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Deferasirox Dispersible Tablets

General Notices

(Ph. Eur. monograph 2934)

Action and use

Selective iron(III) chelator; treatment of iron overload.

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DEFINITION

Dispersible tablets containing *Deferasirox (2933)*, for human use.

They comply with the monograph Tablets (0478) and with the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of deferasirox ($C_{21}H_{15}N_3O_4$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 200-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with the reference solution. Additional absorption bands may be present.

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Use only colourless glassware*.

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

Solvent mixture *acetonitrile R*, *water R*, *tetrahydrofuran R* (30:30:40 *V/V/V*).

Test solution *Prepare as rapidly as possible*. Crush 20 tablets to obtain a homogeneous powder. Accurately weigh a quantity of the powder containing the equivalent of 500 mg of deferasirox. Add 250.0 mL of the solvent mixture. Stir for about 5 min and sonicate for about 10 min. Filter the solution and dilute 2.0 mL of the filtrate to 25.0 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 the contents of a vial of *deferasirox for system suitability A CRS* (containing impurity D) in 3.0 mL of 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 - 2	65	35
2 - 10	65 → 60	35 → 40
10 - 15	60 → 20	40 → 80
15 - 16	20	80

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

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

Relative retention With reference to deferasirox (retention time = about 12 min): impurity D = about 0.95.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and deferasirox.

Calculation of percentage contents:

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

Limits:

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

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Dissolution

[1] (*2.9.3, Apparatus 2*).

Dissolution medium Mix 112 mL of an 8.4 g/L solution of *sodium hydroxide R* and 250 mL of a 27.2 g/L solution of *potassium dihydrogen phosphate R* and dilute to 1000 mL with *water R*. Adjust to pH 6.8 if necessary, using an 8.4 g/L solution of *sodium hydroxide R* or a 27.2 g/L solution of *potassium dihydrogen phosphate R*. Add 5 g of *polysorbate 20 R* and mix. Use 900 mL of the medium.

Rotation speed 50 r/min.

Time 30 min.

Analysis Ultraviolet and visible absorption spectrophotometry (2.2.25), using a path length of 1 mm.

Test solutions Samples withdrawn from the dissolution vessel and filtered. Mix 1 volume of the clear filtrate and 1 volume of *acetonitrile R*.

When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 10-fold dilution for 125 mg, 250 mg and 500 mg tablets).

Measure the absorbance of the solutions at 285 nm.

Calculate the amount of dissolved deferasirox ($C_{21}H_{15}N_3O_4$), expressed as a percentage of the content stated on the label, taking the specific absorbance to be 365.

Acceptance criterion:

— *Q* = 75 per cent after 30 min.

ASSAY

Liquid chromatography (2.2.29).

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

Solvent mixture *acetonitrile R*, *water R*, *tetrahydrofuran R* (30:30:40 *V/V/V*).

Test solution. Prepare as rapidly as possible Crush 20 tablets to obtain a homogeneous powder. Accurately weigh a quantity of the powder containing the equivalent of 500 mg of deferasirox. Add 250.0 mL of the solvent mixture. Stir for about 5 min and sonicate for about 10 min. Filter the solution and dilute 2.0 mL of the filtrate to 25.0 mL with the solvent mixture.

Reference solution Dissolve 16.0 mg of *deferasirox CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.05 m, Ø = 4.6 mm;

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

— *temperature*: 30 °C.

Mobile phase Buffer solution, *water for chromatography R*, *acetonitrile R* (10:40:50 *V/V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL.

Run time Twice the retention time of deferasirox (retention time = about 1.8 min).

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.5 per cent determined on 6 injections.

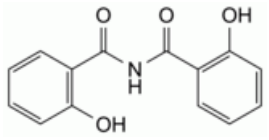
Calculate the percentage content of deferasirox ($C_{21}H_{15}N_3O_4$) taking into account the assigned content of *deferasirox CRS*.

STORAGE

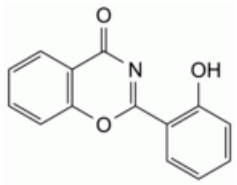
Protected from moisture.

IMPURITIES

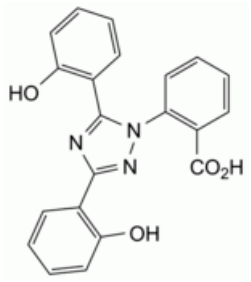
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, B, C, D, E*.



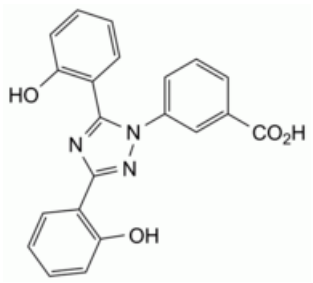
A. 2-hydroxy-*N*-(2-hydroxybenzoyl)benzamide,



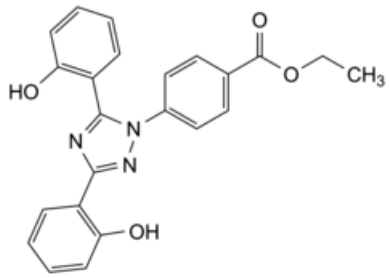
B. 2-(2-hydroxyphenyl)-4*H*-1,3-benzoxazin-4-one,



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.

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[1] The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.