CPMP/1001/97-EN

OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED FOR

Medicinal products

International non-proprietary names:	**Terfenadine and Pseudoephedrine hydrochloride**
Names:	see Annex A
Pharmaceutical forms:	tablet (including coated tablet and film coated tablet)
Strength:	terfenadine: 60 mg pseudoephedrine hydrochloride: 120 mg
Route of administration:	oral use

Basis for opinion

On 10 February 1997 France presented to the EMEA a referral under Article 12 of Council Directive 75/319/EEC as amended. The grounds for referral were submitted on 10 February 1997 and are appended to this opinion. The question referred by France to the CPMP was:

"to give an opinion on whether there is an unfavourable benefit/risk ratio for terfenadine in relation to its arrhythmogenic potential and to its serious cardiac adverse effects. The opinion should take into account the global safety profile of terfenadine in comparison with existing alternative non sedative anti-histaminic drugs available for the same indications in the European Union."

The matter was referred to the CPMP on 19 February 1997.

The above mentioned referral has been administered as outlined below.

The initial time frame agreed by the CPMP on 19 February 1997 was 90 days, extended by an extra period of 90 days on 14 May 1997.

On the basis of the grounds for referral, the following questions were forwarded to the Marketing Authorisation Holders:

1. Please provide information on your terfenadine containing product(s) available on the EU market (indications, recommended doses, duration, sales figures and legal status).
2. Please provide information on the profile and incidence of adverse reactions to terfenadine in comparison with other non sedative anti-histamines on the EU market used to alleviate the same pathological conditions, with particular reference to serious adverse events (with respect to cardiotoxicity and other effects), outcome and risk factors.
3. Please provide evidence of efficacy of terfenadine in its indications, in comparison with other non sedative anti-histamines already available on the EU market (comparative study design, patient population, efficacy end points).
4. What previous measures have been taken in order to minimise the risk of cardiac adverse reactions, especially as to the information provided in the SPC, and what has been the effect of it?
5. What new measures and information could be taken in order to improve the control, the occurrence and consequences of serious cardiac reactions?

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Written explanations were provided by the Marketing Authorisation Holders by 9 July 1997.
Oral explanations were given by Marketing Authorisation Holders on 23 July 1997.
Supplementary written information was provided by Marketing Authorisation Holders during the period 15 August 1997 to 30 October 1997.

Opinion
The CPMP, having considered the matter as set out in the appended Assessment Report, recommends the withdrawal of the Marketing Authorisations for all medicinal products referred to in Annex A.

The Scientific Conclusions and the grounds for withdrawal are set out in Annex B.

This opinion is forwarded to the European Commission, to Member States and to the Marketing Authorisation Holders together with its annexes and appendices.

London, 19 November 1997.

On behalf of the CPMP
Prof. J.-M. Alexandre, Chairman

ANNEX A
LIST OF THE NAMES OF THE MEDICINAL PRODUCTS AND OF THE MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Product Name	Pack Size (tablets)
Austria	Albert Roussel Pharma Altmansdorferstr. 104 1121 Wien	Teldafed-Manteltabletten	10 30
Belgium	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels	Teldafen	20
Italy	Lepetit Via R. Lepetit 8 20020 Lainate (MI)	Teldane D	20
Luxembourg	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels Belgium	Teldafen	20
Portugal	Hoechst Marion Roussel, Lda Estrada Nacional 249, Km 15 Apartado 39 2726 Mem Martins Codex	Trilufen	20

ANNEX B
SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA ON THE BASIS OF THE OPINION OF THE CPMP FORMULATED UNDER ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC

SCIENTIFIC CONCLUSIONS PRESENTED BY THE EMEA ON THE BASIS OF THE OPINION OF THE CPMP FORMULATED UNDER ARTICLE 12 OF COUNCIL DIRECTIVE 75/319/EEC

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF TERFENADINE-PSEUDOEPHEDRINE HYDROCHLORIDE TABLET FORMULATIONS (referred as terfenadine-pseudoephedrine tablet formulations)

On 10 February 1997 France requested that the CPMP, under Article 12 of Council Directive 75/319/EEC as amended, give an opinion on whether there is an unfavourable benefit/risk ratio for terfenadine in relation to its arrhythmogenic potential and to its serious cardiac adverse effects. The opinion should take into account the global safety profile of terfenadine in comparison with existing alternative non sedative anti-histamines (NSAHs) drugs available for the same indications in the European Union.

The CPMP at their meeting of 17-19 November 1997 considered the matter and reached the following conclusions, based on the evaluation of the Ad Hoc Expert Group and on the assessment reports distributed by the Rapporteur and the Co-Rapporteur:

SAFETY

Pharmacological data

Terfenadine is a potent inhibitor of several cardiac potassium channels. In animals and in humans, the effect of terfenadine on QTc is dose dependent. The effect is more marked in cardiac patients. Statistically significant prolongation of QTc has been observed after concomitant administration of terfenadine with grapefruit juice, azole antifungals and macrolide antibiotics.

Terfenadine is rapidly transformed to metabolites which apparently do not affect cardiac action potential duration. However, overdosage or disregarding contraindications may result in increased plasma levels and consequent cardiotoxicity.

From the electrophysiological viewpoint, some alternative NSAHs might be more favourable but some others, for which either the parent substance or the metabolite is cardiotoxic, seem to bear a similar cardiotoxic potential.

Spontaneous ADR reporting

As far as can be assessed from spontaneous reports, serious ADRs in relation to terfenadine are rare. The number of spontaneous reports of serious cardiac ADRs, including fatal cases, are relatively higher for terfenadine than for other NSAHs. The increase in some MS, since 1992, of spontaneous ADR-reports related to terfenadine (absolute and relative to sales figures) has not been seen with other NSAHs and is likely to indicate a reporting bias.

A considerable number of the cases of spontaneously reported serious cardiac terfenadine-related ADRs was apparently caused by improper use of that drug. Several risk factors have been recognised which appear to predispose to cardiotoxicity with terfenadine.

Pharmacoepidemiological data

Seven cohort studies, with a size of study population between 23,949 and 1,007,467 patients, were taken in account (five published studies: Herings (1993), Pratt (1994), Hanrahan (1995), Staffa (1995), Brandebourg (abstract 1996) and two unpublished studies: Martinez and Suissa and Garcia Rodriguez).

Taking all of the epidemiological data together the evidence indicated that the risk of cardiotoxicity for all non-sedating antihistamines was low but was higher than in non users. There was no evidence of a difference in risk between the NSAHs evaluated**.** Despite the inevitable limitations of epidemiological studies it was considered that the studies conducted had shown that the cardiotoxic risk could be identified. The Pratt study indicated that the risk of cardiotoxicity associated with terfenadine could be substantially increased in the presence of risk factors such as concomitant treatment with cytochrome P450 3A4 inhibitors (RR 23.6, CI 7.3-75.9). The epidemiological studies also showed a level of concomitant use of those inhibitors studied with NSAHs of 0.5-1%.

EFFICACY

The main indications were seasonal allergic rhinitis, perennial allergic rhinitis, chronic urticaria, and other skin disorders with chronic itching. When used for the approved indications, the efficacy of terfenadine containing medicinal products is considered similar to other NSAHs.

RISK-BENEFIT ANALYSIS

Pharmacoepidemiological evidence and spontaneous reports suggest that in spite of restrictions and repeated provision of information on the risks associated with terfenadine, coprescription with contraindicated drugs and misuse in the form of overdose occur. Misuse of terfenadine (including ingestion with grapefruit juice, or taking 2-3 times the daily dose) may lead to serious consequences.

Pseudoephedrine is a sympathomimetic agent with both direct and indirect effects on adrenergic receptors. Its use is contraindicated in patients with cardiovascular disease. There are well known proarrhythmic effects of pseudoephedrine which, in addition to those of terfenadine, have the potential of precipitating serious cardiac arrhythmia disease.

Therefore the combination product of terfenadine-pseudoephedrine has an unacceptable risk/benefit balance.

GROUNDS FOR THE WITHDRAWAL OF THE MARKETING AUTHORISATIONS

Whereas

-the Committee considered the referral made under Article 12 of Council Directive 75/319/EEC for terfenadine.

-the Committee agreed that there was particular concern related to the safety of terfenadine containing medicinal products in relation to its arrhythmogenic potential and to its serious cardiac adverse effects for which various risk factors (including concomitant use of arrhythmogenic drugs) have been identified.

-the Committee considered that the addition of pseudoephedrine to terfenadine does not increase the efficacy of terfenadine alone.

-the Committee considered the risk/benefit balance of terfenadine containing medicinal products. It considered that the addition of pseudoephedrine to terfenadine can increase its arrhythmogenic potential, therefore the risk/benefit balance of terfenadine-pseudoephedrine tablet formulations was considered to be unfavourable. It concluded that terfenadine-pseudoephedrine tablet formulations should not be maintained on the market.

the EMEA has recommended the withdrawal of the Marketing Authorisations for terfenadine-pseudoephedrine tablet formulations.