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EUROPEAN PHARMACOPOEIA 6th EDITION

published 16 July 2007

replaces the 5th Edition on 1 January 2008

Volumes 1 and 2 of this publication 6.0 constitute the 6th Edition of the European Pharmacopoeia. They will be complemented by **non-cumulative supplements** that are to be kept for the duration of the 6th Edition. 2 supplements will be published in 2007 and 3 supplements in each of the years 2008 and 2009. A cumulative list of reagents will be published in supplements 6.4 and 6.7.

If you are using the 6th Edition at any time later than 1 April 2008, make sure that you have all the published supplements and consult the index of the most recent supplement to ensure that you use the latest versions of the monographs and general chapters.

EUROPEAN PHARMACOPOEIA - ELECTRONIC VERSION

The 6th Edition is also available in an electronic format (CD-ROM and online version) containing all of the monographs and general chapters found in the printed version. With the publication of each supplement the electronic version is replaced by a new, fully updated, cumulative version.

In addition to the official English and French online versions, a Spanish online version is also available for the convenience of users.

PHARMEUROPA

Quarterly Forum Publication

Pharmeuropa contains preliminary drafts of all new and revised monographs proposed for inclusion in the European Pharmacopoeia and gives an opportunity for all interested parties to comment on the specifications before they are finalised. Pharmeuropa also contains information on the work programme and on certificates of suitability to monographs of the European Pharmacopoeia issued by the EDQM, and articles of general interest. Pharmeuropa is available on subscription from the EDQM. The subscription also includes Pharmeuropa Bio and Pharmeuropa Scientific Notes (containing scientific articles on pharmacopoeial matters). Pharmeuropa Online is also available as a complementary service for subscribers to the printed version of Pharmeuropa.

INTERNATIONAL HARMONISATION

See the information given in chapter 5.8. *Pharmacopoeial Harmonisation*.

WEBSITE

<http://www.edqm.eu>

<http://www.edqm.eu/store> (for prices and orders)

HELPDESK

To send a question or to contact the EDQM, use the HELPDESK, accessible through the EDQM website (visit http://www.edqm.eu/site/page_521.php).

KNOWLEDGE

Consult KNOWLEDGE, the new free database at <http://www.edqm.eu> to obtain information on the work programme of the European Pharmacopoeia, the volume of Pharmeuropa and of the European Pharmacopoeia in which a text has been published, trade names of the reagents (for example, chromatography columns) that were used at the time of the elaboration of the monographs, the history of the revisions of a text since its publication in the 5th Edition, reference chromatograms, the list of reference standards used, and the list of certificates granted.

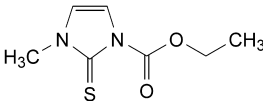
COMBISTATS

CombiStats is a computer program for the statistical analysis of data from biological assays in agreement with chapter 5.3 of the 6th Edition of the European Pharmacopoeia. For more information, visit the website (<http://www.edqm.eu/combistats>).

KEY TO MONOGRAPHS

Carbimazole

EUROPEAN PHARMACOPOEIA 6.0

Version date of the text	01/2008:0884 corrected 6.0
Text reference number	CARBIMAZOLE Carbimazolum
Modification to be taken into account from the publication date of volume 6.0	
CAS number	C ₇ H ₁₀ N ₂ O ₂ S [22232-54-8] <i>M_r</i> 186.2
Chemical name in accordance with IUPAC nomenclature rules	DEFINITION Ethyl 3-methyl-2-thioxo-2,3-dihydro-1 <i>H</i> -imidazole-1-carboxylate. <i>Content</i> : 98.0 per cent to 102.0 per cent (dried substance).
Application of the first and second identification is defined in the General Notices (chapter 1)	CHARACTERS <i>Appearance</i> : white or yellowish-white, crystalline powder. <i>Solubility</i> : slightly soluble in water, soluble in acetone and in ethanol (96 per cent). IDENTIFICATION <i>First identification</i> : B. <i>Second identification</i> : A, C. A. Melting point (2.2.14): 122 °C to 125 °C. B. Infrared absorption spectrophotometry (2.2.24). <i>Preparation</i> : discs. <i>Comparison</i> : carbimazole CRS. C. Thin-layer chromatography (2.2.27). <i>Test solution</i> . Dissolve 10 mg of the substance to be examined in methylene chloride <i>R</i> and dilute to 10 ml with the same solvent. <i>Reference solution</i> . Dissolve 10 mg of carbimazole CRS in methylene chloride <i>R</i> and dilute to 10 ml with the same solvent. <i>Plate</i> : TLC silica gel GF ₂₅₄ plate <i>R</i> . <i>Mobile phase</i> : acetone <i>R</i> / methylene chloride <i>R</i> (20:80 V/V). <i>Application</i> : 10 µl. <i>Development</i> : over a path of 15 cm. <i>Drying</i> : in air for 30 min. <i>Detection</i> : examine in ultraviolet light at 254 nm. <i>Results</i> : the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.
Reference standard available from the Secretariat (see www.edqm.eu)	
Reagents described in chapter 4	
Further information available on www.edqm.eu (KNOWLEDGE)	
Reference to a general chapter	TESTS Related substances . Liquid chromatography (2.2.29). <i>Test solution</i> . Dissolve 5.0 mg of the substance to be examined in 10.0 ml of a mixture of 20 volumes of acetonitrile <i>R</i> and 80 volumes of water <i>R</i> . Use this solution within 5 min of preparation. <i>Reference solution (a)</i> . Dissolve 5 mg of thiamazole <i>R</i> and 0.10 g of carbimazole CRS in a mixture of 20 volumes of acetonitrile <i>R</i> and 80 volumes of water <i>R</i> and dilute to 100.0 ml with the same mixture of solvents. Dilute 1.0 ml
Line in the margin indicating where part of the text has been modified (technical modification)	

of this solution to 10.0 ml with a mixture of 20 volumes of acetonitrile *R* and 80 volumes of water *R*.

Reference solution (b). Dissolve 5.0 mg of thiamazole *R* in a mixture of 20 volumes of acetonitrile *R* and 80 volumes of water *R* and dilute to 10.0 ml with the same mixture of solvents. Dilute 1.0 ml of this solution to 100.0 ml with a mixture of 20 volumes of acetonitrile *R* and 80 volumes of water *R*.

Column:

– *size*: *l* = 0.15 m, Ø = 3.9 mm,

– *stationary phase*: octadecylsilyl silica gel for chromatography *R* (5 µm).

Mobile phase: acetonitrile *R*, water *R* (10:90 V/V).

Flow rate: 1 ml/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µl.

Run time: 1.5 times the retention time of carbimazole.

Retention time: carbimazole = about 6 min.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to impurity A and carbimazole.

Limits:

– *impurity A*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent).

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in a desiccator over diphosphorus pentoxide *R* at a pressure not exceeding 0.7 kPa for 24 h.

Sulphated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

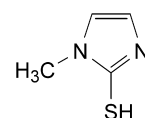
Dissolve 50.0 mg in water *R* and dilute to 500.0 ml with the same solvent. To 10.0 ml add 10 ml of dilute hydrochloric acid *R* and dilute to 100.0 ml with water *R*. Measure the absorbance (2.2.25) at the absorption maximum at 291 nm.

Calculate the content of C₇H₁₀N₂O₂S taking the specific absorbance to be 557.

IMPURITIES

Specified impurities: A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use* (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. *Control of impurities in substances for pharmaceutical use*): B.



A. 1-methyl-1*H*-imidazole-2-thiol (thiamazole),

See the information section on general monographs (cover pages)
General Notices (1) apply to all monographs and other texts

IMPORTANT NOTICE

GENERAL MONOGRAPHS

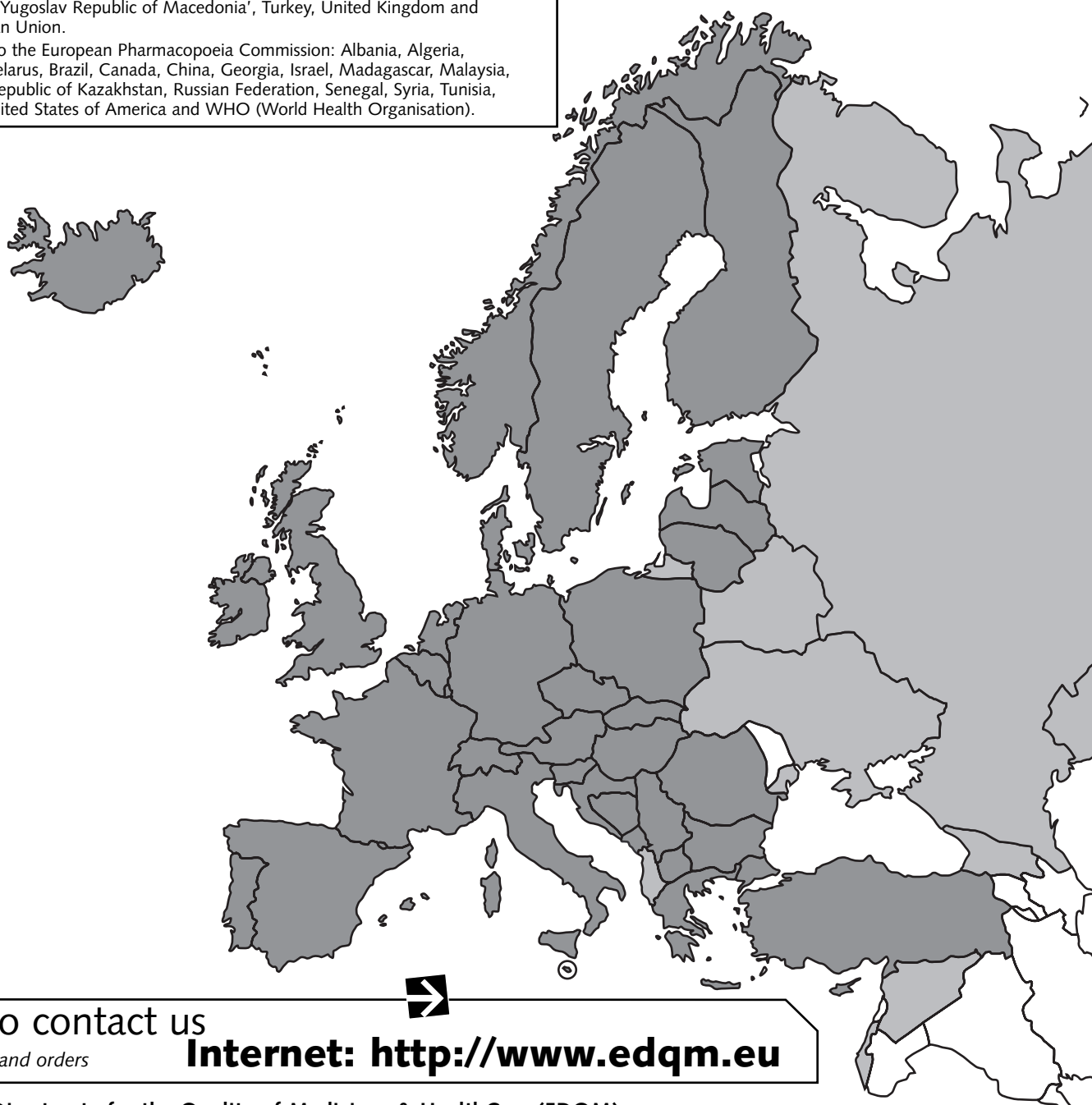
The European Pharmacopoeia contains a number of general monographs covering classes of products. These general monographs give requirements that are applicable to all products in the given class or, in some cases, to any product in the given class for which there is a specific monograph in the Pharmacopoeia (see *1. General Notices*, General monographs). Where no restriction on scope of a general monograph is given in a preamble, it is applicable to all products in the class defined, irrespective of whether there is an individual monograph for the product in the Pharmacopoeia.

Whenever a monograph is used, it is essential to ascertain whether there is a general monograph applicable to the product in question. The general monographs listed below are published in the section General Monographs (unless otherwise stated). This list is updated where necessary and republished in each Supplement.

Allergen products (1063)
Dosage Forms monographs
(published in the Dosage Forms section)
Essential oils (2098)
Extracts (0765)
Herbal drug preparations (1434)
Herbal drugs (1433)
Herbal drugs for homoeopathic preparations (2045)
(published in the Homoeopathic Preparations section)
Herbal teas (1435)
Homoeopathic preparations (1038)
(published in the Homoeopathic Preparations section)
Immunosera for human use, animal (0084)
Immunosera for veterinary use (0030)
Methods of preparation of homoeopathic stocks and potentisation (2371)
(published in the Homoeopathic Preparations section)
Monoclonal antibodies for human use (2031)
Mother tinctures for homoeopathic preparations (2029)
(published in the Homoeopathic Preparations section)
Products of fermentation (1468)
Products with risk of transmitting agents of animal spongiform encephalopathies (1483)
Radiopharmaceutical preparations (0125)
Recombinant DNA technology, products of (0784)
Substances for pharmaceutical use (2034)
Vaccines for human use (0153)
Vaccines for veterinary use (0062)
Vegetable fatty oils (1579)

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Correspondence Via the online HELPDESK (http://www.edqm.eu/site/page_521.php)

How to place an order

Publications <http://www.edqm.eu/store>

Reference standards <http://www.edqm.eu>

Reference standards online order form http://www.edqm.eu/site/page_649.php

Further information, including answers to the most frequently asked questions regarding ordering, is available via the HELPDESK.

All other matters info@edqm.eu

All reference standards required for application of the monographs are available from the EDQM. A catalogue of reference standards is available on request; the catalogue is included in the Pharmeuropa subscription; it can also be consulted on the EDQM website.

EUROPEAN PHARMACOPOEIA

SIXTH EDITION

Volume 2

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*Published in accordance with the
Convention on the Elaboration of a European Pharmacopoeia
(European Treaty Series No. 50)*



Council of Europe
Strasbourg

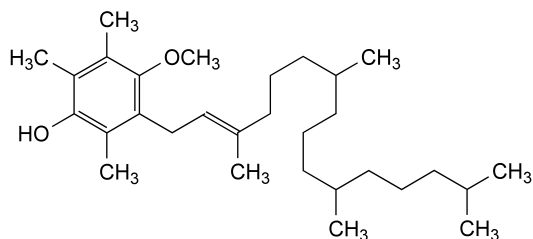
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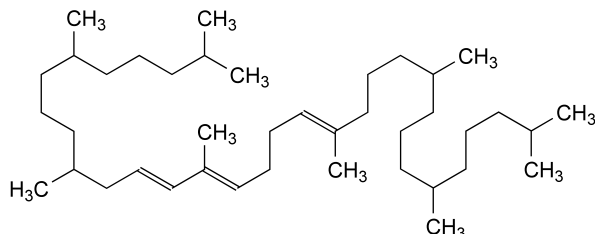
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ISBN: 978-92-871-6054-6

Printed in Germany by Druckerei C. H. Beck, Nördlingen



C. 4-methoxy-2,3,6-trimethyl-5-[(all-*RS,E*)-3,7,11,15-tetramethylhexadec-2-enyl]phenol,

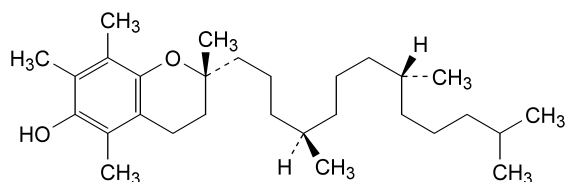


D. (all-*RS,all-E*)-2,6,10,14,19,23,27,31-octamethyldotriacont-12,14,18-triene.

01/2008:1256

RRR-α-TOCOPHEROL

RRR-α-Tocopherolum



$C_{29}H_{50}O_2$
[59-02-9]

M_r 430.7

DEFINITION

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R,8R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol.

Content: 94.5 per cent to 102.0 per cent.

CHARACTERS

Appearance: clear, colourless or yellowish-brown, viscous, oily liquid.

Solubility: practically insoluble in water, freely soluble in acetone, in anhydrous ethanol, in methylene chloride and in fatty oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

A. Optical rotation (2.2.7): + 0.05° to + 0.10°.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 ml with the same solvent.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison: *α*-tocopherol CRS.

C. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 10 mg of the substance to be examined in 2 ml of *cyclohexane R*.

Reference solution. Dissolve 10 mg of *α*-tocopherol CRS in 2 ml of *cyclohexane R*.

Plate: TLC silica gel F_{254} plate *R*.

Mobile phase: ether *R*, cyclohexane *R* (20:80 V/V).

Application: 10 µl.

Development: over 2/3 of the plate.

Drying: in a current of air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances. Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution. Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 ml with the same solvent.

Test solution (a). Dissolve 0.100 g of the substance to be examined in 10.0 ml of the internal standard solution.

Test solution (b). Dissolve 0.100 g of the substance to be examined in 10 ml of *cyclohexane R*.

Reference solution (a). Dissolve 0.100 g of *α*-tocopherol CRS in 10.0 ml of the internal standard solution.

Reference solution (b). Dissolve 10 mg of *α*-tocopherol *R* and 10 mg of *α*-tocopheryl acetate *R* in *cyclohexane R* and dilute to 100.0 ml with the same solvent.

Column:

- **material:** fused silica;
- **size:** $l = 30$ m, $\varnothing = 0.25$ mm;
- **stationary phase:** poly(dimethyl)siloxane *R* (film thickness 0.25 µm).

Carrier gas: helium for chromatography *R*.

Flow rate: 1 ml/min.

Split ratio: 1:100.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 15	280
Injection port		290
Detector		290

Detection: flame ionisation.

Injection: 1 µl of test solution (b) and reference solution (b).

System suitability: reference solution (b):

- **resolution:** minimum 3.5 between the peaks due to *α*-tocopherol and *α*-tocopheryl acetate.

Limits:

- **total:** maximum 4.0 per cent;
- **disregard limit:** 0.1 per cent.

The thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for pharmaceutical use (2034)* do not apply.

ASSAY

Gas chromatography (2.2.28) as described in the test for related substances with the following modification.

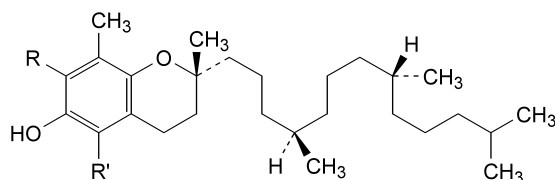
Injection: test solution (a) and reference solution (a).

Calculate the percentage content of $C_{29}H_{50}O_2$ taking into account the declared content of *α*-tocopherol CRS.

STORAGE

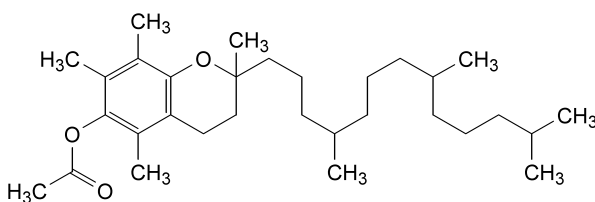
Under an inert gas, protected from light.

IMPURITIES



- A. $R = R' = H$: (2*R*)-2,8-dimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*- δ -tocopherol),
- B. $R = H$, $R' = CH_3$: (2*R*)-2,5,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*- β -tocopherol),
- C. $R = CH_3$, $R' = H$: (2*R*)-2,7,8-trimethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-2*H*-1-benzopyran-6-ol (*RRR*- γ -tocopherol).

01/2008:0439

all-*rac*- α -TOCOPHERYL ACETATEint-*rac*- α -Tocopherylis acetate

$C_{31}H_{52}O_3$
[7695-91-2]

 M_r 472.7

DEFINITION

all-*rac*-2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-1-benzopyran-6-yl acetate.

Content: 96.5 per cent to 102.0 per cent.

CHARACTERS

Appearance: clear, colourless or slightly greenish-yellow, viscous, oily liquid.

Solubility: practically insoluble in water, freely soluble in acetone, in anhydrous ethanol and in fatty oils.

IDENTIFICATION

First identification: A, B.

Second identification: A, C.

- A. Optical rotation (2.2.7): -0.01° to $+0.01^\circ$.

Dissolve 2.50 g in *anhydrous ethanol R* and dilute to 25.0 ml with the same solvent.

- B. Infrared absorption spectrophotometry (2.2.24).

Comparison: α -tocopheryl acetate CRS.

- C. Thin-layer chromatography (2.2.27).

Test solution. Dissolve about 10 mg of the substance to be examined in 2 ml of *cyclohexane R*.

Reference solution. Dissolve about 10 mg of α -tocopheryl acetate CRS in 2 ml of *cyclohexane R*.

Plate: TLC silica gel F_{254} plate *R*.

Mobile phase: ether *R*, *cyclohexane R* (20:80 V/V).

Application: 10 μ l.

Development: over 2/3 of the plate.

Drying: in a current of air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS

Related substances. Gas chromatography (2.2.28): use the normalisation procedure.

Internal standard solution. Dissolve 1.0 g of *squalane R* in *cyclohexane R* and dilute to 100.0 ml with the same solvent.

Test solution (a). Dissolve 0.100 g of the substance to be examined in 10.0 ml of the internal standard solution.

Test solution (b). Dissolve 0.100 g of the substance to be examined in 10 ml of *cyclohexane R*.

Reference solution (a). Dissolve 0.100 g of α -tocopheryl acetate CRS in 10.0 ml of the internal standard solution.

Reference solution (b). Dissolve 10 mg of the substance to be examined and 10 mg of α -tocopherol *R* in *cyclohexane R* and dilute to 100.0 ml with the same solvent.

Reference solution (c). Dissolve 10 mg of all-*rac*- α -tocopheryl acetate for peak identification CRS (containing impurities A and B) in *cyclohexane R* and dilute to 1 ml with the same solvent.

Reference solution (d). Dilute 1.0 ml of test solution (b) to 100.0 ml with *cyclohexane R*. Dilute 1.0 ml of this solution to 10.0 ml with *cyclohexane R*.

Column:

- *material*: fused silica;
- *size*: $l = 30$ m, $\varnothing = 0.25$ mm;
- *stationary phase*: poly(dimethyl)siloxane *R* (film thickness 0.25 μ m).

Carrier gas: helium for chromatography *R*.

Flow rate: 1 ml/min.

Split ratio: 1:100.

Temperature:

- *column*: 280 $^\circ$ C;
- *injection port and detector*: 290 $^\circ$ C.

Detection: flame ionisation.

Injection: 1 μ l of test solution (b) and reference solutions (a), (b), (c) and (d); inject directly onto the column or via a sufficiently inert, glass-lined injection port using an automatic injection device or other reproducible injection method.

Run time: twice the retention time of all-*rac*- α -tocopheryl acetate.

Identification of impurities: use the chromatogram supplied with all-*rac*- α -tocopheryl acetate for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention with reference to all-*rac*- α -tocopheryl acetate (retention time = about 15 min): squalane = about 0.4; impurity A = about 0.7; impurity B = about 0.8; impurity C = about 0.9; impurities D and E = about 1.05 (eluting immediately after the all-*rac*- α -tocopheryl acetate peak).

System suitability:

- *resolution*: minimum 3.5 between the peaks due to impurity C and all-*rac*- α -tocopheryl acetate in the chromatogram obtained with reference solution (b);