CPMP/256/98-EN

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

Medicinal product

International non-proprietary name:	**Terfenadine**
Name:	see Annex A
Pharmaceutical form:	tablet
Strength:	30 mg
Route of administration:	oral use

Background

A CPMP Opinion for terfenadine containing medicinal products, pursuant to Article 12 of Council Directive 75/319/EEC as amended, was adopted on 19 November 1997, recommending by a majority of 21 out of 24 votes, the maintenance of the Marketing Authorisations in accordance with the draft Summary of Product Characteristics set out in Annex I to that opinion. The Scientific Conclusions and the grounds for the amendment of the Summaries of Product Characteristics were set out in Annex B to that opinion. Some Members expressed divergent positions which were appended to that opinion. Such opinion with its Annexes is set out in Annex C.

An intent of appeal against the opinion was submitted on 12 December 1997 by Prodes S.A., Marketing Authorisation Holder for a terfenadine 60 mg tablet formulation.

On 21 January 1998, the grounds for appeal were submitted to the EMEA.

Supplementary written information was provided by Prodes S.A. during the period 28 January 1998 to 20 February 1998.

The CPMP conclusion in the appeal procedure concerning the terfenadine 60 mg tablet formulation was considered by the CPMP to also apply to the CPMP opinions concerning the terfenadine 30 mg tablet and the 6 mg/ml oral suspension formulations.

Grounds for appeal

The grounds for appeal submitted by Prodes S.A. were based on the wording of section 4.5 of the Summary of Product Characteristics (Interaction with other medicinal products and other forms of interaction) and are appended to this opinion.

Basis for opinion

On the basis of the grounds for appeal in relation to the Summary of Product Characteristics, the CPMP considers that:

1. Section 4.5 of the draft Summary of Product Characteristics for terfenadine containing medicinal products should be amended as set out in Annex I.

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2. Such amendment to the draft Summary of Product Characteristics for terfenadine 60 mg tablet formulation also applies to the draft Summaries of Product Characteristics of terfenadine 30 mg tablet and 6 mg/ml oral suspension formulations which were annexed to their respective opinions of November 1997 and therefore are to be revised accordingly.

Final opinion

The CPMP having considered the grounds for appeal in relation to the draft Summary of Product Characteristics as set out in the appended assessment report has concluded that its opinion of 19 November 1997 should be revised and that the draft Summary of Product Characteristics should be amended.

The Members of the CPMP who expressed divergent positions concerning the CPMP opinion of 19 November 1997 maintained their positions in relation to this opinion.

The amended draft Summary of Product Characteristics is set out in Annex I.

The Scientific Conclusions and the grounds for amendment of the Summary of Product Characteristics are set out in Annex B.

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

London, 25 February 1998

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)
United Kingdom	Norton Healthcare Ltd Gemini House Harlow Essex CM19 5TY	Terfenadine	7 10 14 20 28 30 40 56 60 100

ANNEX B
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR RESTRICTION

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 30 MG TABLET.

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 its meetings of 17-19 November 1997 and of 23-25 February 1998 considered the issues raised by the referral and, based on all the information brought to its attention, reached the following conclusions:

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.

It is concluded that the safety of terfenadine was acceptable if used as recommended in the Summary of Product Characteristics (SPC). However the precautions for safe use were extensive and had become even more complicated. Precautions are also required for the safe use of some other NSAHs and there was considered to be no basis for discriminating terfenadine from these NSAHs.

It has been considered that the risk-benefit of terfenadine 30 mg is acceptable and the Marketing Authorisation should be maintained provided that:
- the indications are restricted to adults and children over 12 years and 50 kg of body weight because the 6 mg/ml terfenadine suspension would permit a more accurate dose based on body weight for children.
- the Summary of Product Characteristics (SPC) is revised with emphasis on contraindications due to hepatic or cardiac diseases and pharmacokinetic or pharmacodynamic interactions between terfenadine and other substances as stated in Annex I.

These conclusions were not endorsed by the following CPMP members: Madame Genoux-Hames, Prof Trouvin, Dr Abadie:
In the light of the experience gained in France particularly since 1992, and because of the seriousness of cardiac ADRs which included fatal cases, they considered that the safe use of terfenadine would not be sufficiently ensured by a more restrictive SPC and that the Marketing Authorisations for all terfenadine containing medicinal products must be withdrawn.

GROUNDS FOR THE AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS

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 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. It considered the risk-benefit balance of terfenadine 30 mg tablet acceptable and that the Marketing Authorisation should be maintained provided that the SPC is amended as stated in Annex I.

the EMEA has recommended the maintenance of the Marketing Authorisation for terfenadine 30 mg tablets in accordance with the draft SPC as stated in Annex I.

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

See Annex A

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
One tablet contains 30 mg terfenadine.
For inactive ingredients see section 6.1

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of allergic rhinitis and conjunctivitis and of allergic skin disorders

4.2 Posology and method of administration

The recommended dose must not be exceeded.

Patients should be advised, in case of insufficient symptom relief
- not to exceed the maximum dose
- not to add another antihistamine (even OTC preparations) but consult their physician.

Terfenadine should not be taken with grapefruit juice.

Adults and children over 12 years:

This dosage recommendation for 30 mg tablets applies to children over 12 years only if their body weight exceeds 50 kg.

Allergic rhinitis and conjunctivitis:
Starting dose is 60 mg daily (two tablets), increasing to 120 mg (four tablets) daily if required.
The total daily dose may be taken as a single dose or in two divided doses.

Allergic skin disorders:
60 mg (two tablets) twice daily. Alternatively, 120 mg (four tablets) may be taken in the morning.

Dosage adjustment in renal failure:
Normal age-related decrease of renal function does not require dosage adjustment for terfenadine. However, dose reduction by 50% is advisable for patients with significant renal impairment, particularly with creatinine clearance below 40 ml/minute.

4.3 Contra-indications

Terfenadine preparations must not be used in patients with hypersensitivity to terfenadine or any of the excipients of the formulation.
Significant impairment of hepatic function or concomitant treatment with inhibitors of the hepatic cytochrome P4503A4 isoenzyme (CYP3A4) can result in a decrease of terfenadine metabolism.

Accumulation of unmetabolised terfenadine may cause prolongation of the QT interval in the ECG with risk of life-threatening cardiac arrhythmias.

Therefore, terfenadine is contraindicated in the following conditions:
- significant impairment of hepatic function (e.g. in patients with jaundice, hepatitis, cirrhosis).
- concomitant treatment with azole antifungals/antimicrobials (including topical antifungals)
- concomitant treatment with macrolide antibiotics (including topical macrolide antibiotics)
- concomitant treatment with mibefradil dihydrochloride
- concomitant treatment with other medicinal products known to inhibit hepatic metabolism of terfenadine.

These are listed under 4.5 (Interactions).
Grapefruit juice should not be taken during terfenadine treatment.

Terfenadine is also contraindicated in patients having known QT prolongation (corrected QT, QTc > 440 ms), e.g. congenital long QT Syndrome, or conditions which may lead to QT prolongation, such as
- clinically significant bradycardia
- history of symptomatic arrhythmias
- any other clinically significant cardiac disease
- concomitant treatment with Class I or III anti-arrhythmics
- concomitant treatment with other medicinal products known to prolong the QT interval

These are also listed under 4.5 (Interactions).
- electrolyte imbalance, particularly hypokalemia or hypomagnesemia, and medical conditions or concomitant treatment with drugs with the potential of inducing such imbalance. These include anorexia, vomiting, and diarrhea.

4.4 Special warnings and special precautions for use

Elevated concentrations of terfenadine, whether due to terfenadine overdose, significant impairment of hepatic function or concomitant administration of inhibitors of CYP3A4, may cause QT interval prolongation with risk of life-threatening ventricular tachyarrhythmias (such as severe ventricular tachycardia, torsades de pointes, and ventricular fibrillation).

Patients having other conditions leading to QT prolongation may also be at risk of these cardiac reactions to terfenadine.

Terfenadine should be discontinued if symptoms such as palpitations, dizziness, syncope or convulsion occur, and the patient should be evaluated for QT prolongation and arrhythmias.

In the majority of cases where serious cardiac adverse reactions were reported as related to terfenadine, underlying predisposing conditions for arrhythmias were identified. This underlines the importance of careful adherence to the above mentioned contra-indications and safeguards.

See also section 4.3 and 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with inhibitors of the hepatic CYP 3A4 may result in a decrease of terfenadine metabolism. Accumulation of unmetabolised terfenadine may cause prolongation of the QT interval in the ECG with risk of life-threatening cardiac arrhythmias.

Pharmacokinetic interactions between terfenadine and the following medicinal products which inhibit the hepatic terfenadine metabolism are expected:
- azole antifungals / antimicrobials, such as miconazole, ketoconazole and itraconazole (including topical antifungals)

– macrolide antibiotics, such as erythromycin, clarithromycin, josamycin, and troleandomycin (including topical macrolide antibiotics)
– mibefradil dihydrochloride
– zileutone
– the serotonin reuptake inhibitors fluvoxamine, fluoxetine, nefazodone, paroxetine, citalopram
– the HIV protease inhibitors indinavir, ritonavir, saquinavir, nelfinavir.

Grapefruit juice should not be taken during terfenadine treatment because this may inhibit its metabolism.

Pharmacodynamic interactions between terfenadine and other potentially arrhythmogenic drugs may occur e.g.:
– other antihistamines that prolong QT interval
– antiarrhythmics, in particular those of class I and III
– bepridil
– trimethoprime
– sparfloxacin
– cisapride
– tricyclic antidepressants, neuroleptics, lithium
– probucol
– pentamidine
– halofantrine

Drugs known to induce electrolyte imbalance may also precipitate QT prolongation and thus interact with terfenadine.
These include
– diuretics and laxatives
– supraphysiological use of steroid hormones with mineralocorticoid potential (e.g. systemic fludrocortisone)

Concomitant treatment with the medicinal products mentioned in this section is contraindicated. These drugs are also referred to under section 4.3 (Contra-indications).
These lists may not be exhaustive, and any drug known to have the potential to either significantly inhibit terfenadine metabolism (via inhibition of CYP 3A4) or to prolong the QT interval should also not be used together with terfenadine.

Before co-administration of another drug, particularly a newly available drug, and terfenadine, product information of the other drug should be consulted to determine if an interaction (by CYP 3A4 inhibition or QT prolongation) between that drug and terfenadine is possible.

4.6 Use during pregnancy and lactation

Pregnancy
Teratogenic/non-teratogenic effects: No evidence of teratogenicity was observed in animal reproduction studies. Foetal toxicity was not observed in the absence of maternal toxicity.

Fertility effects: Studies with terfenadine in rats showed no effects on male or female fertility in the absence of maternal toxicity.

Terfenadine should not normally be used in pregnancy unless, in the opinion of the physician, potential benefits outweigh possible risks.

Lactation

The carboxylic acid metabolite (fexofenadine) is detectable in human breast milk after terfenadine administration. Therefore, infants should not be fed breast milk by a patient receiving terfenadine unless, in the physician's judgement, the potential benefit to the patient outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

In objective tests no adverse effects of terfenadine on the central nervous system have been detected. Reports of drowsiness are rare. This means that patients usually may drive or perform tasks requiring concentration. Patients should check their individual response before driving or performing complicated tasks.

4.8 Undesirable effects

Cardiovascular adverse reactions:
The most serious, although rare, adverse reactions which may be caused by terfenadine are those related to QT prolongation. These include serious potentially fatal ventricular tachyarrhythmias, such as severe ventricular tachycardia, torsades de pointes, ventricular fibrillation, and cardiac arrest. Early symptoms might be palpitations, while hypotension, dizziness, syncopes, and convulsions might be the consequences.

Other adverse reactions of various kinds have been reported spontaneously during marketing of terfenadine. These include:

- confusion, insomnia, depression, nightmares, drowsiness, fatigue, headache, dizziness
- tremor, sweating, paresthesia, visual disturbances
- anaphylaxis, angioedema, bronchospasm
- pruritus, skin eruption (including rash, urticaria, erythema multiforme and photosensitivity), hair loss or thinning
- dry mouth, nose, throat, gastrointestinal distress
- transaminase elevations, cholestasis, jaundice, hepatitis
- thrombocytopenia
- galactorrhea, menstrual disorders (including dysmenorrhea)
- increased urinary frequency
- musculoskeletal symptoms

4.9 Overdose

Human Experience
In some cases, QT prolongation, cardiac arrest and serious and potentially fatal arrhythmias including ventricular tachycardia or fibrillation or torsades de pointes have occurred at overdoses as low as 360 mg and up to 15 hours after the dose

Symptoms
Dry mouth, nausea, vomiting, tiredness, dizziness, confusion, headache, tremor, in some cases seizures. Sinus tachycardia, hypotension, palpitation, ventricular arrhythmias (mainly torsades de pointes). Cardiac reactions might occur without CNS symptoms.

Management
Cardiac monitoring for at least 24 hours and control of QT interval is recommended, along with standard measures to remove any unabsorbed drug.
Temporary cardiac pacing is the suggested mode of therapy in recurrent episode of torsades de pointes.

Hemodialysis or hemoperfusion does not effectively remove the carboxylic acid metabolite of terfenadine from blood. There is no information about the dialysability of terfenadine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic classification: Antihistamine H_1-antagonist, ATC-code: R06A X12.

Mechanism of action: Antagonistic effect on H_1-receptors.

Terfenadine is a substance with extensive first-pass metabolism and practically acts through its active metabolite carboxy terfenadine. The preparation exhibits specific antagonistic actions on H1-receptors and affects histamine-induced skin wheals with a maximum effect reached after 4 hours. In clinical dosage regimen, it causes neither anticholinergic, adrenergic or serotoninergic nor sedative effects.

With in vitro experiments, terfenadine, but not its active metabolite, has been shown to exhibit strong inhibitory actions on certain cardiac potassium channels, even at concentrations which might be reached in human plasma with moderate overdoses, in patients with significant impairment of hepatic function or concomitant treatment with CYP 3A4 inhibitors. This effect may explain the prolongation of cardiac repolarisation manifested as prolonged QT in cases of increased levels of unmetabolised terfenadine.

5.2 Pharmacokinetic properties

Terfenadine is fast absorbed and after oral administration undergoes almost complete first pass biotransformation into two metabolites formed by the enzyme CYP 3A4; the carboxy terfenadine metabolite (fexofenadine) is active, the other (N-dealkylated terfenadine) is inactive: As a consequence of this extensive first-pass biotransformation, less than 1% of unmetabolised terfenadine reaches systemic circulation. The terminal elimination half-life of carboxy terfenadine is about 20 hours. Following single dose terfenadine administration, plasma kinetics of this active metabolite were linear up to 180 mg. At therapeutic doses (60 mg twice daily), mean steady state peak plasma concentrations of 1.7 ng/ml for terfenadine and 340 ng/ml for carboxy terfenadine are observed. One third of the latter is excreted in urine and two thirds in faeces.

In patients with impaired liver function, increased plasma levels of terfenadine and decreased concentrations of carboxy terfenadine may be found (see also section 4.3).

Normal age-related decrease of renal function does not require dosage adjustment for terfenadine. However, dose reduction by 50% is advisable for patients with significant renal impairment, particularly with creatinine clearance below 40 ml/minute.

5.3 Preclinical safety data

In repeated dose toxicity studies in dogs, high dose levels induced some central nervous symptoms such as ataxia, trembling, rigidity and weakness. Lower doses were tolerated without adverse effects. Terfenadine has no specific mutagenic effects and long term studies in rats and mice revealed no carcinogenic potential.
Studies in rats and rabbits indicated no teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

One 30 mg tablet contains:

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6.2 Incompatibilities

None known

6.3 Shelf life

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6.4 Special precautions for storage

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6.5 Nature and contents of container

Pack sizes: see Annex A

7. MARKETING AUTHORISATION HOLDER

See Annex A

8. MARKETING AUTHORISATION NUMBER

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9. DATE FOR FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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