Adapalene

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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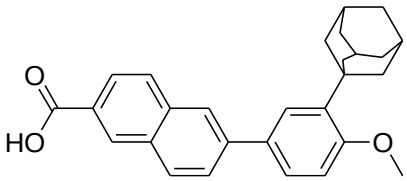
Adapalene



$C_{28}H_{28}O_3$ Mol. Wt. 412.5

Adapalene is 2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo [3.3.1.1^{3,7}]dec-1-ylphenyl)

Adapalene contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{28}H_{28}O_3$, calculated on the dried basis.

Category. Treatment of acne vulgaris

Description. A white or almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *adapalene IPRS* or with the reference spectrum of adapalene.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances.

NOTE- On the basis of the synthetic route, perform either Related substances A or Related substances B.

A. Determine by liquid chromatography (2.4.14). [*If adapalene related compounds A and B may be present.*]

Test solution. Dissolve 20 mg of the substance under examination in 5 ml of *tetrahydrofuran*, with the aid of ultrasound and dilute to 100.0 ml with the mobile phase.

Reference solution. Dissolve 3 mg of *adapalene related compound A IPRS* and 2 mg, each of, *adapalene IPRS* and *adapalene related compound B IPRS* in 5 ml of *tetrahydrofuran*, with the aid of ultrasound and dilute to 100.0 with the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil BDS C-18),
- mobile phase: a mixture of 42 volumes of *acetonitrile*, 32 volumes of *tetrahydrofuran*, 26 volumes of *water* and 0.02 volume of trifluoroacetic acid,
- flow rate: 1 ml per minute,
- spectrophotometer set at 235 nm,
- injection volume: 20 µl.

Name	Relative retention time
Adapalene related compound A[1]	0.52
Adapalene	1.0
Adapalene related compound B[2]	1.57

[1]methyl 6-bromo-2-naphthoate,
[2]methyl 6-[3-Adamantyl)-4-methoxyphenyl]-2-naphthoate.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 theoretical plates and the relative standard deviation for replicate injections is not more than 3.0 per cent, for adapalene peak.

Inject the reference solution and the test solution. Run the chromatogram twice the retention time of adapalene peak, for reference solution and six times the retention time of adapalene peak, for test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to adapalene related compound A is not more than 0.66 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent), the area of any peak corresponding to adapalene related compound B is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

B. Determine by liquid chromatography (2.4.14). [*If adapalene related compounds E, C and D may be present.*]

Solvent mixture. 37 volume of *acetonitrile,* 20 volumes of *tetrahydrofuran* and 43 volumes of *water.*

Test solution. Dissolve 100 mg of the substance under examination in 25 ml of *tetrahydrofuran,* with the aid of ultrasound and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.02 per cent w/v solution of *adapalene IPRS* in *tetrahydrofuran*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). a solution containing 0.02 per cent w/v of *adapalene IPRS* and 0.00012 per cent w/v of *adapalene related compound C IPRS,* and *adapalene related compound D IPRS* and *adapalene related compound E IPRS* in *tetrahydrofuran* (equivalent to 50% of the final volume) and dilute to volume with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with phenyl group bonded to porous silica (5 µm) (Such as Altima phenyl),
- mobile phase: A. a 0.1 per cent v/v solution of *glacial acetic acid* in *water,*
  B. a mixture of 65 volumes of *acetonitrile* and 35 volumes of *tetrahydrofuran,*
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 25 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	50	50
2.5	50	50
40	28	72
42	28	72
42.1	50	50
50	50	50

Name	Relative retention time	Correction factor
Adapalene related compound E[1]	0.3	0.71
Hydroxyadapalene[2]	0.5	1.1
Adapalene related compound C[3]	0.9	7.14
Adapalene	1.0	-
Adapalene related compound D[4]	1.9	1.41

[1]2,2'-binaphthyl-6,6'-dicarboxylic acid.
[2]6-[3-(3-Hydroxyadamant-1-yl)-4-methoxyphenyl]-2-naphthoic acid

[3]2-adamant-1-yl)methoxybenene
[4]4,4'-dimethoxy-3,3'-di(Adamant-1-yl)biphenyl

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to adapalene and adapalene related compound C is not less than 4.5 and the signal to noise ratio is not less than 10, for adapalene related compound C peak.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to adapalene related compound E is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to adapalene related compound D is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to hydroxyadapalene and adapalene related compound C, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Limit of Triethylamine. Not more than 80ppm

(NOTE—This test should be performed if triethylamine is used in the manufacturing process)

Determine by gas chromatography (2.4.13).

Test solution. Dissolve 0.5 g of the substance under examination in *dimethyl sulphoxide* and dilute to 10.0 ml with *dimethyl sulphoxide*. Transfer 4.0 ml of the solution to a 20-ml headspace vial and add 1.0 ml of 0*.1 M sodium hydroxide.*

Reference solution. A 0.0004 per cent w/v solution of *triethylamine IPRS* in *dimethyl sulphoxide*. Transfer 4.0 ml of the solution to a 20-ml headspace vial and add 1.0 ml of 0*.1 M sodium hydroxide.*

Chromatographic system
– a capillary column 30 m × 0.53 mm, packed with 5 per cent phenyl and 95 per cent methylpolysiloxane (film thickness 3 µm), (Such as Rtx-5 Amine),
– temperature:
– column. 40°, hold for 5 minutes, 40° to 240° @ 40° per minute, hold for 5 minutes,
– inlet port 250° and detector 300°,
– equilibration temperature. 95°,
– equilibration time: 15 minutes,
– transfer line temperature: 125°,
– pressurization time: 3 minutes,
– flame ionization detector,
– flow rate: 4.8 ml per minutes using nitrogen as the carrier gas,
– injection volume: 1 ml

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 15.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution the area of any peak corresponding to triethylamine is not more than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution.

Sulphated ash (2.3.18). Not more than 0.20 per cent.

Loss on drying (2.4.19). Not more than 0.6 per cent, determined by drying in an oven at 105° for 4 hours.

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances A with the following modifications.

Test solution. Dissolve 20 mg of the substance under examination in 5 ml of *tetrahydrofuran*, with the aid of ultrasound and dilute to 100.0 ml with the mobile phase. Dilute 2.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution. Dissolve 20 mg of *adapalene IPRS* in 5 ml of *tetrahydrofuran*, with the aid of ultrasound and dilute to 100.0 with the mobile phase. Dilute 2.0 ml of the solution to 10.0 ml with the mobile phase.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{28}H_{28}O_3$.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Labelling. If a test for Related substances other than Related substances A is used, the labelling states the test with which the article complies.

2.4.26 Solubility.

Adapalene. Soluble in *tetrahydrofuran*, sparingly soluble in *ethanol* and practically insoluble in *water*.