CPMP/113-114/96

FINAL OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS IN ACCORDANCE WITH ARTICLE 12 OF DIRECTIVE 75/319/EEC AS AMENDED

International non-proprietary name (INN): **Type III**[1]
Name of product: see Annex II

Basis for Opinion

On May 17, 1995 Germany presented a referral under Article 12 of Council Directive 75/319/EEC as amended, and asked the CPMP to formulate an opinion on risks and benefits of medicinal products which are classified as centrally acting anorectic agents.

The ground for the referral was a discussion in the Pharmacovigilance Working Party on a report of an unpublished prospective case control study of primary pulmonary hypertension which became available on March 7, 1995. A French national inquiry recorded 78 cases between 1985 and 1994. The study confirmed the relationship between the use of anorectic agents and the occurrence of primary pulmonary hypertension.

Given the seriousness of the adverse reaction and the implications on public health it was agreed on May 17, 1995 by the CPMP that the issue was of community interest and anorectic agents concerned were identified on June 8, 1995. The initial time frame of 90 days was extended by an extra period of 90 days on October 18, 1995.

Written explanation were provided by the Marketing Authorisation Holders between July 5, and August 31, 1995. Oral explanation was provided by the Marketing Authorisation Holders at two hearings on 11 July 1995 and on 18 October 1995.

A first opinion was given on 15 February 1996 (Annex III) restricting the indications, the duration of treatment adding contra-indications, special warnings, precautions for use and undesirable effects.

For some of the anorectic agents, some Marketing Authorisation Holders (Annex IV) appealed against the opinion and the grounds for appeal were received on 15 and 30 April 1996. The grounds were on the wording of the excerpt of the Summary Product Characteristics: first in the indication, denying the usefulness of the term android to define obesity and secondly in the special warnings and undesirable effects sections, objecting to the statement of causality and requesting to specify the BMI level.

Opinion related to the Appeal

The Committee, having considered the grounds for appeal is of the opinion that the opinion should be revised by suppressing the word “android” in the indication, specifying the BMI level and amending two sentences of the previous text in the section special warnings and undesirable effects. The marketing authorisations for **Type III**-containing medicinal products, categorised as anorectic agent, should be maintained provided that

- the Summary of Product Characteristics is amended as stated in Annex I.

The final opinion is forwarded to the Commission, to Member States and to the marketing authorisation holders together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions together with its annexes and appendices.

London 17 July 1996

Prof. J M Alexandre
Chairman, on behalf of the CPMP

[1] Fenbutrazate, Propylhexedrine

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Annex I

AMENDMENTS TO THE TERMS OF THE NATIONAL MARKETING AUTHORISATIONS OF MEDICINAL PRODUCTS CONTAINING THE ACTIVE SUBSTANCE

Type III[2]

TO BE INTRODUCED

Excerpt of the Summary Product Characteristics (as defined in article 4a of Council Directive 65/65/EEC as amended) :

CLINICAL PARTICULARS

Therapeutic indications

Adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m^2 or higher who have not responded to an appropriate weight-reducing regimen alone.

Note: short-term efficacy only has been demonstrated with regard to weight reduction. No significant data on changes in morbidity or mortality are yet available.

Posology and method of administration

It is recommended that treatment should be conducted under the care of physicians experienced in the treatment of obesity.

Secondary organic causes of obesity must be excluded by diagnosis before prescribing this agent.

The management of obesity should be undertaken using a global approach and should include dietary, medical and psychotherapeutic methods.

Evening dosing should be avoided, as this agent may induce nervousness and insomnia

Duration of treatment

The duration of treatment is 4-6 weeks and should not exceed three months.

Contraindications

- Pulmonary artery hypertension
- Severe arterial hypertension
- Current or past medical history of cardio-vascular or cerebro-vascular disease
- Current or past medical history of psychiatric disorders including anorexia nervosa and depression
- Propensity towards drug abuse, known alcoholism.
- Children below 12 years

Combination drug therapy with any other centrally acting anorectic agent is contraindicated due to the increased risk of potentially fatal pulmonary artery hypertension

[2] Fenbutrazate, Propylhexedrine

Special warnings and precautions for use

Special warnings

Cases of severe, often fatal, pulmonary artery hypertension, have been reported in patients who have received anorectics of the type in this product. An epidemiological study has 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. No case has today been reported with this agent. Nevertheless, in view of this rare but serious risk which could be a class effect, it must be emphasized that :

- **careful compliance with the indication and the duration of treatment is required,**
- **duration of treatment greater than 3 months and a BMI ≥ 30 kg/m^2 increase the risk of pulmonary artery hypertension,**
- **the onset or aggravation of exertional dyspnea suggests the possibility of occurrence of pulmonary artery hypertension. Under these circumstances, treatment should be immediately discontinued and the patient referred to a specialised unit for investigation.**

Special precautions for use

- Prolonged treatment may give rise to pharmacological tolerance and drug dependence, and more rarely to severe psychotic disorders in predisposed patients.
- Rarely, cases of cardiac and cerebro-vascular accidents have been reported, often following rapid weight loss. Special care should be taken to ensure gradual and controlled weight loss in obese patients, who are subject to a risk of vascular disease. This anorectic agent should not be prescribed in patients with a current or a past medical history of cardio-vascular or cerebro-vascular disease.
- This anorectic agent should be used with caution in epileptic patients.

Undesirable effects

- An epidemiological study has snown 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. Pulmonary artery hypertension is a severe and often fatal disease. Although no spontaneous reports have been received with this agent, the occurrence or aggravation of exertional dyspnea requires treatment discontinuation and investigation in a specialised unit, as it is the first sign of occurrence (see special warnings).

CNS effects :

- the prolonged use of this agent is associated with a risk of pharmacological tolerance, dependence and withdrawal syndrome
- the most common adverse reactions which have been described are : psychotic reactions or psychosis, depression, nervousness, agitation, sleep disorders and vertigo.
- convulsions have been reported

Cardio-vascular effects :

- the most common reported reactions are tachycardia, hypertension.
- rarely, cases of cardio-vascular or cerebro-vascular accidents have been described in patients treated with anorectic agents. In particular stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.