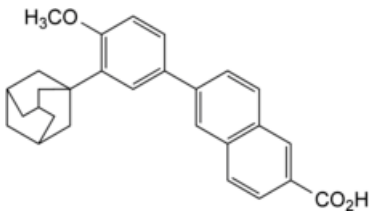
Edition: BP 2025 (Ph. Eur. 11.6 update)

Adapalene

General Notices

(Ph. Eur. monograph 2445)



$C_{28}H_{28}O_3$ 412.5 *106685-40-9*

Action and use

Vitamin A analogue (retinoid); treatment of acne.

Preparations

Adapalene Cream

Adapalene Gel

Ph Eur

DEFINITION

6-(4-Methoxy-3-tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl)naphthalene-2-carboxylic acid.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, sparingly soluble in tetrahydrofuran, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison adapalene CRS.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution BY_6 (2.2.2, Method II).

Dissolve 0.2 g in tetrahydrofuran R and dilute to 20 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture tetrahydrofuran R, acetonitrile R, water R (20:37:43 *V/V/V*).

Test solution (a) Dissolve 40.0 mg of the substance to be examined in 10 mL of tetrahydrofuran R, add 7 mL of the solvent mixture and dilute to 20.0 mL with tetrahydrofuran R.

Test solution (b) Dissolve 20.0 mg of the substance to be examined in 50 mL of tetrahydrofuran R, add 35 mL of the solvent mixture and dilute to 100.0 mL with tetrahydrofuran R. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 10.0 mL with tetrahydrofuran R. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.4 mg of adapalene impurity C CRS in 2 mL of tetrahydrofuran R and dilute to 20.0 mL with the same solvent. Dilute 2.0 mL of the solution to 20.0 mL with the solvent mixture. To 2.0 mL of this solution add 2.0 mL of reference solution (a) and dilute to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of adapalene for peak identification CRS (containing impurities A, C and D) in 0.5 mL of tetrahydrofuran R and dilute to 1.0 mL with the solvent mixture.

Reference solution (d) Dissolve 20.0 mg of adapalene CRS in 50 mL of tetrahydrofuran R, add 35 mL of the solvent mixture and dilute to 100.0 mL with tetrahydrofuran R. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped phenylsilyl silica gel for chromatography R (5 µm) with a carbon loading of 7.5 per cent;

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: glacial acetic acid R, water R (0.1:100 *V/V*);

— *mobile phase B*: tetrahydrofuran R, acetonitrile R (35:65 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2.5	50	50
2.5 - 40	50 → 28	50 → 72
40 - 42	28	72

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 270 nm.

Injection 25 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *adapalene for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, C and D.

Relative retention With reference to adapalene (retention time = about 20 min): impurity A = about 0.3; impurity C = about 0.9; impurity D = about 1.9.

System suitability Reference solution (b):

— *resolution*: minimum 4.5 between the peaks due to impurity C and adapalene;

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity C.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 0.7; impurity C = 7; impurity D = 1.4;

— *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

— *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 4 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

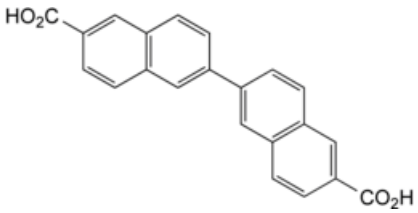
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of adapalene from the declared content of *adapalene CRS*.

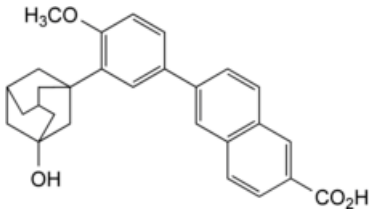
IMPURITIES

Specified impurities *A, C, D.*

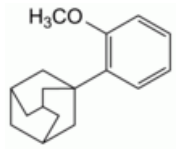
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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.*



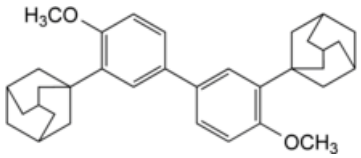
A. 2,2′-binaphthalene-6,6′-dicarboxylic acid,



B. 6-[3-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-4-methoxyphenyl]naphthalene-2-carboxylic acid,



C. 1-(2-methoxyphenyl)tricyclo[3.3.1.1^{3,7}]decane,



D. 1,1′-[4,4′-bis(methoxy)biphenyl-3,3′-diyl]bis(tricyclo[3.3.1.1^{3,7}]decane).

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