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Aripiprazole Oral Solution

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

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Notes	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Dopamine D_2 receptor antagonist; neuroleptic.

DEFINITION

Aripiprazole Oral Solution is a solution containing Aripiprazole in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of aripiprazole, $C_{23}H_{27}Cl_2N_3O_2$

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 200 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.

Solution A Equal volumes of *acetonitrile* and *methanol*.

Solution B Dissolve 1.11 g of *potassium dihydrogen orthophosphate* in 1000 mL of water.

Solution C 28 volumes of solution B and 72 volumes of *acetonitrile*.

(1) Mix with the aid of ultrasound a volume of the oral solution containing 25 mg of Aripiprazole with 15 mL of solution A, dilute to 50 mL with solution B and filter (a regenerated cellulose 0.45 µm filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes with solution C. Dilute 1 volume of this solution to 2 volumes with solution C.
(3) 0.05% w/v of *aripiprazole impurity mixture BPCRS* in solution B.
(4) Dilute 1 volume of solution (2) to 5 volumes with solution C.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use an autosampler temperature of 5°.
(f) Use a detection wavelength of 215 nm.
(g) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Equal volumes of solution A and 0.12% w/v of *sodium pentanesulfonate*, previously adjusted to pH 3.0 with 10% v/v of *orthophosphoric acid*.

Mobile phase B *Acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-10	72→70	28→30	linear gradient
10-40	70→60	30→40	linear gradient
40-50	60→37	40→63	linear gradient
50-60	37	63	isocratic
60-61	37→72	63→28	linear gradient
61-70	72	28	re-equlibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to aripiprazole (retention time about 32 minutes) are: impurity F, about 1.1; impurity E, about 0.9; impurity 2, about 0.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between impurity E and aripiprazole is at least 3.0;

the *resolution* between aripiprazole and impurity F is at least 3.0.

CALCULATION OF IMPURITIES

For impurities E, F and 2, use the concentration of aripiprazole in solution (2).

For any *unspecified impurities*, use the concentration of aripiprazole in solution (4).

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

For peak identification, use solution (3).

Aripiprazole retention time: about 32 minutes.

Relative retention (in elution order): impurity A, about 0.1; impurity B, about 0.3; impurity E, about 0.9; impurity 2, about 0.9; impurity 1, about 0.9; impurity F, about 1.1.

LIMITS

— impurity E and F: for each impurity, not more than 0.5%;

— impurity 2: not more than 0.4%;

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

— total impurities: not more than 1%;

— reporting threshold: 0.1%.

ASSAY

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

(1) Mix with the aid of ultrasound a volume of the oral solution containing 10 mg of Aripiprazole with 40 mL of *acetonitrile* and 30 mL of a 0.2% v/v solution of *orthophosphoric acid*. Dilute to 100 mL with 0.2% v/v solution of *orthophosphoric acid* and filter through a 0.45-µm filter.
(2) Mix with the aid of ultrasound 0.1 g of *aripiprazole BPCRS* in 5 mL of *dichloromethane*, and dilute to 100 mL with *acetonitrile*. Dilute 1 volume of this solution to 10 volumes with a 0.2% v/v solution of *orthophosphoric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 3.0 mm) packed with *end-capped cyanosilyl silica gel for chromatography* (2.7 µm) (Poroshell 120 EC-CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 2 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile* and 70 volumes of a solution containing 0.264% w/v of *diammonium hydrogen orthophosphate* in *water* previously adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to aripiprazole is about 4 minutes.

DETERMINATION OF CONTENT

Calculate the content of aripiprazole, $C_{23}H_{27}Cl_2N_3O_2$, in the oral solution from the chromatograms obtained and using the declared content of $C_{23}H_{27}Cl_2N_3O_2$ in *aripiprazole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B, E and F listed under Aripiprazole and:

 1. 1-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl-7-hydroxy-3,4-dihydrocarbostyril

1. 1-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butyl-7-hydroxy-3,4-dihydrocarbostyril

 2. 7-[4-[[2-[(2,3-Dichlorophenyl)amino]ethyl]amino]butoxy]-3,4-dihydro-2(1H)-quinolinone

2. 7-[4-[[2-[(2,3-Dichlorophenyl)amino]ethyl]amino]butoxy]-3,4-dihydro-2(1H)-quinolinone