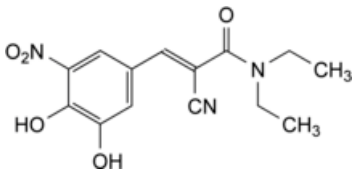
Edition: BP 2025 (Ph. Eur. 11.6 update)

Entacapone

General Notices

(Ph. Eur. monograph 2574)



$C_{14}H_{15}N_3O_5$ 305.3 *130929-57-6*

Action and use

Catechol-O-methyl transferase inhibitor; treatment of Parkinson's disease.

Ph Eur

DEFINITION

(2*E*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide.

Content

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

CHARACTERS

Appearance

Greenish-yellow or yellow powder.

Solubility

Practically insoluble in water, soluble or sparingly soluble in acetone, slightly soluble in anhydrous ethanol.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *entacapone CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use freshly prepared solutions.*

Solvent mixture *tetrahydrofuran R*, *methanol R* (30:70 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 5.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 5 mg of *entacapone impurity A CRS* in the solvent mixture, add 5.0 mL of test solution (a) and dilute to 25.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (b) to 100.0 mL with the solvent mixture.

Reference solution (c) Dissolve 50.0 mg of *entacapone CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. 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 propyl-2-phenylsilyl amorphous organosilica polymer R* (5 µm).

Mobile phase Mix 2 volumes of *tetrahydrofuran R*, 44 volumes of *methanol R* and 54 volumes of a 2.34 g/L solution of *sodium dihydrogen phosphate R* previously adjusted to pH 2.1 with *phosphoric acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 300 nm.

Injection 10 µL of test solution (a) and reference solutions (a) and (b).

Run time 2.5 times the retention time of entacapone.

Relative retention With reference to entacapone (retention time = about 17 min): impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 3.0 between the peaks due to impurity A and entacapone.

Limits:

— *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 (b) (0.10 per cent);

— *sum of impurities other than A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C.

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 (c).

Calculate the percentage content of $C_{14}H_{15}N_3O_5$ from the declared content of *entacapone CRS*.

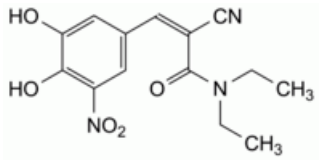
STORAGE

Protected from light.

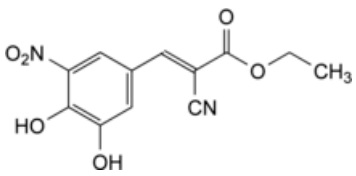
IMPURITIES

Specified impurities *A.*

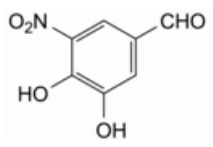
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



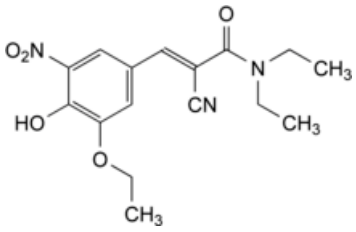
A. (2*Z*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide,



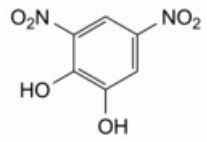
B. ethyl (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate,



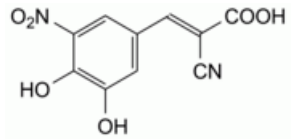
C. 3,4-dihydroxy-5-nitrobenzaldehyde,



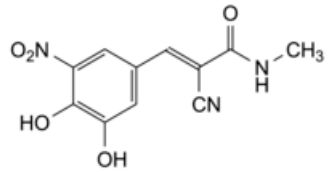
D. (2*E*)-2-cyano-3-(3-ethoxy-4-hydroxy-5-nitrophenyl)-*N*,*N*-diethylprop-2-enamide,



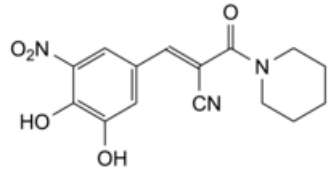
E. 3,5-dinitrobenzene-1,2-diol,



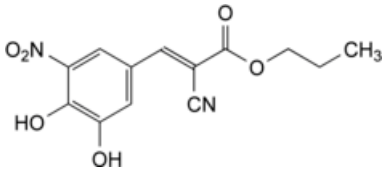
F. (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoic acid,



G. (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N*-methylprop-2-enamide,



H. (2*E*)-3-(3,4-dihydroxy-5-nitrophenyl)-2-(piperidin-1-ylcarbonyl)prop-2-ennitrile,



I. propyl (2*E*)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)prop-2-enoate.

Ph Eur