CPMP/1000/97-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 name:	**Terfenadine**
Names:	see Annex A
Pharmaceutical forms:	tablet (including coated tablet and film coated tablet)
Strength:	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	Triludan	10 30
Austria	Mundipharma GmbH Apollogasse 16-18 1072 Wien	Terlane	10 30
Belgium	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels	Triludan 120	10 20
Denmark	Astra Danmark A/S Roskildevej 22 DK-2620 Albertslund	Teldanex	10 30 100
Denmark	Durascan Medical Products AS Svendborgvej 243 DK-5260 Odense S	Histanex	
Finland	Suomen Astra OY PL 6 02431 Masala	Teldanex	10 30 100
France	Cassenne Marion (Merrel Dow) Tour Roussel Hoechst 92910 Paris la Défense Cedex	Teldane 120 mg	7 15 20
France	Laboratoires Cox France Tour Roussel Hoechst 1 Terrasse Bellini 92910 Paris la Défense Cedex	Terfenadine Henning	15
Germany	Azupharma GmbH Dieselstrasse 5 D-70839 Gerlingen	Histaterfen 120	20 50
Germany	BASF Generics GmbH Carl-Zeiss-Ring 3 D-85737 Ismaning	Terfum forte	20 50 100 200
Germany	betapharm Arzneimittel GmbH Steinerne Furt 78 D-86167 Augsburg	Terfami forte	20 50 100 200 (5x40)
Germany	ct-Arzneimittel Chemische Tempelhof GmbH Lengeder Str. 42a D-13407 Berlin	Terfenadin 120 von ct	20 50
Germany	Dermapharm GmbH Arzneimittel Lochhamer Schlag 10 D-82166 Gräfelfing	Terfederm 120	20 50
Germany	Dr August Wolf GmbH & Co Arzneimittel Sudbrackstrasse 56 D-33611 Bielefeld	Hisfedin 120	20 50 100
Germany	Heumann Pharma GmbH Heideloffstrasse 18-28 D-90478 Nürnberg	Terfenadin 120 Heumann	20 50

Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfium forte 120	20 50 100 200
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfallerg T 120	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfium 120 akut	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Lergium T 120	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Neuroterf T 120	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfen T 120	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfhexal T 120	20 50 100 200 (5x40)
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Fomos	20 50 100
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Teldane 120	20 50 100
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Teldane 120	20 50 100
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Terfenadin- ratiopharm forte	20 50 100
Germany	Karl Engelhard Fabrik pharm. Präparate GmbH & Co KG Sandweg 94 D-60316 Frankfurt	Terf 120 Eng	20 50
Germany	Neosan Arzneimittel- Vertriebsgesellschaft mbH Filchnerstr. 22 D-89231 Neu-Ulm	Terf 120 Neurax	20 50
Germany	Neosan Arzneimittel- Vertriebsgesellschaft mbH Filchnerstr. 22 D-89231 Neu-Ulm	Terfen 120 mg Neosan	20 50

Germany	Neosan Arzneimittel- Vertriebsgesellschaft mbH Filchnerstr. 22 D-89231 Neu-Ulm	Terfenadin 120 mg Tab Neosan	20 50
Germany	Neosan Arzneimittel- Vertriebsgesellschaft mbH Filchnerstr. 22 D-89231 Neu-Ulm	Terfenadin Tab 120 mg Neosan	20 50
Germany	Neosan Arzneimittel- Vertriebsgesellschaft mbH Filchnerstr. 22 D-89231 Neu-Ulm	Terfenadin 120 mg NeosanTab	20 50
Germany	ratiopharm GmbH Graf-Arco-Strasse 3 D-89079 Ulm	Terfen 120 TA	20 50
Germany	ratiopharm GmbH Graf-Arco-Strasse 3 D-89079 Ulm	Terfen-ratiopharm 120	20 50
Germany	Stadapharm GmbH Stadastrasse 2-18 D-61118 Bad Vilbel	Terfenadin Stada 120	20 50 100
Germany	TAD Pharmazeutisches Werk GmbH Heinz-Lohmann-Strasse 5 D-27472 Cuxhaven	Terfenat T 120	20 50 100 200 (5x40)
Greece	Zikidis Victor Hugo 45 Athen 104 37	Terfenadine/ Zikidis	15
Greece	BIOMEDICA A.E. G. Lira 25, P.O. Box. 511 70 K. Kifisia 145 10	Tricosal	15
Greece	Hoescht Marion Roussel Tatoïou Av. 146 10 Nea Erythraea Athen	Syneptine	14 15
Greece	KLEVA E.M.E. Parnithos 189 Aharnae 136 71	Terfedin	15
Greece	RAFARM Kapodistriov and Korinthov 12 Psichico 154 51	Sminosan	15
Greece	Sanofi Winthrop A 1st km Avenue Peania-Markopoulo 19002 Peania	Terfesan	15
Greece	VIOFAR Ethn. Antistaseos and Trifilias Aharnae 136 71	Voromin	15
Ireland	Hoechst Marion Roussel Broadwater Park Denham, Uxbridge Middlesex UB9 5HP UK	Triludan Forte	7 30

Italy	Astra Farmaceutici Via Messina 38 20154 Milan	Allerplus	15
Italy	Bruno Farmaceutici Via Castello della Magliana 38 00100 Rome	Allerzil Forte	15
Italy	Hoechst Farmaceutici Via Garofalo 39 20133 Milan	Triludan	15
Italy	Lepetit Via R. Lepetit 8 20020 Lainate (MI)	Teldane Forte	15
Luxembourg	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels Belgium	Triludan 120 mg	20
Netherlands	Albic B.V. Govert van Wijnkade 48 3144 EG Maassluis	Terfenadine Albic 120	30
Netherlands	Apothecon PO 514 3440 AM Woerden	Terfenadine 120 A	10 30 300
Netherlands	B.V. Pharbita Ronde Tocht 11 1507 CC Zaandam	Terfenadine 120 "pharbita"	10 30 50 250
Netherlands	Dumex B.V. Bothalaan 2 1217 JP Hilversum	Terfenadine Dumex 120	30 100
Netherlands	Eli Lilly Nederland B.V. Krijtwal 17-23 3432 ZT Nieuwegein	Terfenadine EB 120	30
Netherlands	Genfarma B.V. Sterrebaan 14 3606 EB Maarssen	Terfenadium 120	30
Netherlands	Hexal Pharma Nederland B.V. Pastoorslaan 28 2182 BX Hillegom	Terfenadine120	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan Forte	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan OTC tablet 120	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Terfenadine YM tablet 120	30
Netherlands	Katwijk farma B.V. Archimedesweg 2 2333 CN Leiden	Terfenadine 120 Katwijk	30
Netherlands	Multipharma B.V. Gemeenschapspolderweg 28 1382 GR Weesp	MP-Terfenadine 120	10 30 300

Netherlands	Pharmachemie B.V. Swensweg 5 2003 RN Haarlem	Terfenadine 120 PCH	30
Netherlands	Rhone-Poulenc Rorer B.V. Bovenkerkenweg 6-8 1185 XE Amstelveen	Terfenadine Pharbil 120	3 6 10
Netherlands	Samenwerkende Apothekers Nederland Europalaan 2 3526 KS Utrecht	Sterke Terfenadine-Tabletten 120 Bij overgevoeligheidsreacties Samenwerkende Apothekers, tabletten	10
Portugal	Hoechst Marion Roussel, Lda Estrada Nacional 249, Km 15 Apartado 39 2726 Mem Martins Codex	Triludan Forte	10
Spain	Ifidesa Aristegue Alameda de Urquijo, 27 48008 Bilbao	Rapidal Plus	20
Spain	Marion Merrell, S.A. Rda. General Mitre, 72-74 08017 Barcelona	Triludan Forte	20
Spain	Sigma Tau España SA Pl. Ind. Axque, Parcelas 13,14 Alcala de Henares 28806 Madrid	Cyater Forte	20
Sweden	Tika Läkemedel AB Box 2 22100 Lund	Teldanex	10 30 100 250
United Kingdom	AH Cox & Co Ltd Whiddon Valley Barnstaple Devon EX32 8NS	Terfenadine	7 30
United Kingdom	Approved Prescription Services Ltd Brampton Road Hampden Park Eastbourne East Sussex BN22 9AG	Terfenadine (Histafen)	7 10 28 30 56 60
United Kingdom	Dallas Burston Healthcare Ltd c/o Ashbourne Pharmaceuticals Victors Barns Hill Farm Brixworth Northampton NN6 9DQ	Terfenadine	7 10 28 30 500
United Kingdom	Hoechst Marion Roussel Broadwater Park Denham Uxbridge MIDDX UB9 5HP	Seldane	7

United Kingdom	Hoechst Marion Roussel Broadwater Park Denham Uxbridge MIDDX UB9 5HP	Triludan forte	2 7 10 30
United Kingdom	Lagap Pharmaceuticals Ltd 37 Woolmer Way Bordon HANTS GU35 9QE	Terfenadine forte	30
United Kingdom	Norton Healthcare Ltd Gemini House Flex Meadow, Harlow Essex CM19 5TY	Terfenadine	7 10 20 28 30 56 60 100
United Kingdom	Sanofi Winthrop Ltd One Onslow Street Guilford Surrey GU16 5SG	Terfenadine	7 30
United Kingdom	Wallis Laboratory Ltd Laporte Way Luton, Beds LU4 8WL	Terfenadine	7 10 28 30 56 60

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 120 MG 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 metabolites are 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.

Taking this into account, a single dose of 120 mg is at the upper daily dose limit. Given the likelihood that some people may occasionally take two of these tablets, the risk of overdose is increased. Therefore in order to improve the margin of safety it is recommended that the Marketing Authorisation for 120 mg terfenadine tablet formulations should be withdrawn.

Based on these considerations, terfenadine 120 mg tablet formulations have 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 exceeding the recommended dose) have been identified and that, as a consequence, the safety of terfenadine may only be considered acceptable if it is used according to very strict instructions since association to any risk factor may lead to serious consequences.

-the Committee agreed that the efficacy of terfenadine containing medicinal products is considered similar to the other NSAHs.

-the Committee considered the risk/benefit balance of terfenadine containing medicinal products. Due to the higher risk of overdose, the risk/benefit balance of terfenadine 120 mg tablet formulations was considered to be unfavourable. It concluded that terfenadine 120 mg tablet formulations should not be maintained on the market.

the EMEA has recommended the withdrawal of the Marketing Authorisations for terfenadine 120 mg tablet formulation.