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

Phentermine 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
Austria	Gerot Pharmazeutika GmbH Arnethgasse 3 A-1160 Wien Austria	Adipex Retard-Kapseln	capsule	75 mg	oral	blister 30 100
Belgium	Bio-Therabel SA Rue Egide Van Ophem 110 B-1180 Bruxelles Belgium	Panbesy Nyscaps	capsule	15,18 mg	oral	bottle 20 50
Ireland	Fisons Pharmaceuticals Ireland LTD Lake Drive 3004 City West Naas Rd Co. Dublin Ireland	Ionamin	capsule	15 mg 30 mg	oral	polypropilene container 100
Luxembourg	Bio-Therabel SA Rue Egide Van Ophem 110 B-1180 Bruxelles Belgium	Panbesy Nyscaps	capsule	15 mg	oral	bottle 50
United Kingdom	Cambridge Healthcare Suppliers Limited 57-58 King Street	Ionamin	capsule modified release	15 mg 30 mg	oral	screw cap plastic container 100

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
	Great Yarmouth Norfolk NR30 2PW					blister 28 4

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
Belgium	Medeva Pharma S.A. Avenue du Commerce, 23 B-1420 Braine L'alleud Belgium	Ionamin-15*	capsule	75 mg	oral	blister 30
Belgium	Medeva Pharma SA Avenue du Commerce, 23 B-1420 Braine L'alleud Belgium	Ionamin Forte*	capsule	150 mg	oral	blister 30
Luxembourg	Medeva Pharma SA Avenue du Commerce, 23 B-1420 Braine L'alleud Belgium	Ionamin-15*	capsule	15 mg	oral	blister 30
Luxembourg	Medeva Pharma SA Avenue du Commerce, 23 B-1420 Braine L'alleud	Ionamin Forte*	capsule	30 mg	oral	blister 30

*Phentermine resinate

Member State	Marketing Authorisation Holder	Product Name	Pharmaceutical Form	Strength	Route of Administration	Packaging/ Package size
	Belgium					
United Kingdom	3M Health Care 1 Morley Street Loughborough Leicestershire LE11 1EP United Kingdom	Duromine*	Capsule modified release	15 mg 30 mg	oral	bottle 30

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 PHENTERMINE CONTAINING MEDICINAL PRODUCTS

Following reports of cardiac valve disorders in patients receiving phentermine and amfepramone in combination with other anorectic agents, Belgium referred the matter to the CPMP, under article 15a of Council Directive 75/319 as amended, on 7 November 1997.

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).

Body weight loss has been shown in a number of short-term studies including relatively few patients. In general these studies are not recent and methodologically they do not fulfil the current scientific criteria in this field:

- For phentermine, only a slight decrease in body weight can be achieved.
- No studies are available concerning phentermine effects on cardiovascular or other recognised risk factors of obesity (i.e. blood pressure, cardiac function, biochemical parameters such as serum lipid or glucose concentration).

Results from a new unpublished clinical study have been presented by certain Marketing Authorisation Holders (MAHs). No additional relevant information is provided by this study.

It has been argued by certain 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.

Phentermine has not been studied in long term clinical trials and data on long term effects of the substance and, all the more, on maintenance of weight loss are lacking.

In spite of the fact that obesity is considered nowadays a chronic disorder and that its management should be envisaged as a long-term strategy, phentermine has only been shown to produce modest short term weight reductions of dubious and unproven relevance for the outcome of the disorder. Furthermore, the claims that it may facilitate or improve longer-term strategies when used as an adjunct have not been substantiated with adequate evidence. On the basis of the available evidence on efficacy, it is no longer possible to consider that phentermine has therapeutic efficacy in the treatment of obesity.

SAFETY

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

Effects on the central nervous system (CNS)

Phentermine, as an amphetamine related agent, has 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.

The MAHs disputed in their grounds for appeal and during the oral explanations in the July 1999 CPMP meeting the assumption of the CPMP to consider phentermine as an amphetamine related agent and to share the same adverse effects as amphetamine.

After discussion of this issue the CPMP considered that the reported cases of abuse and dependence with phentermine are the best available data supporting that the substance may have such a potential. No epidemiological study has been performed to quantify the risk. The evidence as a whole, however, would suggest that the risk of drug abuse and dependence, although likely to be lower than that of amphetamine itself, is real and should be taken into consideration.

The risk of drug abuse and drug dependence precludes that phentermine 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 procedure and was reflected in the amendments of the Summary of Product Characteristics as adopted by the CPMP.

Concerning data from spontaneous reporting, several cases of primary pulmonary hypertension with phentermine have been reported. These data can not be used to express incidence.

In the grounds for appeal the MAHs contested that is not scientifically justified to directly apply the results of the IPPH Study to phentermine. The CPMP acknowledged that the IPPH Study did not consider phentermine among the exposure and so, a formal evidence from epidemiological studies is lacking. However, assessment of available data does not provide reassurance that there is no association between phentermine and PPH and therefore the possibility of an increased risk of PPH associated with phentermine cannot be excluded.

Cardiac Valve Disorders

On 8 July 1997 the US drug agency FDA issued a “Public Health Advisory” on reports of valvular heart disease in patients receiving concomitant fenfluramine and phentermine. Subsequently, the FDA received numerous reports of heart valve disorders associated mainly with the use of fenfluramine in combination therapy with phentermine.

In addition five cases of cardiac valve disorders associated with phentermine monotherapy were reported. In two out of these five cases the treatment duration was less than 3 months.

No cases of cardiac valve disorders associated with phentermine monotherapy were notified to EU spontaneous reporting systems. There were, however, ten reports from Belgium on the combined use of phentermine with other anorectic agents.

The specific contribution of phentermine in the cases of combined therapy is not established. From the few reported cases with phentermine monotherapy it can not be excluded that phentermine may cause cardiac valve disorders.

During the Article 15a procedure two epidemiologic studies relevant in this context have been published in the New England Journal of Medicine (Khan *et al* 1998, Jick *et al* 1998).

The CPMP concluded that although there is not enough evidence to assert that phentermine increases the risk of cardiac valve disorders, such hypothesis cannot be ruled out for the time being.

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 efficacy and safety:

Regarding efficacy, in spite of the fact that obesity is considered nowadays a chronic disorder and that its management should be envisaged as a long-term strategy, phentermine has only been shown to produce modest short term weight reductions of dubious and unproven relevance for the outcome of the disorder. Furthermore, the claims that it may facilitate or improve longer-term strategies when used as an adjunct have not been substantiated with adequate evidence. On the basis of the available evidence on efficacy, it is no longer possible to consider that phentermine has therapeutic efficacy in the treatment of obesity or(as a consequence) that its benefit-risk balance is positive.

Regarding safety, although the data available suggest that the potential for dependence of phentermine is lower than that of amphetamine, some risk appears real and should be taken into account. In addition, the concerns raised by the possible association of phentermine with primary pulmonary hypertension and cardiac valve disorders have not been substantiated in formal epidemiological studies but a potential risk cannot be excluded.

Further clinical trials with phentermine 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 would not probably be enough; a clinical programme would be necessary and would last for several years.

Based on these considerations, phentermine 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 phentermine containing medicinal products

- the Committee agreed that phentermine 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 phentermine containing medicinal products regarding the potential risk for cardiac valve disorders with phentermine monotherapy, 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 phentermine 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 1999, still recommending that the Marketing Authorisations for phentermine 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 phentermine containing medicinal products .