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Doxazosin Prolonged-release Tablets

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 1
Contact Details	michael.whaley@mhra.gov.uk graziella.li-ship@mhra.gov.uk maryna.dmitriieva@mhra.gov.uk
Deadline for Comment	30th June 2023
Target Publication Date (subject to change)	BP 2025
Notes	**NEW MONOGRAPH** If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Doxazosin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

Action and use

Alpha$_1$-adrenoceptor antagonist.

DEFINITION

Doxazosin Prolonged-release Tablets contain Doxazosin Mesilate. They are formulated so that the medicament is released over a period of several hours.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Doxazosin Mesilate. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

Risk assessment should be used to evaluate the potential for mutagenic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

Content of doxazosin, $C_{23}H_{25}N_5O_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 1 volume of mobile phase B and 9 volumes of mobile phase A.

(1) Shake a quantity of powdered tablets containing the equivalent of 20 mg of doxazosin in 150 mL and mix with the aid of ultrasound. Dilute to produce 250 mL and filter (a 0.45-µm regenerated cellulose membrane filter is suitable).
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.008% w/v of *doxazosin impurity standard BPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil (or Kromasil) 100-5 C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 246 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of doxazosin.

MOBILE PHASE

Mobile phase A Dissolve 1.5 g of *orthophosphoric acid* in *water* and dilute to 1000 mL with *water.*.

Mobile phase B Dissolve 1.5 grams of *orthophosphoric acid* in *acetonitrile R1* and dilute to 1000 mL with *acetonitrile R1.*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-5	90	10	isocratic
5-40	90→50	10→50	linear gradient
40-45	50	50	isocratic
45-46	50→90	50→10	linear gradient
46-50	90	10	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity D and impurity F is at least 10.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of doxazosin in solution (2).

For the reporting threshold, use the concentration of doxazosin in solution (4).

Doxazosin retention time: about 32 minutes.

Relative retention: impurity G, about 0.18; impurity D, about 0.49; impurity F, about 0.65.

LIMITS

— impurity G: not more than 0.5%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution B.

Solution B Dissolve 1.5 grams of *orthophosphoric acid* in a mixture of 1 volume *acetonitrile* and 9 volumes of *water* and dilute to 1000 mL with the same solvent mixture.

(1) Shake a quantity of powdered tablets containing the equivalent of 20 mg of doxazosin in 150 mL and mix with the aid of ultrasound. Dilute to produce 250 mL and filter (a 0.45-µm regenerated cellulose membrane filter is suitable).
(2) 0.0097% w/v of *doxazosin mesilate BPCRS*.
(3) 0.008% w/v of *doxazosin impurity standard BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between doxazosin and impurity F is at least 10.

DETERMINATION OF CONTENT

Calculate the content of doxazosin, $C_{23}H_{25}N_5O_5$, in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{25}N_5O_5,CH_4O_3S$ in *doxazosin mesilate BPCRS*.

Each mg of $C_{23}H_{25}N_5O_5,CH_4O_3S$ is equivalent to 0.824 mg of $C_{23}H_{25}N_5O_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of doxazosin.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity G listed under Doxazosin Mesilate.