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Pioglitazone Tablets

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

EAG/Panel/Working Party	Medicinal Chemicals 1
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Deadline for Comment	30 June 2022
Target Publication Date (subject to change)	BP 2024
Notes	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Peroxisome proliferator-activated receptor (PPAR)-gamma agonist; treatment of diabetes mellitus

DEFINITION

Pioglitazone Tablets contain Pioglitazone Hydrochloride.

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

Content of pioglitazone, $C_{19}H_{20}N_2O_3S$

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

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1, using the following solutions.

Solution A: 1 volume of 0.2M *hydrochloric acid*, 3 volumes of 2M *potassium chloride*, diluted to 20 volumes with *water*. Adjust to pH 2.0 with 5M *hydrochloric acid*.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of solution A, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.0017% w/v of pioglitazone, at the maximum at 269 nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.0019% solution of *pioglitazone hydrochloride BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of pioglitazone, $C_{19}H_{20}N_2O_3S$, in the medium from the absorbances obtained and using the declared content of $C_{19}H_{20}N_2O_3S$,HCl in *pioglitazone hydrochloride BPCRS*. Each mg of *pioglitazone hydrochloride BPCRS* is equivalent to 0.9071 mg of pioglitazone.

LIMITS

The amount of pioglitazone released is not less than 80% (Q) of the stated amount.

Related substances

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

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.18 g of pioglitazone with 40 mL of 0.01M *hydrochloric acid, methanolic*, and dilute to 50 mL with 0.01M *hydrochloric acid, methanolic*. Centrifuge a portion of the solution, dilute 1 volume of the supernatant liquid to 20 volumes with the mobile phase.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase, and further dilute 1 volume of this solution to 5 volumes with the mobile phase.

(3) To 5 mg of *pioglitazone for system suitability EPCRS* add 5 mL of *methanol* and heat at 60° for about 30 seconds. Cool to room temperature and dilute to 25 mL with the mobile phase.

(4) Dilute 1 volume of solution (2) to 2 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC Pack ODS-A is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.7 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 269 nm.

(f) Inject 40 µL of each solution.

(g) Allow the chromatography to proceed for 4 times the retention time of pioglitazone.

MOBILE PHASE

1 volume of *glacial acetic acid*, 25 volumes of *acetonitrile*, and 25 volumes of 0.1M *ammonium acetate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to pioglitazone and impurity B is at least 5.0.

CALCULATION OF IMPURITIES

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

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

For peak identification, use solution (3).

Pioglitazone retention time: about 7 minutes.

Relative retention: impurity B, about 1.4; impurity C, about 3.2.

LIMITS

— 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.

Solution B: A mixture of 35 volumes of *methanol* and 65 volumes of 0.05M *potassium dihydrogen orthophosphate*, adjust the pH to 2.3 with *hydrochloric acid*.

(1) Mix with the aid of ultrasound a quantity of the powdered tablets containing the equivalent of 0.3 g of pioglitazone with 100 mL of 0.1M *hydrochloric acid*. Mix the resulting mixture with the aid of ultrasound using 200 mL of *methanol*, and dilute to 500 mL with solution A. Centrifuge a portion of the solution and dilute a volume of the supernatant liquid with solution A to produce a solution containing the equivalent of 0.009% w/v of pioglitazone.

(2) 1.0% w/v of *pioglitazone hydrochloride BPCRS* in *methanol*. Dilute with solution B to produce a solution containing 0.01% w/v of Pioglitazone Hydrochloride

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 268 nm.

(f) Inject 25 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.01M *ammonium acetate*, adjusted to pH 4.0 with *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of the peak due to pioglitazone is about 8 minutes.

DETERMINATION OF CONTENT

Calculate the content of pioglitazone, $C_{19}H_{20}N_2O_3S$, in the tablets from the chromatograms obtained and using the declared content of $C_{19}H_{20}N_2O_3S$,HCl in *pioglitazone hydrochloride BPCRS*. Each mg of *pioglitazone hydrochloride BPCRS* is equivalent to 0.9071 mg of pioglitazone.

LABELLING

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

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Pioglitazone Hydrochloride.