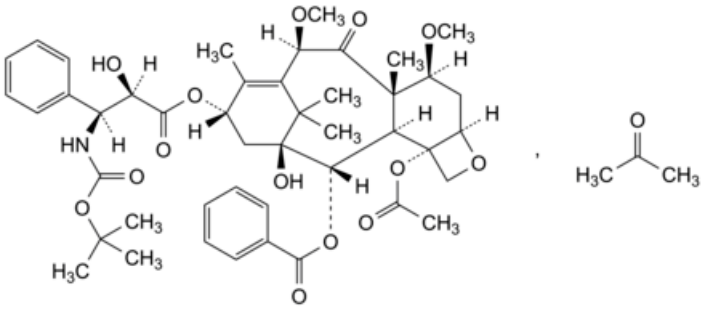
Edition: BP 2025 (Ph. Eur. 11.6 update)

Cabazitaxel Acetone

General Notices

(Ph. Eur. monograph 3060)



$C_{45}H_{57}NO_{14},C_3H_6O$ 894 *1426815-65-7*

Action and use

Taxane antineoplastic; treatment of prostate carcinoma.

Preparation

Cabazitaxel Concentrate for Infusion

Ph Eur

DEFINITION

4-(Acetyloxy)-13α-[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate as a solvate with propan-2-one.

Content

97.0 per cent to 102.0 per cent (anhydrous and acetone free substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison cabazitaxel acetone CRS.

B. Acetone (see Tests).

TESTS

Specific optical rotation (2.2.7)

-44 to -40 (anhydrous and acetone free substance).

Dissolve 0.125 g in methanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R previously adjusted to pH 4.0 with dilute phosphoric acid R1 (35:65 *V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in 20 mL of acetonitrile R and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 20.0 mL with the solvent mixture.

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

Reference solution (b) Dissolve 50.0 mg of cabazitaxel acetone CRS in 20 mL of acetonitrile R and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of cabazitaxel for peak identification CRS (containing impurities C, D, E, F and G) in 2 mL of acetonitrile R and dilute to 20 mL with the solvent mixture.

Reference solution (d) Dissolve 5 mg of cabazitaxel for system suitability CRS (containing impurity A) in 2 mL of acetonitrile R and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped solid core octadecylsilyl silica gel for chromatography R (2.7 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile for chromatography R, water for chromatography R (35:65 *V/V*);

— *mobile phase B*: water for chromatography R, acetonitrile for chromatography R (25:75 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 9	100 → 62	0 → 38
9 - 38	62 → 22	38 → 78

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 230 nm.

Autosampler Set at 10 °C.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *cabazitaxel for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C, D + E, F and G; use the chromatogram supplied with *cabazitaxel for system suitability CRS* and the chromatogram obtained with reference solution (d) to identify the peak due to impurity A.

Relative retention With reference to cabazitaxel (retention time = about 16 min): impurity A = about 0.9; impurity C = about 1.4; impurities D + E = about 1.8; impurity F = about 1.9; impurity G = about 1.95.

System suitability Reference solution (d):

— *resolution*: minimum 1.5 between the peaks due to cabazitaxel and impurity A.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurities D + E = 1.4; impurity F = 0.7;

— for each impurity, use the concentration of cabazitaxel acetone in reference solution (a).

Limits:

— *impurities A, G*: for each impurity, maximum 0.2 per cent;

— *sum of impurities D and E*: maximum 0.2 per cent;

— *impurities C, F*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.8 per cent;

— *reporting threshold*: 0.05 per cent.

Acetone

Head-space gas chromatography (*2.2.28*).

Internal standard solution Mix 1.0 mL of *methyl isobutyl ketone R* and 10 mL of *dimethyl sulfoxide R*, and dilute to 100.0 mL with *dimethyl sulfoxide R*.

Test solution Dissolve 0.100 g of the substance to be examined in 1.0 mL of the internal standard solution and dilute to 10.0 mL with *dimethyl sulfoxide R*.

Reference solution Mix 0.650 g of *acetone R* and 10 mL of *dimethyl sulfoxide R*, and dilute to 20.0 mL with *dimethyl sulfoxide R*. To 1.0 mL of this solution add 5.0 mL of internal standard solution and dilute to 50.0 mL with *dimethyl sulfoxide R*.

Close the vials immediately with a butyl rubber membrane stopper coated with polytetrafluoroethylene and secured with an aluminium crimp cap. Mix to obtain a homogeneous solution.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *trifluoropropylmethylpolysiloxane R* (film thickness 1 µm).

Carrier gas *helium for chromatography R*.

Flow rate 2.5 mL/min.

Split ratio 1:20.

Static head-space conditions that may be used:

— *equilibration temperature*: 110 °C;

— *equilibration time*: 15 min;

— *injection time*: 1 min;

— *injection volume*: 1.0 mL.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 6	35
	6 - 11.5	35 → 120
	11.5 - 15.5	120 → 220
	15.5 - 25.5	220
Injection port		200
Detector		250

Detection FLame ionisation.

Identification of peaks Use the chromatogram obtained with the reference solution to identify the peak due to acetone.

Relative retention With reference to methyl isobutyl ketone (retention time = about 9.7 min): acetone = about 0.4.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 3.0 per cent determined on 3 injections.

Calculation of percentage content Use the internal standard method.

Limit:

— *acetone*: 5.0 per cent *m/m* to 7.0 per cent *m/m*.

Water (*2.5.32*)

Maximum 1.0 per cent, determined on 200 mg by direct sample introduction. [*Stir for a minimum of 180 s.*]

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14, Method D*)

Solution A A 0.20 mg/mL solution of the substance to be examined in a 0.25 per cent *V/V* solution of *polysorbate 80 R*.

Solution C A 0.5 per cent *V/V* solution of *polysorbate 80 R*.

ASSAY

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

Injection Test solution and reference solution (b).

Calculate the percentage content of $C_{45}H_{57}NO_{14}$ taking into account the assigned content of *cabazitaxel acetone CRS*.

STORAGE

At a temperature of 2 °C to 8 °C.

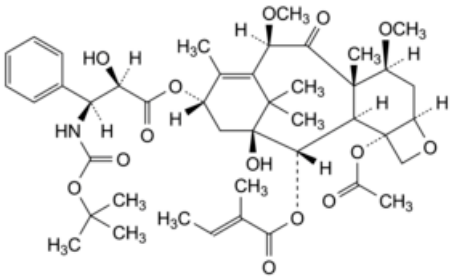
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

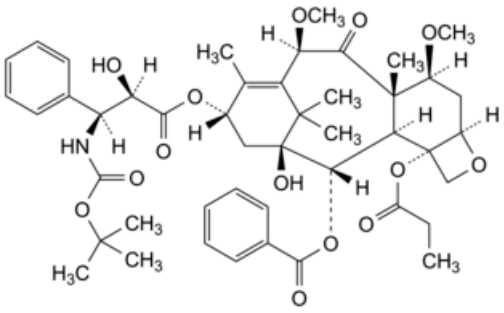
IMPURITIES

Specified impurities A, C, D, E, F, G.

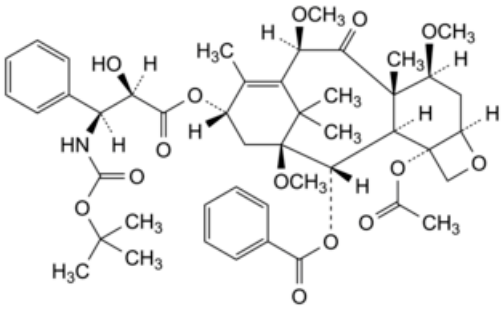
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



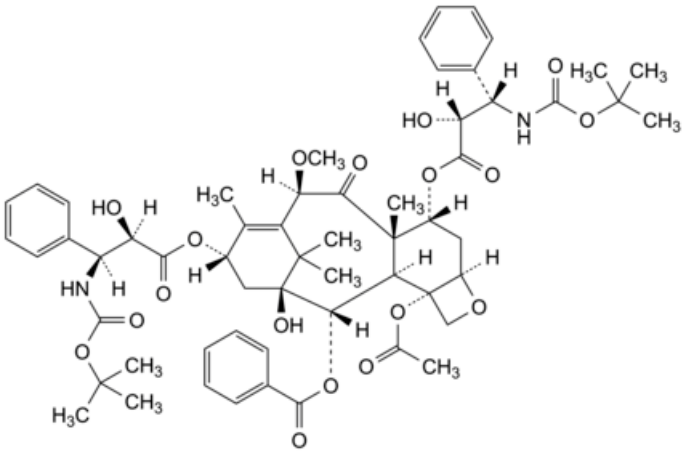
A. 4-(acetyloxy)-13α-[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl (2*E*)-2-methylbut-2-enoate,



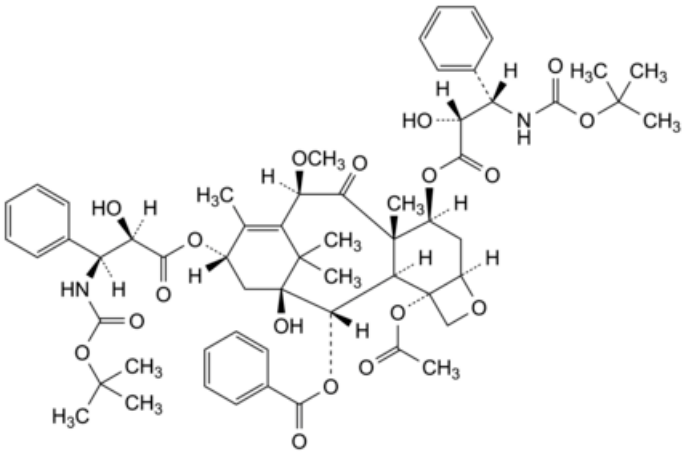
B. 13α-[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-7β,10β-dimethoxy-9-oxo-4-(propanoyloxy)-5β,20-epoxytax-11-en-2α-yl benzoate,



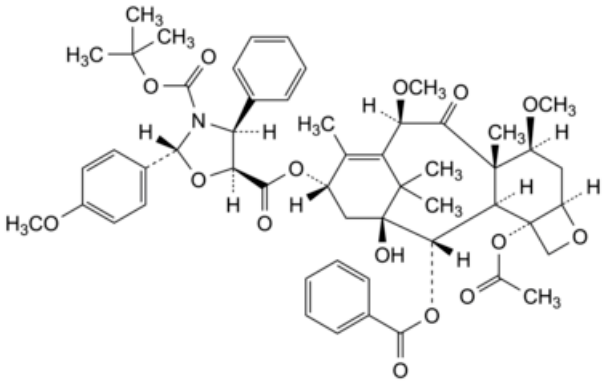
C. 4-(acetyloxy)-13α-[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1,7β,10β-trimethoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate,



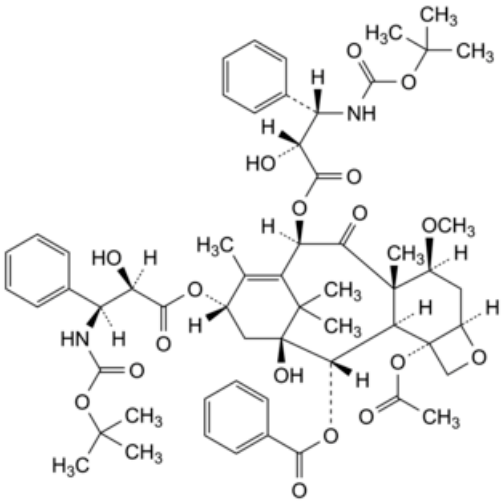
D. 4-(acetyloxy)-7α,13α-bis[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-10β-methoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate,



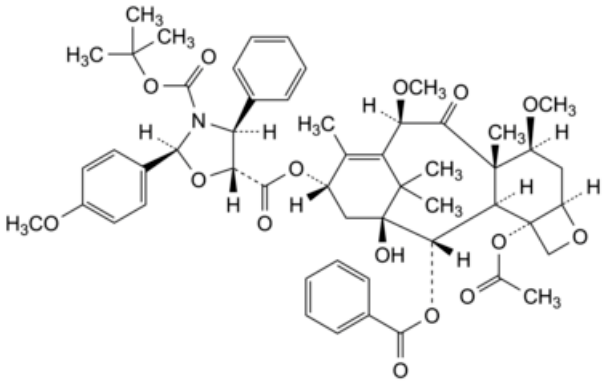
E. 4-(acetyloxy)-7β,13α-bis[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-10β-methoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate,



F. 5-[4-(acetyloxy)-2α-(benzoyloxy)-1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-en-13α-yl] 3-*tert*-butyl (2*R*,4*S*,5*S*)-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate,



G. 4-(acetyloxy)-10β,13α-bis[[(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl]oxy]-1-hydroxy-7β-methoxy-9-oxo-5β,20-epoxytax-11-en-2α-yl benzoate,



H. 5-[4-(acetyloxy)-2α-(benzoyloxy)-1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-en-13α-yl] 3-*tert*-butyl (2*S*,4*S*,5*R*)-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate.

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