ANNEX I

LIST OF THE NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, PHARMACEUTICAL FORMS, STRENGTHS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Clobenzorex containing medicinal products with Marketing Authorisation in the European Union

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
France	Laboratoires Roussel Diamant Tour Roussel Hoechst 1 terrasse Bellini 92910 Paris La Défense France	Dinintel	capsule	30 mg	oral	blister 60
Portugal	Laboratórios Roussel Lda Estrada Nacional 249, Km 15 2725 Mem Martins Portugal	Dinintel	capsule	30 mg	oral	blister 80
Spain	Instituto Llorente SA C/. Montevideo 33 28000 Madrid Spain	Finedal	capsule	30 mg	oral	blister 30

Fenproporex containing medicinal products with Marketing Authorisation in the European Union

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
France	Laboratoires Theranol Deglaude 5 bis, rue du Pont des Halles 94656 Rungis Cedex France	Fenproporex action prolongée Deglaude	tablet	20 mg	oral	blister 15 20
Portugal	Laboratoires Zimaia Lda Rua de Andaluz, n. 38 P-1050 Lisboa Portugal	Pesex-R	tablet	22.4 mg (fenproporex hydrocholride)	oral	blister 20 50
Portugal	Laboratórios Laquifa S.A. Rua Alfredo da Silva, n. 3-C 1300 Lisboa Portugal	Drenur	tablet	11.2 mg (fenproporex hydrocholride)	oral	blister 20 100
Portugal	Laboratórios Roussel Lda Estrada Nacional 249, Km 15 2725 Mem Martins Portugal	Tegisec	tablet	11.2 mg (fenproporex hydrocholride)	oral	blister 80
Spain	Berenguer Infale SA (Grupo Prodes) R. General Mitre 151 08022 Barcelona Spain	Grasmin	tablet	10 mg	oral	blister 30

Spain	Roussel Iberica SA R. General Mitre, 72-74 08017 Barcelona Spain	Tegisec	tablet	10 mg	oral	blister 30
Spain	Novartis Consumer Health Gran via de las Cortes Catalanes, 764 SP-08013 Barcelona Spain	Antiobes Retard	tablet	20 mg	oral	blister 30

Mazindol containing medicinal products with Marketing Authorisation in the European Union

At the time of this Opinion for Mazindol containing medicinal products, there was no longer any Marketing Authorisation in the European Union.

Mefenorex containing medicinal products with Marketing Authorisation in the European Union

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
France	Pierre Fabre Santé 45, Place Abel Gance F-92654 Boulogne Cedex France	Incital	tablet	40 mg	oral	polypropylene tube 21
Germany	Asta Medica AG An der Pikardie 10 D-01277 Dresden Germany	Rondimen	coated tablet	40 mg	oral	blister 30

Norpseudoephedrine containing medicinal products with Marketing Authorisation in the European Union

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Germany	Dieter Funcke (Apotheker) Bahnhofstrasse 64 D-46145 Oberhausen Germany	Fasupond	coated tablet	15 mg	oral	blister 60
Germany	Haenseler GmbH Gottlieb-Daimler-Strasse 1 D-78467 Konstanz Germany	Antiadipositum x-112 S Dragees	coated tablet	15 mg	oral	blister 60
Germany	Haenseler GmbH Gottlieb-Daimler-Strasse 1 D-78467 Konstanz Germany	Antiadipositum x-112 S Tropfen	oral drops, solution	3.5 g/100 ml	oral	bottle 30 ml
Germany	Salutas Pharma GmbH Otto-von-Guericke-Allee 1 D-39179 Barleben Germany	Exponcit N	coated tablet	15 mg	oral	blister 30 60
Germany	Schuck GmbH Arzneimittelfabrik Industriestrasse 11 D-90571 Schwaig Germany	Vita - Schlanktropfen Schuck	oral solution	4 g/100 g	oral	bottle 15 ml

Luxembourg	Heinrich Mack Nachf. (Pfizer) PO Box 4949 Pfizerstraße 1 D-76139 Karlsruhe Germany	Mirapront-N	capsule	20 mg	oral	blister 30

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Germany	Heinrich Mack Nachf. GmbH & Co. Heinrich-Mack-Str. 35 D-89257 Illertissen Germany	Mirapront-N*	capsule	20 mg	oral	blister 30

* Norpseudoephedrine polystyrol

Phenmetrazine/Fenbutrazate containing medicinal products with Marketing Authorisation in the European Union

At the time of this Opinion for Phenmetrazine/Fenbutrazate containing medicinal products, there was no longer any Marketing Authorisation in the European Union.

Phendimetrazine containing medicinal products with Marketing Authorisation in the European Union

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Belgium	Labima N.V. Van Volxemlaan No 328 1190 Brussels Belgium	Anoran	tablet	20 mg	oral	blister 24
Italy	Wyeth Lederle SpA Via Nettunense 90 IT-04011 Aprilia (Latina) Italy	Plegine	tablet	10 mg	oral	blister 20 30

Propylhexedrine containing medicinal products with Marketing Authorisation in the European Union

At the time of this Opinion for Propylhexedrine containing medicinal products, there was no longer any Marketing Authorisation in the European Union.

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR WITHDRAWAL PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CLOBENZOREX, FENBUTRAZATE, FENPROPOREX, MAZINDOL, MEFENOREX, NORPSEUDOEPHEDRINE, PHENMETRAZINE, PHENDIMETRAZINE AND PROPYLHEXEDRINE

Following reports of cardiac valve disorders with amfepramone and phentermine which have a similar mechanism of action as the above mentioned active substances and considering the recent developments concerning the efficacy of anorectic agents, on 31 August 1998 Austria requested the CPMP, under article 15a of Council Directive 75/319, as amended, to give an opinion on the benefit/risk balance of these medicinal products.

Clobenzorex, fenbutrazate, fenproporex, mazindol, mefenorex, norpseudoephedrine, phenmetrazine, phendimetrazine and propylhexedrine containing medicinal products were the subject of this article 15a referral procedure. It should be noted that clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine, and phendimetrazine containing medicinal products were evaluated during this referral procedure. For fenbutrazate and phenmetrazine containing medicinal products the Marketing Authorisations in the EU were withdrawn during this referral procedure. For mazindol and propylhexedrine containing medicinal products no evaluations were carried out because for propylhexedrine containing medicinal products there were no existing Marketing Authorisations in the EU when this article 15a procedure was started and for mazindol containing medicinal products the Marketing Authorisations in the EU were withdrawn a short time after the start of this article 15a referral procedure.

EFFICACY

Therapeutic efficacy for treating obesity requires a significant and long term lowering of body weight (at least one year). This is based on accumulated scientific knowledge acquired over the years and is laid down in current medical recommendations; this is reflected in the Note for Guidance on Clinical Investigation of Drugs Used in Weight Control (CPMP/EWP/281/96). This is also expressed in current guidelines, e.g. the Scottish guideline (1996), a guideline from the Royal College of Physicians (1998) and in a guideline from the American Society for Clinical Nutrition (1998).

The majority of clinical studies have been performed many years ago and methodologically they do not fulfil the current scientific criteria in this field:

- Very few double blind placebo studies have established that at least for a short time period amphetamine related agents can lower body weight to a very limited degree. With higher doses a more pronounced weight loss is possible, but with significant side effects. However, tolerance develops within weeks of treatment.

It has been argued by certain Marketing Authorisation Holders (MAHs) that a short term lowering of body weight might be helpful within an anti-obesity program. Rapid weight regain occurs once treatment is discontinued and there are no controlled studies which demonstrate that a limited short term effect has any long term clinically relevant influence on body weight or provides a clinical benefit within an anti-obesity program.

There are no controlled studies demonstrating a long term weight lowering beyond 3 months with these active substances. In fact such studies can not be performed due to the potential for dependence of these substances.

In conclusion, considering the current scientific knowledge and medical recommendations in the treatment of obesity, clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine lack therapeutic efficacy in the treatment of obesity when used for 3 months or less. This lack of efficacy is substantiated by a rapid weight regain back to the initial value. In this timeframe, these medications are of no therapeutic value.

At present the above-mentioned medications have not been used for periods longer than 3 months, due to safety concerns. These concerns relate to tolerance and/or dependence. So long-term use of these medications is irrelevant as long as a therapeutic use for more than 3 months cannot be considered. As a consequence in no case (short-term nor long-term) clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine can be envisaged for a safe and efficacious treatment of obesity.

SAFETY

The main safety concerns discussed were serious adverse effects on the central nervous system, primary pulmonary hypertension and cardiac valve disorders , under normal conditions of use.

Effects on the central nervous system (CNS)

These active substances, as amphetamine related agents, have typical central effects like stimulation and loss of sleep and serious effects such as psychotic reactions or psychosis, depression and convulsions.

The potential for drug abuse and drug dependence is well known for the centrally acting amphetamine related agents. For all the active substances evaluated cases of drug dependence have been reported.

The risk of drug abuse and drug dependence precludes that these active substances should be used for long-term treatment.

Primary pulmonary hypertension

In March 1995 the report on the International Primary Pulmonary Hypertension Study (IPPHS) confirmed that the use of anorectics is strongly associated with an increased risk for primary pulmonary hypertension (PPH). Specific risk factors which increase the risk of primary pulmonary hypertension were identified, including a BMI>30kg/m^2 and a cumulative duration of treatment in excess of 3 months. This risk was thoroughly discussed during the previous article 12 referral and was reflected in the amendments of the Summary of Product Characteristics (SPCs) as adopted by the CPMP.

The CPMP acknowledges that further data published by Abenhaim *et al* provided an adjusted odds ratio (OR) of 1.3 for all amphetamine-like anorectics with a wide confidence interval (95% CI; 0.4 – 4.7) which makes the IPPH Study inconclusive on this regard.

Concerning data from spontaneous reporting, single cases of pulmonary hypertension have been reported for all evaluated active substances, but these data can not be used to express incidence.

The CPMP concluded that taking into account data from spontaneous reports and in the absence of more formal epidemiological evidence, the possibility of an increased risk of PPH associated with these active substances cannot currently be ruled out.

Cardiac valve disorders

During the last two years evidence emerged that some anorectic agents were associated with cardiac valve disorders. The majority of cases occurred with anorectics with serotoninergic activity used alone

or in combination with other anorectic agents. Apparently there were no cases reported for the anorectic agents evaluated in this procedure.

Concerning the available data it can be concluded that at present there is no evidence of an association between cardiac valve disorders and these amphetamine related agents.

ANALYSIS OF EFFICACY AND SAFETY

After consideration of the grounds for appeal submitted by the Marketing Authorisation Holders and of all available data, the CPMP reached the following conclusions on the overall safety and efficacy:

Regarding efficacy, current national and consensus guidelines in the treatment of obesity, based on accumulated scientific knowledge acquired over the years, emphasise the need for a long term lowering of body weight. Clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine should only be used for 3 months or less due to their potential for dependence. Therefore, considering the current scientific knowledge and medical recommendations in the treatment of obesity, clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine lack therapeutic efficacy in the treatment of obesity when used for 3 months or less. This lack of efficacy is substantiated by a rapid weight regain back to the initial value. In this timeframe, these medications are of no therapeutic value.

At present these substances have not been used for periods longer than 3 months, due to safety concerns. These concerns relate to tolerance and/or dependence. So long-term use of these medications is irrelevant as long as a therapeutic use for more than 3 months cannot be considered. As a consequence in no case (short-term nor long-term) clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine can be envisaged for a safe and efficacious treatment of obesity.

Regarding safety, these medicinal products are associated with other serious cardiovascular and CNS adverse reactions, such as dependence. The risk of primary pulmonary hypertension has been fully taken into account in the Decisions of the European Commission of 9 December 1996. Further data published on the IPPH Study made the study inconclusive regarding the association between amphetamine related anorectic agents and the occurrence of PPH. However, there are data from spontaneous reporting and therefore a potential risk cannot be excluded. No cases of cardiac valve disorders have been reported with these medicinal products.

Further clinical trials with these active substances would require not only demonstration of long term efficacy but should also prove that the safety concerns (particularly abuse potential) do not interfere with the eventual benefits. One clinical trial for each substance would not probably be enough; a clinical programme would be necessary and would last for several years.

Based on these considerations clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine containing medicinal products have an unfavourable benefit/risk balance.

GROUNDS FOR WITHDRAWAL OF THE MARKETING AUTHORISATIONS

In April 1999

- the Committee considered the referral made under article 15a of Council Directive 75/319/EEC as amended for clobenzorex, fenbutrazate, fenproporex, mazindol, mefenorex, norpseudoephedrine, phenmetrazine, phendimetrazine and propylhexedrine containing medicinal products

- the Committee evaluated clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine containing medicinal products and did not evaluate mazindol and propylhexedrine containing medicinal products, because for propylhexedrine containing medicinal products there were no existing Marketing Authorisations in the EU when this article 15a procedure was started and for mazindol containing medicinal products the Marketing Authorisations in the EU were withdrawn a short time after the start of this article 15a referral procedure

- the Committee agreed that clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine containing medicinal products lack therapeutic efficacy in the treatment of obesity when assessed on the basis of accumulated scientific knowledge acquired over the years and current medical recommendations

- the Committee agreed that there were concerns related to the safety profile of clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine containing medicinal products concerning the risk of primary pulmonary hypertension and other serious cardiovascular and CNS adverse reactions such as dependence

- the Committee, as a consequence, considered the benefit/risk balance of clobenzorex, fenbutrazate, fenproporex, mefenorex, norpseudoephedrine, phenmetrazine and phendimetrazine containing medicinal products to be unfavourable and concluded that these medicinal products should not be maintained on the market, and therefore their Marketing Authorisations should be withdrawn

In May 1999, the Marketing Authorisation Holders appealed the CPMP Opinion. The CPMP reviewed the grounds for the appeal and heard oral explanations from the Marketing Authorisation Holders at its July 1999 meeting. The CPMP adopted a final opinion on 31 August, still recommending that the Marketing Authorisations for clobenzorex, fenproporex, norpseudoephedrine, mefenorex, and phendimetrazine containing medicinal products should be withdrawn and that Annex I of its opinion of 22 April 1999 should be revised.

As a result, the EMEA has recommended the withdrawal of the Marketing Authorisations for medicinal products containing clobenzorex, fenproporex, norpseudoephedrine, mefenorex, phendimetrazine; the EMEA took into account that, on this date, there were no existing Marketing Authorisations in the European Union for medicinal products containing fenbutrazate, mazindol, phenmetrazine and propylhexedrine.