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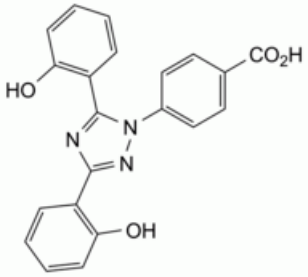
Deferasirox

General Notices

(Ph. Eur. monograph 2933)



$C_{21}H_{15}N_3O_4$ 373.4 *201530-41-8*

Action and use

Selective iron(III) chelator; treatment of iron overload

Preparation

Deferasirox Dispersible Tablets

Ph Eur

DEFINITION

4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.

Content

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

CHARACTERS

Appearance

White or slightly yellow powder.

Solubility

Practically insoluble in water, very soluble in dimethyl sulfoxide, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison deferasirox CRS.

TESTS

Related substances

Liquid chromatography (2.2.29). *Use only colourless glassware. Store the solutions at 2-8 °C.*

Buffer solution 0.100 g/L solution of sodium edetate R adjusted to pH 2.1 with phosphoric acid R.

Solvent mixture 0.040 g/L solution of sodium edetate R, acetonitrile R (25:75 *V/V*).

Test solution (a) Dissolve 30.0 mg of the substance to be examined in 15 mL of the solvent mixture with vigorous shaking (this may take up to 20 min) and dilute to 20.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of deferasirox CRS in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of deferasirox for system suitability A CRS (containing impurity D) in 1.0 mL of the solvent mixture.

Reference solution (d) Dissolve 3.0 mg of deferasirox impurity B CRS in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 100.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R (3.5 µm);

— *temperature*: 60 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, buffer solution, water for chromatography R (10:10:80 *V/V/V*);

— *mobile phase B*: buffer solution, acetonitrile R (10:90 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	62	38
10 - 14	62 → 0	38 → 100
14 - 16	0	100

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

Injection 5 µL of test solution (a) and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with *deferasirox for system suitability A CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to deferasirox (retention time = about 10 min): impurity B = about 0.5; impurity D = about 0.95.

System suitability:

— *resolution*: minimum 1.5 between the peaks due to impurity D and deferasirox in the chromatogram obtained with reference solution (c);

— *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— for each impurity, use the concentration of deferasirox in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.2 per cent;

— *reporting threshold*: 0.03 per cent.

Impurity F

Liquid chromatography (2.2.29). *Protect the solutions from light*.

Solvent mixture *phosphoric acid R*, *water R*, *acetone R* (25:100:900 *V/V/V*).

Test solution Dissolve 0.600 g of the substance to be examined in 1 mL of *dimethyl sulfoxide R*, add 2 mL of the solvent mixture and mix thoroughly using a vortex mixer. Heat the solution at 45 °C for 35 min, then cool to 2-8 °C for 1 h. Dilute to 5.0 mL with mobile phase A, previously cooled to 2-8 °C. Shake vigorously using a mechanical shaker for 2 min. Centrifuge immediately at 4000 *g* for 5 min and filter the supernatant through a membrane filter (nominal pore size 0.45 µm). If a precipitation is still observed, allow to stand for 1 h at 2-8 °C. Filter again through a membrane filter (nominal pore size 0.45 µm) immediately before injection.

Reference solution (a) Dissolve 6.0 mg of *deferasirox impurity F CRS* in 1 mL of *dimethyl sulfoxide R* and dilute to 20.0 mL with *water R*. Dilute 1.0 mL of the solution to 10.0 mL with *dimethyl sulfoxide R*.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *dimethyl sulfoxide R*. To 1.0 mL of this solution add 5 mL of *dimethyl sulfoxide R* and 20 mL of the solvent mixture. Heat this solution at 45 °C for 35 min, cool to 2-8 °C and dilute to 50.0 mL with mobile phase A, previously cooled to 2-8 °C.

Reference solution (c) To 2.0 mL of reference solution (b) add 1 mL of *dimethyl sulfoxide R* and 4 mL of the solvent mixture and dilute to 10.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *phosphoric acid R*, *acetonitrile R*, *water for chromatography R* (2:100:900 *V/V/V*);

— *mobile phase B*: *phosphoric acid R*, *water for chromatography R*, *acetonitrile R* (2:100:900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	90	10
2 - 8	90 → 58	10 → 42
8 - 8.1	58 → 0	42 → 100
8.1 - 16	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 316 nm.

Injection 25 µL of the test solution and reference solutions (b) and (c).

Relative retention With reference to deferasirox (retention time = about 10 min): impurity F acetone derivative = about 0.5.

System suitability:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity F acetone derivative in the chromatogram obtained with reference solution (c);

— *repeatability*: maximum relative standard deviation of 5.0 per cent for the area of the peak due to impurity F acetone derivative determined on 6 injections of reference solution (b).

Calculation of percentage content:

— for impurity F, use the concentration of impurity F in reference solution (b).

Limit:

— *impurity F*: maximum 0.5 ppm.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

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.

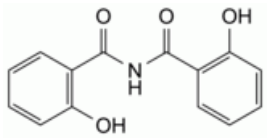
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{21}H_{15}N_3O_4$ taking into account the assigned content of *deferasirox CRS*.

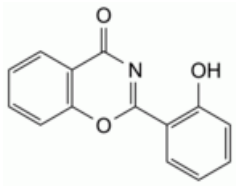
IMPURITIES

Specified impurities *F*.

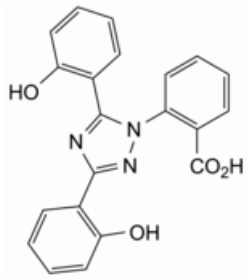
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



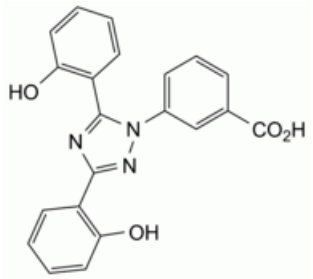
A. 2-hydroxy-*N*-(2-hydroxybenzoyl)benzamide,



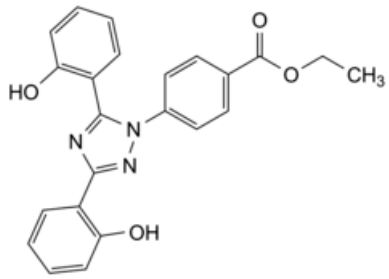
B. 2-(2-hydroxyphenyl)-4*H*-1,3-benzoxazin-4-one,



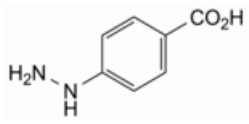
C. 2-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



D. 3-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid,



E. ethyl 4-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoate,



F. 4-hydrazinylbenzoic acid.

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