ANNEX I

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.

1. 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.

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 60 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 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.

2. 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 60 mg tablet formulations is acceptable and the Marketing Authorisations should be maintained provided that:

-the indications are restricted to adults and children over 12 years and 50 kg of body weight to avoid the likelihood of overdose in children.

-the Summaries of Product Characteristics (SPCs) are 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: Mrs 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 SUMMARIES 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 60 mg tablet formulations acceptable and that the Marketing Authorisations should be maintained provided that the SPC is amended as stated in Annex I.

the EMEA has recommended the maintenance of the Marketing Authorisations for terfenadine 60 mg tablet formulations in accordance with the draft SPC as stated in Annex I.

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 6 MG/ML ORAL SUSPENSION 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 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.

3. 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 6 mg/ml oral suspension formulations is acceptable and the Marketing Authorisations should be maintained provided that:
-the Summaries of Product Characteristics (SPCs) are 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: Mrs 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 SUMMARIES 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 6 mg/ml oral suspension formulations acceptable and that the Marketing Authorisations should be maintained provided that the SPC is amended as stated in Annex I.

the EMEA has recommended the maintenance of the Marketing Authorisations for terfenadine 6 mg/ml oral suspension formulations in accordance with the draft SPC as stated in Annex I.

ANNEX II

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

TERFENADINE 30 MG TABLET

Member State	3.1.1.1.1.1.1 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

TERFENADINE 60 MG TABLET FORMULATIONS

Member *3.1.1.1.1.2 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 60	14 28
Belgium	Cox Pharma Belgium Brixtonlaan 7 B-1930 Zaventem	Seldane 60	14 28
Denmark	Astra Danmark A/S Roskildevej 22 DK-2620 Albertslund	Teldanex	20 50 100
Denmark	Durascan Medical Products AS Svendborgvej 243 DK-5260 Odense S	Histanex	
Denmark	Stada Arzneimittel AG Stadastrasse 2-18 Bad Vilbel D-61118 Germany	Terfenadin "Stada"	
Finland	Suomen Astra OY PL 6 02431 Masala	Teldanex	10 20 50 100

France	Biogalenique 82 rue Curial 75019 Paris	Terfenadine RPG	14
France	Cassenne Marion (Merrel Dow) Tour Roussel Hoechst 92910 Paris la Défense Cedex	Teldane	14 30
France	Laboratoires Cox France Tour Roussel Hoechst 1 Terrasse Bellini 92910 Paris la Défense Cedex	Terfenadine Henning	14
France	Teva Pharma Mme Boutin 3 Parc Ariane Immeuble Saturne 78284 Guyancourt Cedex	Terfenadine Teva Pharma	14
Germany	Aliud Pharma GmbH & Co KG Gottlieb-Daimler-Strasse 19 D-89150 Laichingen	Terfenadin AL 60	20 50 100
Germany	Azupharma GmbH Dieselstrasse 5 D-70839 Gerlingen	Histaterfen	20 50 100
Germany	BASF Generics GmbH Carl-Zeiss-Ring 3 D-85737 Ismaning	Terfum	20 50 100 200
Germany	betapharm Arzneimittel GmbH Steinerne Furt 78 D-86167 Augsburg	Terfami	20 50 100 200 (5x40)
Germany	ct-Arzneimittel Chemische Tempelhof GmbH Lengeder Str. 42a	Terfenadin von ct	20 50

	D-13407 Berlin		100
Germany	ct-Arzneimittel Chemische Tempelhof GmbH Lengeder Str. 42a D-13407 Berlin	Terfenadin akut von ct	6
Germany	Dermapharm GmbH Arzneimittel Lochhamer Schlag 10 D-82166 Gräfelfing	Terfederm 60	20 50 100
Germany	Dolorgiet GmbH & Co KG Otto-von-Guericke-Str. 1 D-53754 Sankt Augustin	Aeroparan 60	20 50 250 (5x50)
Germany	Dr August Wolf GmbH & Co Arzneimittel Sudbrackstrasse 56 D-33611 Bielefeld	Hisfedin	20 50 100
Germany	Dr. Gerhard Mann Chem. Pharm. Fabrik GmbH Brunsbütteler Damm 165/173 13581 Berlin	Vividrin-Tabletten mit Terfenadin	20 50 100
Germany	Heumann Pharma GmbH Heideloffstrasse 18-28 D-90478 Nürnberg	Terfenadin 60 Heumann	20 50 100 500 (5x100)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Hexaterfen	20 50 100 200
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfat	20 50 100

			200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Lergium T 60	20 50 100 200 (5x40)
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfium	20 50 100
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Teldane 60	20 50 100 200 (10x20)
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Hisfedin	20 50 100
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Zeladin	20 50
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Terfenadin Merrel	10 50
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Terfenadin-ratiopharm	20 50
Germany	Karl Engelhard Fabrik pharm. Präparate GmbH & Co KG Sandweg 94 D-60316 Frankfurt	Terfen-Diolan	20 50 100
Germany	Logomed Pharma GmbH Eckenheimer Landstrasse 100-104 D-60318 Frankfurt	Logomed Allergie-tabletten	20 50 100

Germany	Mundipharma GmbH Mundipharmastrasse 2 D-65549 Limburg	Terfemundin Tabletten	20 50 100
Germany	Mundipharma GmbH Mundipharmastrasse 2 D-65549 Limburg	Terfemundin	20 50 100
Germany	ratiopharm GmbH Graf-Arco-Strasse 3 D-89079 Ulm	Terfenadin 60 Tabletten	20 50 100
Germany	Stadapharm GmbH Stadastrasse 2-18 D-61118 Bad Vilbel	Terfenadin 60 Stada	20 50 100
Germany	TAD Pharmazeutisches Werk GmbH Heinz-Lohmann-Strasse 5 D-27472 Cuxhaven	Terfenat T 60	20 50 100 200 (5x40)
Germany	Wyeth-Gruppe Durachemie GmbH & Co KG Schleebrüggenkamp 15 D-48159 Münster	Terfedura	20 50 100
Ireland	Hoechst Marion Roussel Broadwater Park Denham, Uxbridge Middlesex UB9 5HP UK	Triludan	10 60
Ireland	Norton Healthcare Gemini House Flex Meadow, Harlow Essex CM19 5TY UK	Terfenadine	60
Ireland	Norton Healthcare Gemini House Flex Meadow, Harlow Essex CM19 5TY	Terfenor	10 60

	UK		100
Italy	Astra Farmaceutici Via Messina 38 20154 Milan	Allerplus	30
Italy	Bruno Farmaceutici Via Castello della Magliana 38 00100 Rome	Allerzil	30
Italy	Hoechst Farmaceutici Via Garofalo 39 20133 Milan	Triludan	30
Italy	Lepetit Via R. Lepetit 8 20020 Lainate (MI)	Teldane	30
Luxembourg	Hexal A.G. Industriestrasse 25 D-83607 Holzkirchen Germany	Terfium 60 mg	20 50 100
Luxembourg	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels Belgium	Triludan 60 mg	28
Netherlands	Albic B.V. Govert van Wijnkade 48 3144 EG Maassluis	Terfenadine Albic 60	30
Netherlands	Apothecon PO 514 3440 AM Woerden	Terfenadine 60 A	10 30 300
Netherlands	B.V. Pharbita Ronde Tocht 11 1507 CC Zaandam	Terfenadine 60 "pharbita"	10 30 50 250
Netherlands	Centrafarm Services B.V. Nieuwe Donk 9 4879 AC Etten-Leur	Terfenadine CF 60	10 50

			100
Netherlands	Dumex B.V. Bothalaan 2 1217 JP Hilversum	Terfenadine Dumex 60	30 100
Netherlands	Eli Lilly Nederland B.V. Krijtwal 17-23 3432 ZT Nieuwegein	Terfenadine EB 60	30
Netherlands	Genfarma B.V. Sterrebaan 14 3606 EB Maarssen	Terfenadium 60	30
Netherlands	Hexal Pharma Nederland B.V. Pastoorslaan 28 2182 BX Hillegom	Terfenadine 60	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan OTC tablet 60	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Terfenadine YM tablet 60	30
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan	30
Netherlands	Katwijk farma B.V. Archimedesweg 2 2333 CN Leiden	Terfenadine 60 Katwijk	30
Netherlands	Multipharma B.V. Gemeenschapspolderweg 28 1382 GR Weesp	MP-Terfenadine 60	10 30 300
Netherlands	Pharmachemie B.V. Swensweg 5 2003 RN Haarlem	Terfenadine 60 PCH	30
Netherlands	Rhone-Poulenc Rorer B.V. Bovenkerkenweg 6-8 1185 XE Amstelveen	Terfenadine Pharbil 60	3 6 10

Netherlands	Samenwerkende Apothekers Nederland Europalaan 2 3526 KS Utrecht	Terfenadine 60 Bij overgevoeligheids reacties Samenwerkende Apothekers, tabletten 60 mg	10
Netherlands	Sudco B.V. Valkweg 12 6374 AE Landgraaf	Terfenadine 60	10 100
Portugal	Laboratorio Medinfar - Produtos Farmacêuticos, Lda Rua Manuel Ribeiro de Pavia, 1 -1 Venda Nova 2700 Amadora	Medoraxil	20
Portugal	Laboratórios Vitória Rua Elias Garcia, 28 Venda Nova 2700 Amadora	Terfax	20
Portugal	Hoechst Marion Roussel, Lda Estrada Nacional 249, Km 15 Apartado 39 2726 Mem Martins Codex	Triludan	20
Spain	Cantabria Industrial Farmaceutica Ctra de Cazona Adarzo s/n 39011 Santander	Ternadin	20 30
Spain	Ifidesa Aristegue Alameda de Urquijo, 27 48008 Bilbao	Rapidal	20 30
Spain	Marion Merrell, S.A. Rda. General Mitre, 72-74 08017 Barcelona	Triludan	20 30
Spain	Normon Nierenberg 10 28002 Madrid	Terfenadina Normon	20 30
Spain	Prodes Trabajo s/n San Justo de Desvern 08960 Barcelona	Alergist	20 30
Spain	Sigma Tau España SA Pl. Ind. Axque, Parcelas 13,14 Alcala de Henares	Cyater	20 30

	28806 Madrid		
Spain	Novartis Consumer Health Gran Via de las Cortes Catalanas, 764 08013 Barcelona	Aldira	20 30
Sweden	Tika Läkemedel AB Box 2 22100 Lund	Teldanex	20 50 98 100 250
United Kingdom	AH Cox & Co Ltd Whiddon Valley Barnstaple Devon EX32 8NS	Terfenadine	10 60
United Kingdom	Approved Prescription Services Ltd Brampton Road Hampden Park Eastbourne East Sussex BN22 9AG	Terfenadine (Histafen)	10 14 20 28 30 50 58 60
United Kingdom	Dallas Burston Healthcare Ltd c/o Ashbourne Pharmaceuticals Victors Barns Hill Farm Brixworth Northampton NN6 9DQ	Terfenadine	10 56 60 500
United Kingdom	Hoechst Marion Roussel Broadwater Park Denham, Uxbridge MIDDX UB9 5HP	Triludan	10 60

United Kingdom	Lagap Pharmaceuticals Ltd 37 Woolmer Way Bordon HANTS GU35 9QE	Terfenadine	60
United Kingdom	Norton Healthcare Gemini House Flex Meadow, Harlow Essex CM19 5TY	Terfenadine	10 20 50 60 100
United Kingdom	Penn Pharmaceuticals Ltd Tafarnaubach Industrial Estate Tredegar Gwent NP2 3AA	Terfex	10 28 30 56 60 100
United Kingdom	Sanofi Winthrop Ltd One Onslow Street Guilford Surrey GU16 5SG	Terfenadine	10 60
United Kingdom	Teva Pharma BV Industrieweg 23 PO Box 217 3640 AE Mijderecht Netherlands	Terfenadine	10 60 100 1000
United Kingdom	Wallis Laboratory Ltd Laporte Way Luton Beds LU4 8WL	Terfenadine	10 14 20 28 30 50 58 60

TERFENADINE 6 MG/ML ORAL SUSPENSION FORMULATIONS

Member State	Marketing Authorisation Holder	Product Name	*3.1.1.1.1.3 Pack Size* *3.1.1.1.1.4 (ml)*
Austria	Albert Roussel Pharma Altmansdorferstr. 104 1121 Wien	Triludan	120
Austria	Mundipharma GmbH Apollogasse 16-18 1072 Wien	Terlane	60
Belgium	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels	Triludan sirop	120
Belgium	Cox Pharma Belgium Brixtonlaan 7 B-1930 Zaventem	Seldane suspensie	120
Denmark	Astra Danmark A/S Roskildevej 22 DK-2620 Albertslund	Teldanex	
Denmark	Durascan Medical Products AS Svendborgvej 243 DK-5260 Odense S	Histanex	
Denmark	Stada Arzneimittel AG Stadastrasse 2-18 Bad Vilbel D-61118 Germany	Terfenadin "Stada"	
Finland	Suomen Astra OY PL 6 02431 Masala	Teldanex	300
France	Cassenne Marion (Merrel Dow) Tour Roussel Hoechst 92910 Paris la Défense Cedex	Teldane	90

Germany	ac-Pharma Vertriebs AG Frundsbergstr. 58 D-82064 Strasslach	Terdine	120
Germany	Azupharma GmbH Dieselstrasse 5 D-70839 Gerlingen	Azuterfenad	120
Germany	BASF Generics GmbH Carl-Zeiss-Ring 3 D-85737 Ismaning	Terfen-basan	120
Germany	Dermapharm GmbH Arzneimittel Lochhamer Schlag 10 D-82166 Gräfelfing	Terfederm Saft	120
Germany	Dolorgiet GmbH & Co KG Otto-von-Guericke-Str. 1 D-53754 Sankt Augustin	Balkis Saft Spezial	120
Germany	Dr August Wolf GmbH & Co Arzneimittel Sudbrackstrasse 56 D-33611 Bielefeld	Hisfedin Saft	120
Germany	Dr. Gerhard Mann Chem. Pharm. Fabrik GmbH Brunsbütteler Damm 165/173 13581 Berlin	Vividrin Saft mit Terfenadin	120
Germany	Heumann Pharma GmbH Heideloffstrasse 18-28 D-90478 Nürnberg	Terfenadin Suspension Heumann	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Hexaterfen S 30	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Teref S 30	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terf Inpharmco	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfami	120

Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfat S 30	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfium Suspension	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfen S 30	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfium	120
Germany	Hexal AG Industriestrasse 25 D-83607 Holzkirchen	Terfum S 30	120
Germany	Hoechst AG Brüningstrasse 50 D-65929 Frankfurt	Teldane K Suspension	120 480 (4x120)
Germany	Karl Engelhard Fabrik pharm. Präparate GmbH & Co KG Sandweg 94 D-60316 Frankfurt	Terf Sus Eng	120
Germany	Merz + Co GmbH & Co Eckenheimer Landstrasse 100-104 D-60318 Frankfurt	Terfenadin Merz Suspension	120
Germany	Mundipharma GmbH Mundipharmastrasse 2 D-65549 Limburg	Terfemundin suspension	120
Germany	ratiopharm GmbH Graf-arco-Strasse 3 D-89079 Ulm	Terfenadin-ratiopharm suspension	120
Germany	STADA Arzneimittel AG Stadastrasse 2-18 D-61118 Bad Vilbel	Terf Sus ST	120
Germany	TAD Pharmazeutisches Werk GmbH Heinz-Lohmann-Strasse 5 D-27472 Cuxhaven	Invocan	120

Germany	Wyeth-Gruppe Durachemie GmbH & Co KG Schleebrüggenkamp 15 D-48159 Münster	Terfedura Suspension	120
Ireland	Hoechst Marion Roussel Broadwater Park Denham, Uxbridge Middlesex UB9 5HP UK	Triludan Suspension	200
Italy	Bruno Farmaceutici Via Castello della Magliana 38 00100 Rome	Allerzil sospensione	120
Italy	Hoechst Farmaceutici Via Garofalo 39 20133 Milan	Triludan Sciroppo	120
Italy	Lepetit Via R. Lepetit 8 20020 Lainate (MI)	Teldane	120
Luxembourg	Hoechst Marion Roussel Rue Colonel Bourt, 155 1140 Brussels Belgium	Triludan suspension	120
Netherlands	Centrafarm Services B.V. Nieuwe Donk 9 4879 AC Etten-Leur	Terfenadium CF 6	120
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Terfenadine YM suspensie	200
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan	200
Netherlands	Hoechst Marion Roussel B.V. Bijenvlucht 30 3871 JJ Hoevelaken	Triludan OTC suspensie	200
Netherlands	Pharmachemie B.V. Swensweg 5 2003 RN Haarlem	Terfenadine 30=5 PCH suikervrij	200

Portugal	Laboratórios Vitória Rua Elias Garcia, 28 Venda Nova 2700 Amadora	Terfax	120
Portugal	Hoechst Marion Roussel, Lda Estrada Nacional 249, Km 15 Apartado 39 2726 Mem Martins Codex	Triludan	120
Spain	Ifidesa Aristegue Alameda de Urquijo, 27 48008 Bilbao	Rapidal	120
Spain	Marion Merrell, S.A. Rda. General Mitre, 72-74 08017 Barcelona	Triludan	120
Spain	Sigma Tau España SA Pl. Ind. Axque, Parcelas 13,14 Alcala de Henares 28806 Madrid	Cyater	120
Sweden	Tika Läkemedel AB Box 2 22100 Lund	Teldanex	300
United Kingdom	Hoechst Marion Roussel Broadwater Park Denham, Uxbridge MIDDX UB9 5HP	Triludan Suspension 30 mg/5 ml	30 200

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

TERFENADINE 30 MG TABLET

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:

.....

6.2 Incompatibilities

None known

6.3 Shelf life

.....

6.4 Special precautions for storage

.....

6.5 Nature and contents of container

Pack sizes: see Annex A

7. MARKETING AUTHORISATION HOLDER

See Annex A

8. MARKETING AUTHORISATION NUMBER

.....

9. DATE FOR FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

.....

10. DATE OF REVISION OF THE TEXT

.....

TERFENADINE 60 MG TABLET FORMULATIONS

1. TRADE NAME OF THE MEDICINAL PRODUCT

See Annex A

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
One tablet contains 60 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 60 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 (one tablet), increasing to 120 mg (two 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 (one tablet) twice daily. Alternatively, 120 mg (two 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 60 mg tablet contains:

.....

6.2 Incompatibilities

None known

6.3 Shelf life

.....

6.4 Special precautions for storage

.....

6.5 Nature and contents of container

Pack sizes: see Annex A

7. MARKETING AUTHORISATION HOLDER

See Annex A

8. MARKETING AUTHORISATION NUMBER

.....

9. DATE FOR FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

.....

10. DATE OF REVISION OF THE TEXT

.....

TERFENADINE 6 MG/ML ORAL SUSPENSION FORMULATIONS

1. TRADE NAME OF THE MEDICINAL PRODUCT

See Annex A

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
One ml of suspension contains 6 mg terfenadine.
For inactive ingredients see section 6.1

3. PHARMACEUTICAL FORM

Suspension

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 the suspension applies to children over 12 years only if their body weight exceeds 50 kg.

Allergic rhinitis and conjunctivitis:

Starting dose is 60 mg daily (10 ml), increasing to 120 mg (20 ml) daily if required.
The total daily dose may be taken as a single dose or in two divided doses.

Allergic skin disorders:

60 mg (10 ml) twice daily. Alternatively, 120 mg (20 ml) may be taken in the morning.

Children, 3-12 years:

Allergic rhinitis and conjunctivitis:

Start with a lower dose (1 mg per kg daily), increasing to upper dose (maximum dose 1 mg per kg twice daily), if required.

Allergic skin disorders:

Recommended and maximum dose 1 mg per kg twice daily.

Doses per body weight category:

12-20 kg: 15 mg (2,5 ml) daily, increase to 15 mg twice daily, if required
-30 kg: 22,5 mg (3,75 ml) daily, increase to 22,5 mg twice daily, if required
-40 kg: 30 mg (5 ml) daily, increase to 30 mg twice daily, if required
-50 kg: 45 mg (7,5 ml) daily, increase to 45 mg twice daily, if required
over 50 kg: 60 mg (10 ml) daily, increase to 60 mg twice daily, if required

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 ml suspension 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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