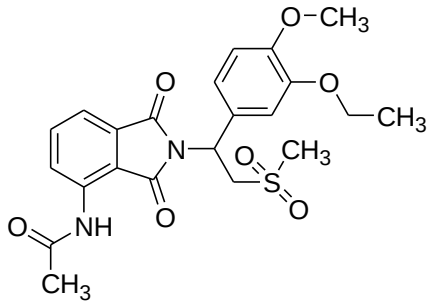
Apremilast



$C_{22}H_{24}N_2O_7S$ Mol. Wt. 460.5

Apremilast is N-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl)-1,3-dioxoisoindolin-4-yl) acetamide.

Apremilast contain not less than 98.0 per cent and not more than 102. 0 per cent of $C_{22}H_{24}N_2O_7S$, calculated on the dried basis.

Category. Antiinflammatory.

Description. White to yellow colour solid.

Identification

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

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. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in 100.0 ml of in *acetonitrile*.

Reference solution (a). A 0.02 per cent w/v solution of *apremilast RS* and 0.1 per cent w/v solution of *apremilast impurity B RS* in *acetonitrile*.

Reference solution (b). A 0.003 per cent w/v solution of *apremilast RS* in *acetonitrile*. Dilute 1.0 ml of the solution to 50.0 ml with *acetonitrile*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm stable bond packed with spherical porous silica protecting siloxane (5 µm) (Such as zorbax SB phenyl) or equivalent ,
- mobile phase: A. a 0.05 per cent v/v solution of *triflouroacetic acid* ,
  B. a mixture of 70 volumes of *acetonitrile*, 30 volumes of *methanol* and 0.05 volume of *triflouroacetic acid*,
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Time (in min.)	mobile phase A (per cent v/v)	mobile phase B (per cent v/v)
0.01	95	5
30	10	90
45	10	90
45.1	95	5
50	95	5

Inject reference solutions (a) and (b). The test is not valid unless the resolution between the peaks due to apremilast impurity B and apremilast is not less than 1.5 in the chromatogram obtained with reference solution (a), the tailing factor for apremilast peak is not more than 2.0 and the relative standard deviation of replicate injections for apremilast peak is not more than 10.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with test solution, the area of any peak (multiplied by correction factor 1.54) corresponding to apremilast impurity B is not more than 1.67 times the area of the principal peak obtained in the chromatogram with reference solution (b) (0.5 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 (b) (0.3 per cent). The sum of the areas of all the secondary peaks is not more than 3.34 times the area of the principal peak in the

chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.17 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Chiral purity. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the 10 ml of *methanol* and dilute to 25.0 ml with *methanol*.

Reference solution. A solution containing 0.2 per cent w/v of *apremilast RS* and 0.001 per cent w/v of *apremilast R-isomer RS* in *methanol*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm stable bond packed with cellulose tris (3,5-dimethylphenylcarbamate) coated on silica-gel (10 µm) (Such as chiralcel OD) ,
- column temperature: 40º,
- mobile phase: a mixture of 60 volumes of *hexane*, 20 volumes of *isopropanol* and 20 volumes of *ethanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to apremilast R- isomer and S- isomer is not less than 1.5.

Inject the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to R-isomer is not more than 0.5 per cent, calculated by area normalization.

Acetic acid content. Not more than 0.5 per cent.

Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of *acetonitrile* and 50 volumes of *water*.

Test solution. Dissolve 50 mg of the substance under examination in 25.0 ml of the solvent mixture.

Reference solution. A 0.025 per cent w/v solution of *sodium acetate trihydrate* in the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Chromatographic system

- a column 25 cm x 4.0 mm, packed with polyvinyl alcohol with quarternary ammonium groups (5µm) (Such as Metrosep A Supp-5),
- mobile phase: a mixture of 0.15 mM *sodium carbonate* and 0.3 mM g *sodium bicarbonate,*
- flow rate: 0.7 ml per minute,
- conductivity detector,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and test solution.

Calculate the content of CH_3COOH by multiplying the content of $C_2H_9NaO_5$ by 0.44.

Heavy metals (2.3.13). 2.0 g complies with the limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1 g by drying in an oven at 105° for 3 hours.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 10 mg of the substance under examination in 100.0 ml of *acetonitrile*.

Reference solution. A 0.01 per cent w/v solution of *apremilast RS* in *acetonitrile*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm stable bond packed with spherical porous silica siloxane bond (5 µm) (Such as Zorbax SB Phenyl) or equivalent,
- mobile phase: a mixture of 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.05 volume of *triflouroacetic acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{24}N_2O_7S$.

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

2.4.26 Solubility.

Apremilast. Soluble in *water.*