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Clopidogrel Oral Suspension

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

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Notes:	New monograph

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Inhibitor of ADP-mediated platelet aggregation.

DEFINITION

Clopidogrel Oral Suspension is a suspension of Clopidogrel Hydrogen Sulfate in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of clopidogrel, $C_{16}H_{16}ClNO_2S$

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).

B. Yields the reactions characteristic of *sulfates*, Appendix VI.

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

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

(1) To a volume of the oral suspension containing the equivalent of 75 mg of clopidogrel, add 60 mL of *methanol* and mix with the aid of ultrasound. Add 40 mL of the mobile phase, shake and then dilute to produce 200 mL and filter (a 0.45-µm nylon filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.375% w/v of *clopidogrel for system suitability EPCRS* and 0.00375% w/v of *clopidogrel impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.
(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *protein derivative of silica gel for chiral separation* (5 µm) (Ultron ES-OVM is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.01M *potassium dihydrogen orthophosphate*

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	87	13	isocratic
3-3.1	87→75	13→25	linear gradient
3.1-25	75	25	isocratic
25-25.1	75→87	25→13	linear gradient
25.1-30	87	13	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and clopidogrel is at least 1.5.

CALCULATION OF IMPURITIES

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

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

For peak identification, use solution (3).

Clopidogrel retention time: about 9 minutes.

Relative retention: impurity A, about 0.4; impurity B, about 0.9; about 1.2; impurity C, about 1.7.

LIMITS

— impurity C: not more than 1.5%;

— impurity A: not more than 1.2%;

— impurity B: not more than 0.3%;

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

— total impurities: not more than 2.5%;

— reporting threshold: 0.1%.

ASSAY

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

(1) To a volume of the oral suspension containing the equivalent of 75 mg of clopidogrel, add 50 mL of *methanol* and mix with the aid of ultrasound. Dilute to produce 100 mL with methanol. Dilute 1 volume to 20 volumes with mobile phase and filter (a 0.45-µm nylon filter is suitable).
(2) 0.1% w/v of *clopidogrel hydrogen sulfate BPCRS* in *methanol*. Dilute 1 volume to 20 volumes with the mobile phase.
(3) 0.375% w/v of *clopidogrel for system suitability EPCRS* and 0.00375% w/v of *clopidogrel impurity A EPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and clopidogrel is at least 1.5.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of clopidogrel, $C_{16}H_{16}ClNO_2S$, in the oral suspension from the chromatograms obtained and using the declared content of $C_{16}H_{16}ClNO_2S,H_2SO_4$ in *clopidogrel hydrogen sulfate BPCRS*.

Each mg of $C_{16}H_{16}ClNO_2S,H_2SO_4$ is equivalent to 0.7664 mg of $C_{16}H_{16}ClNO_2S$.

LABELLING

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

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Clopidogrel Hydrogen Sulfate.