.3/4.6	9.8/5.9
Bratusch-Marrain et al. 1979	13/19	80.3/93.9	---/---	4.7/3.2	---/---
Parsons 1981	12/13	81.1/77.4	4.8/3.5	7.3/4.4	8.9/5.9
Rottiers 1999	22/18	96.7/100.3	4.6/3.6	7.0/5.3	8.1/5.8
Soto Molina et al. 2015	78/79	90.1/88.3	--/--	--/--	5.4/0.8

These studies consistently show a greater short-term weight loss in the amfepramone group, compared to the placebo group. In the 13 studies with results at 11/12 weeks, a mean difference of 3.8% is observed between amfepramone and placebo in term of percentage loss of initial weight. The authors of these small studies concluded that both objective (weight loss) and subjective (patient perception) assessment methods confirmed the superiority of amfepramone over placebo. Whilst data on patients' BMI was largely missing from those studies, this is not considered to have relevant influence on the results.

Studies by Allen (1975), Glazer (1975), Mc Quarries (1975), Nolan (1975), Parsons (1981) compared the efficacy of (continuous and) intermittent amfepramone (over 3 periods of 4 weeks: amfepramone, placebo, amfepramone) with placebo. Of note, in the central period, the intermittent amfepramone group either regained weight (0.1 %) or lost up to 1 % compared to the end of the previous period, the latter was also observed in the placebo arm. In the Albach & Gianoli (1977) study where amfepramone or placebo were administered over two 8-week periods separated by 4 treatment-free weeks, weight regain was observed in the amfepramone group during the first two weeks of the central period. In the study by Rodin a first 4-week cognitive-behavioural therapy (CBT), was followed by 12 weeks of CBT alone or in combination with amfepramone or placebo. Patients were followed up for a year. Weight regain was observed across all groups. After 1 year, weight loss was 4.7% of the mean initial body weight as compared to 3.7% in the placebo group and 4.5% in the group on behavioural treatment alone (Rodin, 1975 (1988)).

A recent systematic review (including 31 studies) / quantitative meta-analysis (including 25 studies) also concluded that the treatment with amfepramone led to greater loss of body weight compared with

placebo (Lucchetta, 2017)[47]. In two other meta-analysis (Haddock et al., 2002 and Li z et al., 2005) patients treated with amfepramone lost an average of 3.0 kg of additional weight compared with placebo.

Amelioration of obesity-related risks has been recorded in a post-marketing surveillance study of amfepramone conducted by the MAH in 2003 (Hechler, 2003). These results show that 62% of the 948 patients still had a BMI ≥ 30 kg/m^2 after 12 weeks of treatment and an average of 10.9 kg was lost. In addition, various CV and metabolic risk indicators (e.g. cholesterol levels and blood pressure) were improved in 18-25% of the patients.

2.4.1. Discussion on efficacy

The main goals of weight management are to reduce body weight and to maintain a lower body weight in order to obtain CV, metabolic and general health benefits. Sustained weight reduction has been associated with beneficial effects on CV risk factors, such as blood pressure and lipid profiles, as well as improved glycaemic control in both patients with and without type 2 diabetes. Relevant decreases in certain risk factors associated with overweight and obesity have been seen with loss of 5 to 10% of initial weight.

Another aim of weight management could be a reduction of the prevalence and severity of other, non-cardiovascular related complications such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations, as well as the reduction of complications during planned surgery (e.g. orthopaedic surgery).

Nowadays the demonstration of a statistically significant, placebo-corrected weight loss of at least 5% of baseline weight after 12 months of treatment is considered a valid primary efficacy criterion (Guideline on clinical evaluation of medicinal products used in weight management EMA/CHMP/311805/2014). In addition, applicants for new marketing authorisations are asked to document the predictive value of weight loss after short-term treatment (e.g. 12 weeks treatment on target treatment dose) with respect to long-term efficacy, in order to better identify a population with expected long-term benefit and include potential "stopping rules" for non-responders in the product label. Weight loss has often been observed to plateau after 5 to 6 months of continuous treatment with currently or previously available pharmacological treatments. However, at least 12 month duration is recommended to fully document the effect on weight development and obesity related comorbidities.

Amfepramone containing products are authorised as adjunctive therapy to diet for a maximum of 3 months, in patients with obesity and a BMI of > 30 kg/m^2, who have not responded to an appropriate weight reducing regimen alone. Available studies submitted in support of the efficacy show a mean difference of 3.8% between amfepramone and placebo in term of loss of initial weight after 12 weeks. A number of limitations are observed in relation to those trials including small sample size, unbalanced genders (predominance of women) and poor description of treatment compliance. The meta-analysis conducted in 2017 also highlights that trial populations are poorly described and results are reported pooled for obese and overweight adults with or without co-morbidities. This practice leads to high heterogeneity and results that are difficult to use in clinical practice. The PRAC sought the views of an *ad hoc* group of experts (AHEG) during the procedure, who also highlighted the lack of sufficient robust data from randomised clinical trials comparing weight loss with amfepramone versus placebo in the setting of exposure limited to 12 weeks.

Trials in which amfepramone was given intermittently, show weight regain upon treatment cessation. Further, the single study providing long-term follow up data also show weight regain after treatment

[47] Lucchetta RC, Riveros BS, Pontarolo R, Radominski RB, Otuki MF, Fernandez-Llimos F, et al. Systematic review and meta-analysis of the efficacy and safety of amfepramone and mazindol as a monotherapy for the treatment of obese or overweight patients. Clinics (Sao Paulo). 2017;72(5):317-24.

cessation and a difference of 1% between amfepramone and placebo in term of loss of initial weight at 1 year.

Hence whilst a modest weight loss may be achieved after a 12-week treatment with amfepramone, the limited data available suggest that this may not have any long-term clinical benefit on body weight and within an anti-obesity program. This was also underlined by the majority of experts of the AHEG who considered the clinical relevance of the marginal and temporary weight loss observed with amfepramone to be questionable in the context of the need for overall long-term weight maintenance to obtain CV, metabolic and general health benefits for obese patients.

Some experts considered that amfepramone could provide a relevant alternative for some obese patients having low CV risk, and offering controlled treatment option which may prevent at risk behaviour, such as extreme dieting or usage of unallowed substances in supplements marketed for obesity. In their view 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, they also acknowledged that there was a lack evidence from randomised trials to support such claims.

Both the PRAC and the AHEG also noted that current treatment guidelines for obesity do not mention amfepramone, which calls into question its place in weight management.

Overall, whilst the data available show that amfepramone can produce modest short-term weight reductions, limitations to those data prevent from making definite conclusions on the efficacy of those products. Further, there is no data demonstrating that this observed weight loss effect at 12 weeks would be sustained in the long term. The only available study with longer follow up time would rather suggest the opposite (Rodin, 1975 (1988)). In conclusion, the clinical relevance of short-term treatment with amfepramone remains questionable.

3. Expert consultation

The PRAC consulted an ad hoc expert group (AHEG), composed of endocrinologists, cardiologists and a patient representative which provided advice on a number of issues.

The majority of experts considered that, as obesity is a chronic disease, the clinical relevance of the observed marginal and temporary weight loss with amfepramone was questionable in the context of the need for the overall long-term weight maintenance to obtain CV, metabolic and general health benefits for the obese patient. The lack of sufficient robust data from randomised clinical trials comparing weight loss with amfepramone to placebo after 12 weeks was also highlighted. In a small study, no significant weight loss was observed at 1 year after an initial 12-week period of treatment with amfepramone. At 12 weeks of treatment, the weight loss phase is still ongoing and duration of treatment should be at a minimum of 6 months treatment, but ideally 1 year would allow to clarify the duration of the achieved weight loss. However, in view of the safety concerns, the current treatment is limited to 12 weeks. Experts voiced that there are currently several other treatment options for chronic use available with a proven significant and relevant weight loss and a well-documented safety profile, which were not authorised before, and which are supported by large-scale and long-term clinical trial data. Some, also suitable for obese patients with a high CV risk such as type II diabetes for which amfepramone would not show add-on effect to those treatments. Overall, the need for additional obesity treatments in adults was acknowledged also due to the prevalence of obesity in adult population within the Europe.

Some experts considered however, mainly because of the current unmet need in the field of obesity, that amfepramone could provide a relevant alternative for some obese patients having low CV risk, and offering controlled treatment option which may prevent at risk behaviour, such as extreme dieting or usage of unallowed substances in supplements marketed for obesity. In their view 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 a reduced weight. However, they also acknowledged that there was a lack evidence from randomised trials to support such claims.

All experts noted that current treatment guidelines for obesity, even in those countries in which amfepramone containing products are marketed, did not mention amfepramone and therefore its place in weight management is questionable.[48,49,50]

In the view of AHEG, it was not possible to define a specific obese patient population which may have a specific clinical benefit with short-term amfepramone treatment, such as exclusively those obese patients who do not tolerate other anti-obesity medicinal products, obese patients without presence of weight-related comorbidities or with compulsory eating disorder, considering efficacy and safety endpoints in these subpopulations are not documented by dedicated clinical trials. In view of present restrictions for use, modalities of further restrictions for use in lower risk patients were discussed. It was considered that before prescribing amfepramone, it is necessary for prescribers to consider benefit short-term treatment with amfepramone for obesity versus the potential risks – individually for each obese patient.

Clinical benefit from a short-term, up to 3-months, obesity treatment with amfepramone is marginal and limited only to individual cases of obese patients in which benefit of temporary effects to be achieved with amfepramone outweighs the potential risks, following detailed assessment for safety concerns before prescribing.

In addition, it was felt by all experts that there were outstanding safety concerns in terms of CV safety, potential for abuse, off-label long-term use and PAH that should be further investigated and that required additional risk minimisation measures/information for patients and healthcare professionals are important to ensure the safe use in clinical practice.

The cardiologists expressed serious concerns over the CV safety, also for a 3 months treatment with amfepramone. The Report on analysis of amfepramone used in the Danish population showed prolonged used of amfepramone in number of patients, and safety risk may be linearly increased for patients with underlying atherosclerosis. In addition, the incidence of pulmonary hypertension in the Danish cohort, was of concern and overall it was felt by all experts that further safety information needed to be gathered to ensure the safety of amfepramone containing products. According to one European research[51], prevalence of subclinical coronary artery atherosclerosis is 40% in general population, therefore it is expected to be even higher in the obese population.

Additional measures were recommended to ensure adherence to the existing prescribing restrictions, especially restrictions related to patients with CV diseases and PAH and exclusion of all other diagnosed CV risk-increasing conditions (for example atherosclerosis, peripheral artery disease,

[48] Yumuk V, Tsigos C, Fried M, et al. European Guidelines for Obesity Management in Adults [published correction appears in Obes Facts. 2016;9(1):64]. Obes Facts. 2015;8(6):402-424.
[49] Durrer Schutz D, Busetto L, Dicker D, et al. European Practical and Patient-Centred Guidelines for Adult Obesity Management in Primary Care. Obes Facts. 2019;12(1):40-66.
[50] Wirth A, Wabitsch M, Hauner H. The prevention and treatment of obesity. Dtsch Arztebl Int. 2014;111(42):705-713.
[51] Bergström G, Persson M, Adiels M, et al. Prevalence of Subclinical Coronary Artery Atherosclerosis in the General Population. *Circulation*. 2021;144(12):916-929.

arrhythmia, reduced ejection fraction, myocardial infarction, arterial hypertension) such as patients card to check and exclude any existing contraindicated condition, providing safety information to the obese patients and distributing materials for the healthcare professionals (prescribers and those supervising patients including primary healthcare professionals). These measures are considered feasible in clinical practice as are already in place for some other medicinal products for treatment of obesity as well as for some medicinal products in other indications.

Another measure considered was placement of amfepramone on the national lists of psychotropic drugs which are nationally specially regulated and with controlled prescription (e.g. as already in place in Romania), in order to raise awareness of prescribers on the CV and other risks, including abuse, and treatment duration.

The AHEG experts discussed that a more careful monitoring of achieved weight loss response and safety follow-up is needed in treated patients within and after 3 months treatment duration (e.g. echocardiography - when indicated).

For older age patients, additional warnings are recommended for amfepramone since obese older people are at higher risk of adverse events and frequently have underlying CV disease.

With regards to the observed discrepancy in age cut off from which amfepramone is currently authorised to be used, the paediatricians commented that age was not the most adequate criteria and that the indication should rather refer to confirmed sexual maturity Tanner stage V) and weight age-specific cut-offs corresponding to BMI >30 kg/m^2 for adults (stating standard deviation by sex).

In addition to the above comments on the overall place and clinical relevance of amfepramone which apply to the authorised patient population as a whole, the following viewpoints were expressed by the paediatricians specifically on the use in adolescents:

- One view is that amfepramone is preferable kept as a treatment option also in adolescents as there is a need for obesity treatments due to the raise of obesity in this young population and they may otherwise revert to unauthorised and potentially dangerous treatment options.
- The other paediatric view expressed concerns related to using short-term treatment with amfepramone in the chronic condition of adolescent obesity, since adolescence is characterised as fast-growing period and a rebound of weight gain is expected after end of treatment. This weight rebound may reduce self-confidence and negatively influence necessary diet and lifestyle changes in later obesity treatments.

The AHEG experts shared the opinion that it is necessary to have long-term safety data by following obese patients for at least 2 years after short-term (up to 3 months) treatment with amfepramone, to address CV and PAH safety concerns. In countries in which amfepramone is used to treat obesity, establishment of quality national patients' registries for long-term follow-up (adherence, occurrence of adverse events) to further investigate whether the use of amfepramone containing products is indeed safe was also found important and considered feasible by the AHEG experts.

The patient representative commented that personally he would not take amfepramone as he would not like to be exposed to the safety risks. He also commented on the lack of new data being generated over the past decades to investigate the safety concerns.

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

Amfepramone belongs to the pharmacotherapeutic group "Centrally acting antiobesity 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 ≥ 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.

4.2. 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.

It is noted that the PRAC is a scientific committee and that while it operates within the framework of the Union legislation regulating medicinal products, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the PRAC, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data focuses only on the scientific grounds for re-examination.

4.2.1. Detailed grounds for re-examination submitted by the MAHs

Detailed grounds for re-examination of the PRAC recommendation have been submitted by the MAHs on 29 August 2022 and are summarised below:

Safety

The MAHs support the conclusions of CPMP in 1996 regarding the increased risk of PAH considered to be a class effect based on the data available at the time, but highlight that since then mechanisms have been identified leading to the occurrence of PAH and valvular heart disease (VHD), whereas at present there is no evidence that amfepramone may activate those pathways. This, in contrast with

fenfluramine, which was also the driver for the results of the two published epidemiological studies (including patients treated with amfepramone) having shown that anorectic intake is a risk factor for PAH. The risks associated to fenfluramine can therefore not be directly extrapolated to amfepramone.

The MAHs consider that the cases from spontaneous reporting do not present convincing evidence of a causal relationship between amfepramone and PAH, which in their view would cast further doubt as to whether pulmonary hypertension can be described as causally associated with amfepramone. Overall, they are of the view that cases reported do not provide any information regarding amfepramone's important identified risks that would alter their characterisation.

The MAHs discuss the evidence on the cardiovascular risk and off label use coming from the two observational studies performed in German and Danish healthcare databases, and their methodological limitations. The MAHs conclude that the studies do not substantiate the conclusions that the current levels of off-label use of amfepramone has led to unacceptably increased risks of PAH, cardiovascular adverse events, dependence or adverse pregnancy outcomes. They further argue that prescription data from Romania suggest good compliance with the recommended treatment duration.

Efficacy

The MAHs consider amfepramone particularly effective in patients with emotional eating that is often observed in obese patients with food addiction symptoms, and therefore that it could encourage patients to begin and continue a low-calorie diet and to lose weight by behavioural changes. The MAHs also consider that there are many situations in which initial treatment with an appetite suppressant for 3 months, despite the weight regain upon discontinuation, may be considered beneficial to a patient with obesity, as part of a comprehensive weight-loss programme, or where obesity treatment with another medicinal product has to be discontinued due to intolerable side effects, and/or possibly prior to initiation of a long-term treatment with another medicinal product. The MAH concludes that the efficacy of amfepramone in its authorised indication is demonstrated.

Risk minimisation measures

The MAHs consider it plausible that prescribers may not be completely familiar with the current risk minimisation measures and reinstated their position that the further measures and communication proposed during the procedure (PI changes, patient card, prescriber's checklist, withdrawal of largest pack size, DHPC) should limit the non-adherence to those measures aimed at minimising the risks of treatment with amfepramone. The MAHs also propose a PASS to monitor their effectiveness.

Medical need

The MAHs claim that removing amfepramone would deprive patients of one of the two oral appetite suppressant, and one of the few treatments for obesity, available, whereas others, due to their safety profiles, may not be suitable for all patients.

Overall

The MAHs consider that no new evidence was presented in the course of this referral procedure that would indicate that the previous positive benefit-risk balance of amfepramone has changed, that the implementation of additional risk minimisation measures would reduce the non-adherence to existing risk minimisation measures, and therefore consider the PRAC recommendation unjustified.

4.2.2. PRAC discussion on grounds for re-examination

The PRAC considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds.

4.2.2.1. Safety

4.2.2.1.1. 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)[52]. 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.

[52] 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.

4.2.2.1.2. 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.

4.2.2.1.3. 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.

4.2.2.2. 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.

4.2.2.3. 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.

4.2.2.4. 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 medicinal products 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.

4.2.3. 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.

5. Summary of new activities and measures

The Committee, having considered the data submitted in the procedure was of the opinion that no feasible and proportionate risk minimisation measures would be able to reduce the risks to an acceptable level.

Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a DHPC, to inform HCP of the conclusions of the review and therefore the upcoming unavailability of amfepramone-containing medical products. The Committee also agreed on a communication plan.

6. Grounds for Recommendation following the re-examination procedure

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.

The Committee, 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 Committee recommends the revocation of the marketing authorisations for amfepramone-containing medicinal products.

Appendix 1

Divergent position to PRAC recommendation

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

Procedure No: EMEA/H/A-31/1501

Amfepramone-containing medicinal products

(INN: Amfepramone)

Divergent statement :

We undersigned do not find that sufficient documentation is available to support a significant change in the benefit/risk balance for amfepramone, that would justify revocation of the marketing authorisations.

Superiority over placebo has been proved in accordance with standards at the time of approval, although the efficacy is modest. No new efficacy data are available. Although amfepramone is today not recommended as an obesity treatment option in any EU or national clinical guideline, some participants at the ad hoc expert meeting expressed that there may be a patient population where this treatment may be useful.

There are concerns about known serious risks, as already listed in the product information (mainly cardiac, pulmonary, neuropsychiatric, use in pregnancy, drug abuse). However, no significant new scientific data or information with regards to these known risks for amfepramone was identified during the current referral procedure.

A Danish registry study revealed off-label use (longer than 3 months, use of higher doses and use in pregnancy, in the period from 1997-2022) which could lead to an increased risk of adverse reactions including drug abuse and dependence, as well as adverse birth outcomes. Although the study could not identify serious adverse consequences linked to the off-label use, due to methodological limitations, it is not possible to refute these risks based on these data.

Based on these considerations, a package of further Risk Minimisation Measures (including Product Information update, limited package size, a DHPC, Physician´s Checklist, Patient Card) have been proposed, to reduce off-label use and to warn about serious risks. Furthermore, 2 PASS to assess the effectiveness of these RMMs have been proposed. Since currently only routine risk minimisation measures (product information) are in place, implementing additional measures as proposed are considered proportionate at the present time. There is no evidence that these measures together would not be effective in enhancing adherence to the current product information. Nevertheless, evaluation of effectiveness is critical.

Taken together, we consider that in case these measures are implemented, and that adherence is further evaluated within a Drug utilisation study, the benefit/risk balance of amfepramone remains unchanged.

To conclude, after reviewing all the data presented as part of this procedure, including the re-examination, no significant new data and information was identified that would alter the benefit/risk balance of amfepramone, and justify a revocation of the marketing authorisations. We consider that

the observed non-adherence to the current risk minimisation measures of amfepramone can be sufficiently mitigated by implementing new, both routine and additional, risk minimisation measures.

PRAC Members expressing a divergent opinion:

- Eva Jirsová (Czech Republic)
- Anette Kirstine Stark (Denmark)
- Ulla Wändel Liminga (Sweden)