3.2.S.4.1 Specification

The specifications of Irbesartan manufactured by Changjiang Pharm have been established in accordance with the current Ph.Eur. monograph for Irbesartan (04/2010:2465) with supplemental tests for the residual solvents of ethanol, toluene and benzene and microbial limit. The specifications are listed in Table 3.2.S.4.1-1.

Table 3.2.S.4.1-1 Specifications for Irbesartan

Test		Acceptance Criteria	Analytical Method
Appearance		White or almost white crystalline powder	Visual examination
Identification		Infrared spectrum is concordant with that of the reference standard	Ph.Eur.2.2.24
Appearance of solution		The solution is clear, and not more intensely colored than reference solution B_7	Ph.Eur.2.2.1 Ph.Eur.2.2.2 Method II
Water		Not more than 0.5%	Ph.Eur.2.5.12
Sulfate ash		Not more than 0.1%	Ph.Eur.2.4.14
Heavy metals		Not more than 20 ppm	Ph.Eur.2.4.8
Impurity B[1]		Not more than 10 ppm	Ph.Eur.2.2.29
Related Substances	Impurity A	Not more than 0.15%	Ph.Eur.2.2.29
	Any other impurity	Not more than 0.10%	
	Total impurities	Not more than 0.2%	
Residual solvents	Ethanol	Not more than 5000 ppm	Ph.Eur.2.2.28
Microbial Examination[2]	Total aerobic microbial count (TAMC)	Not more than 1000 cfu/g	Ph.Eur.2.6.12 Ph.Eur.2.6.13
	Total combined yeasts and molds count (TYMC)	Not more than 100 cfu/g	
	Escherichia coli	Not detected	
Assay		99.0%-101.0% (on the anhydrous basis)	Ph.Eur.2.2.20

[1] Contract test by HEC Pharm R&D Center

[2] At least three batches will be tested when the total batches in one year is less than 10; every three batches of ten will be tested when the total batches in one year is more than 10.

Copies of the Ph.Eur. monograph for Irbesartan are presented in the following pages.

Relative retention with reference to ipratropium (retention time = about 4.9 min): impurity C = about 0.7; impurity B = about 1.2; impurity D = about 1.8; impurity E = about 2.3; impurity F = about 5.1.

System suitability: reference solution (b):

- *resolution*: minimum 3.0 between the peaks due to impurity B and ipratropium;
- *symmetry factor*: maximum 2.5 for the principal peak.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.3; impurity D = 0.2; impurity F = 0.5;
- *impurity D*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);
- *impurities B, C*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);
- *disregard limit*: one-third of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent); disregard the peak due to the bromide ion.

Water (*2.5.12*): 3.9 per cent to 4.4 per cent, determined on 0.50 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

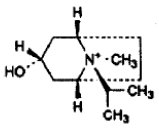
Dissolve 0.350 g in 50 mL of *water R* and add 3 mL of *dilute nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 41.24 mg of $C_{20}H_{30}BrNO_3$.

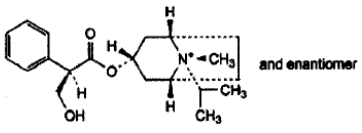
IMPURITIES

Specified impurities: *A, B, C, D*.

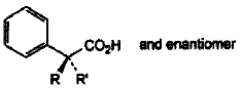
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. (1*R*,3*r*,5*S*,8*r*)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,

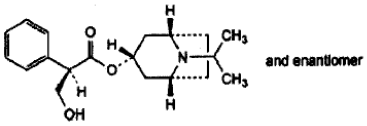


B. (1*R*,3*r*,5*S*,8*s*)-3-[[(2*RS*)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,

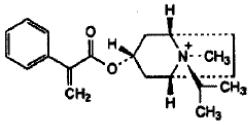


C. R = CH_2-OH, R′ = H: (2*RS*)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),

D. R + R′ = CH_2: 2-phenylpropenoic acid (atropic acid),



E. (1*R*,3*r*,5*S*)-8-(1-methylethyl)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate,

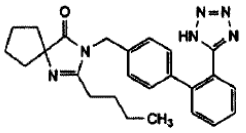


F. (1*R*,3*r*,5*S*,8*r*)-8-methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane.

04/2010:2465
corrected 7.0

IRBESARTAN

Irbesartanum



$C_{25}H_{28}N_6O$ M_r 428.5
[138402-11-6]

DEFINITION

2-Butyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *irbesartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness at 60 °C and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely colored than reference solution B_7 (*2.2.2, Method II*).

Dissolve 0.50 g in a mixture of 1 volume of *2 M sodium hydroxide R* and 9 volumes of *methanol R2* and dilute to 10 mL with the same mixture of solvents.

Impurity B. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution. Dissolve 25.0 mg of *sodium azide R* (sodium salt of impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.25 mL of this solution to 200.0 mL with the mobile phase.

Column:
- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Mobile phase: 4.2 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*.

Flow rate: 1.0 mL/min.

Detection: conductivity detector with a sensitivity of 3 µS; use a self-regenerating anion suppressor.

Neutralisation of the eluent: either chemical or electrochemical:
- *chemical*: by continuous countercurrent circulation in a neutralising micromembrane, performed before detection:
  - *neutralising solvent*: *0.025 M sulfuric acid*;
  - *flow rate*: 10 mL/min;
  - *pressure*: corresponding to about 100 kPa.
- *electrochemical*: 300 mA (for example).

Injection: 200 µL.

Run time: 25 min.

Retention time: impurity B = about 14 min.

System suitability: reference solution:
- *signal-to-noise ratio*: minimum 10 for the peak due to impurity B.

Limit:
- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution pH 3.2. Mix 5.5 mL of *phosphoric acid R* and 950 mL of *water R* and adjust to pH 3.2 with *triethylamine R*.

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R2* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 20.0 mL with *methanol R2*. Dilute 1.0 mL of this solution to 50.0 mL with *methanol R2*.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 5 mg of *irbesartan impurity A CRS* in *methanol R2* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R2*.

Column:
- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R1*, buffer solution pH 3.2 (33:67 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 1.4 times the retention time of irbesartan.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention with reference to irbesartan (retention time = about 23 min): impurity A = about 0.7.

System suitability: reference solution (b):
- *resolution*: minimum 3.0 between the peaks due to impurity A and irbesartan.

Limits:
- *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

Solvent mixture: *acetone R, methanol R* (20:80 *V/V*).

0.25 g complies with test H. Prepare the reference solution using 0.5 mL of *lead standard solution (10 ppm Pb) R*.

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.

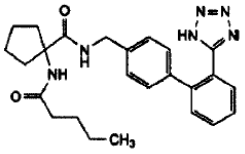
ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 42.85 mg of $C_{25}H_{28}N_6O$.

IMPURITIES

Specified impurities: *A, B.*



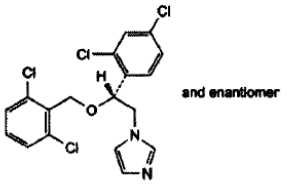
A. 1-(pentanoylamino)-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]cyclopentanecarboxamide,

B. trinitride (azide).

01/2008:1018
corrected 6.0

ISOCONAZOLE

Isoconazolum



$C_{18}H_{14}Cl_4N_2O$ M_r 416.1
[27523-40-6]

DEFINITION

1-[(2*RS*)-2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)-ethyl]-1*H*-imidazole.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, very soluble in methanol, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: *A, B.*

3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification

The specification of Irbesartan drug substance, manufactured by Yichang Changjiang Pharmaceutical Co., Ltd, complies with the European Pharmacopoeia (Ph.Eur.) monograph for Irbesartan (Monograph No.: 2465) and is presented in Table 3.2.S.4.1-1. The test methods are in compliance with the Ph. Eur. Monograph.

Table3.2.S.4.1-1 Specification of Ciprofloxacin Hydrochloride Drug Substance

Tests	Acceptance Criteria	Test Method
Appearance	white or almost white, crystalline powder	Visual examination
Identification		
A: IR absorption	The IR spectrum of the sample corresponds to that of the reference preparation.	Infrared Absorption Ph.Eur. 2.2.24
Appearance of Solution	The solution is clear and not more intensely colored than reference solution B_7	Irbesartan monograph; Ph. Eur. 2.2.1, 2.2.2 Method II
Water	≤ 0.5%	Ph. Eur. 2.5.12
Heavy Metals	≤ 0.002%	Irbesartan monograph; Ph. Eur. 2.4.8
Sulfated Ash	≤ 0.1%	Ph. Eur. 2.4.14
Impurity B[1, 2]	≤ 0.001%	Irbesartan monograph; Ph. Eur. 2.2.29
Related Substances[2]		
Impurity A	≤ 0.15%	Irbesartan monograph; HPLC Ph. Eur. 2.2.29
Any Unspecified Impurity	≤ 0.10%	
Total Impurities	≤ 0.2%	
Assay	99.0% to 101.0% (anhydrous substance)	Irbesartan monograph; Potentiometric Titration Ph. Eur. 2.2.20
Residual Solvents (Headspace GC)		
Ethanol	≤ 0.5%	Ph.Eur. 2.2.28
Microbial Examination[3]		
Total Aerobic Microbial Count	≤ 1000 cfu/g	Ph.Eur.2.6.12
Total Yeasts and Moulds Count	≤ 100 cfu/g	
Escherichia coli	Absent in 1g	Ph.Eur.2.6.13
Particle Size Distribution	D_{90}<15μm	Ph. Eur. 2.9.31

[1] Contract test by HEC Pharm R&D Center

[2] The chemical name of the specified impurities (referring to Ph.Eur.):

Impurity A	1-(pentanoylamino)-N-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]cyclopentanecarboxamide, N_3^-
Impurity B	trinitride (azide)

[3] The test is performed at the first 3 commercial batches and then at least one batch each year.