ABCD

**Analytical Procedures for the Drug Substance**

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|  | Internal Number |
| **BEA 2180 BR** | 04/016 |
|  |  |
|  | Document Number |
|  | U04-1056-02 |
|  |  |
|  | Date |
|  | 22 Feb 2007 |
|  |  |
|  | Page |
|  | 1 of 13 |
|  |  |

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Introduction

This document presents descriptions of the non-compendial chromatographic procedures that are used to control the drug substance BEA 2180 BR.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 2 of 13 |  |
|  |  |
|  |  |  |  |

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**BEA 2180 BR: Purity by HPLC**

**Principle:**

This HPLC method determines the purity of the drug substance BEA 2180 BR. The concentrations of impurities are reported as percent, quantified against a 0.5% solution of the drug substance.

**Reagents:**

Potassium dihydrogen phosphate, KH2PO4, anhydrous

Phosphoric acid 85%

Acetonitrile

Water, taken from a Millipore Milli-Q water purification system or similar system

**Chromatographic conditions:**

|  |  |  |  |
| --- | --- | --- | --- |
| Pump | Constant-flow pump, gradient system e.g. Agilent 1100 | | |
| Injection system | auto injector e.g. Agilent 1100 | | |
| Injection volume | 4.0 µL |  |  |
| Column | 150 mm x 4.6 mm i.d. | |  |
| Stationary phase | Inertsil ODS 2, 5 µm particle size | | |
| Eluent A | 0.3% aqueous solution of KH2PO4, adjusted to pH 2.5 with H3PO4 85 % | | |
| Eluent B | Acetonitrile | |  |
| Linear Gradient | 0 min | 85% eluent A | 15% eluent B |
|  | 2 min | 75% elunet A | 25% eluent B |
|  | 10 min 75% eluent A | | 25% eluent B |
|  | 22 min 30% eluent A | | 70% eluent B |
| Run time | 25 min |  |  |
| Conditioning time 5 min (post run time) | | |  |
| Temperature | 45°C |  |  |
| Flow rate | 1.3 mL/min | |  |
| Detector | UV detector (e.g.Agilent 1100) | | |
| Wavelength | 208 nm |  |  |

**Solutions:**

Blank solution:

Acetonitrile/Water 1+9 (v/v).

**Reference Solution:**

Dilute 100 µl of the sample solution with acetonitrile/water 1+9 (v/v) to make 20.0 ml.

Prepare two separate standard solutions A and B by using both test solutions.

System suitability solution A (0.05% solution):

Dilute one reference solution (0.5%) 1:10 using acetonitrile/Water 1+9 (v/v).

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 3 of 13 |  |
|  |  |
|  |  |  |  |

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System suitability solution B (resolution, tailing factor):

Dissolve approx. 50 mg BEA 2180 BR and approx. 0.15% BEA 2178 in 20.0 ml Acetonitrile/Water 1+9 (v/v).

Test solution:

Dissolve approx. 50 mg of the test sample, accurately weighed, in 20.0 ml acetonitrile/water 1+9 (v/v). Prepare two separate test solutions (A and B).

**System suitability:**

System suitability solution A (0.05% solution): quantitation of the resulting chromatographic peak must be possible (e.g. visual evaluation or signal-to-noise ratio not less than 10:1)

Repeatability: The relative standard deviation of the injections of the reference solution (0.5% solution) must be not more than 0.5%.

Resolution: The resolution between the peak for BEA 2180 BR and the impurity BEA 2178 should be better than 1.

Peak shape: The tailing factor of BEA 2180 BR peak must be in the range from 0.8 to 1.5.

The following retention times have been determined for the impurities:

|  |  |
| --- | --- |
| Drug Substance or Impurity | Retention time |
|  |  |
| BEA 2180 BR | ca. 14.4 min |
| Methsocopolamine bromide | ca. 2.7 min |
| CDBG 262 | ca. 13.9 min |
| BEA 2178 | ca. 14.1 min |
| Diphenylpropionamide | ca. 16.1 min |
| CDBG 258 | ca. 19.3 min |
|  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 4 of 13 |  |
|  |  |
|  |  |  |  |

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**BEA 2180 BR: Purity by TLC**

**Principle**:

This TLC method determines the purity of the drug substance BEA 2180 BR. The concentration of impurities are reported as percent, quantified by visual evaluation against 0.05%, 0.10%, 0.15% and 0.20% standard solutions of BA 338 BR and SCH 731 BR and against 0.05%, 0.15%, 0.30% and 0.40% standard solutions of CDBB 235.

**Reagents:**

Methanol

Dichloromethane

Formic acid

Dragendorff reagent

Titriplex solution (75 mg dissolved in 20 ml water)

Water, taken from a Millipore Milli-Q water purification system or similar system

**Chromatographic conditions:**

|  |  |  |
| --- | --- | --- |
| TLC Plate | Silica gel HPTLC plate | |
| Sample volume | 2 µl |  |
| Sample application | Manually, punctual | |
| Mode | Saturated TLC chamber, TLC plate is vertically developed | |
| Mobile phase | Dichloromethane, methanol, Titriplex, formic acid 60 / 40 / 10 /10 (v/v) | |
| Length of run | 5 cm. | (ca 17 min ) |
| Detection | Dragendorff reagent, visual evaluation | |

**Solutions:**

Stock solutions:

Dissolve approx 5 mg of BA 338 BR and SCH 731 BR accurately weighed in 20.0 ml methanol (S1). Dissolve approx. 5 mg of CDBB 235 BR2 in 10.0 ml methanol (S2).

Standard solutions:

Dilute 1 ml of S1 and 0.5 ml of S2 with methanol to make up 10.0 ml (I).

Dilute 2 ml of S1 and 1.5 ml of S2 with methanol to make up 10.0 ml (II).

Dilute 3 ml of S1 and 3 ml of S2 with methanol to make up 10.0 ml (III).

Dilute 4 ml of S1 and 4 ml of S2 with methanol to make up 10.0 ml (IV).

System suitability solution (resolution):

Dissolve approx. 100 mg BEA 2180 BR in 2 ml of standard solution III.

Test solution:

Dissolve approx. 250 mg of the test sample, accurately weighed, in 5.0 ml methanol.

Prepare two separate test solutions (A and B).

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 5 of 13 |  |
|  |  |
|  |  |  |  |

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**System suitability:**

Selectivity: All components in System suitability solution (BA 338 BR, SCH 731 BR and CDBB 235) must be completely separated.

Limit of quantitation: The resulting spots of all components in standard solution I (BA 338 BR, SCH 731 BR and CDBB 235) must be perceptible.

The following Rf values have be determined for the impurities:

Drug Substance or Impurity Rf value

|  |  |
| --- | --- |
| CDBB 235 | ca. 0.1 |
| BA 338 BR | ca. 0.3 |
| SCH 731 BR | ca. 0.5 |
| BEA 2180 BR | ca. 0.9 |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 6 of 13 |  |
|  |  |
|  |  |  |  |

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**BEA 2180 BR: Assay by HPLC:**

**Principle:**

This assay is based on an HPLC method using an external standard.

**Reagents:**

1 N NaOH solution in water

Acetonitrile

Water, taken from a Millipore Milli-Q water purification system or similar system

|  |  |  |
| --- | --- | --- |
| **Chromatographic conditions:** | |  |
| Pump | Constant-flow pump, e.g. Agilent 1100 | |
| Injection system | auto injector e.g. Agilent 1100 | |
| Injection volume | 5.0 µL |  |
| Column | 75 mm x 4.6 mm i.d. | |
| Stationary phase | Zorbax Eclipse XDB-CN, 3.5 µm particle size | |
| Eluent A | 0.3 % aqueous solution of KH2PO4 adjusted to pH 6.0 with NaOH | |
| Eluent B | Acetonitrile |  |
| Isocratic Elution | 40 % eluent A | 60 % eluent B |
| Run time | 6.5 |  |
|  | min |  |
| Temperature | 45°C |  |
| Flow rate | 1.0 mL/min |  |
| Detector | UV detector (Agilent 1100) | |
| Wavelength | 208 nm |  |

**Solutions:**

**Blank solution:**

Acetonitrile/water 6:4 (v/v).

**Standard solution:**

Dissolve 50 mg of BEA 2180 BR reference substance, accurately weighed, in 100.0 ml acetonitrile/water 6:4 (v/v). Prepare three separate standard solutions (A, B and C).

**System suitability solution (resolution, tailing factor):**

Dissolve 10 mg BEA 2180 BR in about 20 ml acetonitrile/water 6:4 (v/v) and add about 1 mg of BEA 2178.

**Test solution:**

Dissolve 50 mg of BEA 2180 BR test substance, accurately weighed, in 100.0 ml acetonitrile/water 6:4 (v/v). Prepare three separate standard solutions (A, B and C).

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 7 of 13 |  |
|  |  |
|  |  |  |  |

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**System suitability:**

Repeatability: The relative standard deviation of the response factor (area/weight) of 6 successive injections of standard solution (A, B, C) must be not more than 1.0%. The deviation of the average of the response factors of the BEA 2180 BR and the impurity BEA 2178 must be not more than 2.0%.

Resolution: The resolution between the peak for BEA 2180 BR and the impurity BEA 2178 must be better than 8.0.

Peak shape: The tailing factor of BEA 2180 BR must be in the range from 0.8 to 2.2.

**The following retention times have be determined:**

Drug Substance or Impurity Retention time

|  |  |
| --- | --- |
| BEA 2180 BR | ca. 4 min |
| BEA 2178 | ca. 2 min |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 8 of 13 |  |
|  |  |
|  |  |  |  |

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**BEA 2180 BR: Residual Solvents by GC**

**Principle:**

This analytical procedure describes a method for the determination of isopropanol in the drug substance BEA 2180 BR by headspace GC using an external standard.

**Reagents:**

**Isopropanol**

Toluene

N, N-Dimethylacetamide (DMA)

**Solutions:**

Blank solution:

Pipette 1.0 ml of DMA and 0.5 ml water into a 20-ml headspace vial. Prepare at least 2 of these vials.

System suitability solution and reference solution:

Pipette 800 µl isopropanol and 120 µl toluene into a 50 ml volumetric flask and fill to the mark with DMA. Pipette 2 ml of the resulting solution into a 50 ml volumetric flask and fill to the mark with DMA. Pipette 1.0 ml of the resulting solution and 0.5 ml water into a 20 ml head space vial. Prepare at least 3 head space vials.

Test solution:

Dissolve ca. 100 mg of the test sample, accurately weighed, in 1.0 ml DMA and 0.5 ml

water in

20-ml headspace vial. Prepare at least 4 test solutions.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 9 of 13 |  |
|  |  |
|  |  |  |  |

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Chromatographic conditions:** | |  |  |  |
| Apparatus: | gas chromatograph with flame ionisation detector (FID) | | |  |
|  | and head space system (e.g. HS 101/GC 8500 by Perkin Elmer) | | |  |
| Column: | Fused silica capillary |  |  |  |
|  | stationary phase: | CP SIL 5 CB |  |  |
|  | length: | 50 m |  |  |
|  | inner diameter: | 0.53 mm |  |  |
|  | film thickness: | 2.0 µm |  |  |
| Gases: | carrier gas: | helium | 0.8 bar |  |
|  | detector: | hydrogen | 40 ml/min |  |
| Injection: | Split 1:10 | synth. air | 400 ml/min |  |
|  |  |  |
| Temperatures: | Sample tray: | 70 °C |  |  |
|  | Injector: | 220 °C |  |  |
|  | Detector: | 250 °C |  |  |
| Column temp. | Initial temperature: | 60 °C |  |  |
| programme | Initial time: | 3 min |  |  |
|  | Heating rate: | 20 K/min |  |  |
|  | Final temperature: | 220 °C |  |  |
|  | Final time: | 4 min |  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 10 of 13 |  |
|  |  |
|  |  |  |  |

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Sampler settings:

Injection time 0.02 min

GC-Cycle time: 23 min

Withdrawal time: 0.2 min

Vial equilibration time:45 min

The following retention times have be determined for the impurities:

|  |  |
| --- | --- |
| Impurity | Retention time |
|  |  |
| Isopropanol | approx. 2.0 min |
| Toluene | approx. 6.0 min |
|  |  |

**System suitability:**

Resolution: The resolution between the isopropanol peak and the toluene peak should be more than 50.

Repeatability: The %deviation of the average (area toluene or isopropanol) of reference solution B to reference solution A must be not more than 5%.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 11 of 13 |  |
|  |  |
|  |  |  |  |

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**Principle:**

This analytical procedure describes a method for the determination of 1- Methyl-2-pyrrolidon in the drug substance BEA 2180 BR by GC using an internal standard.

**Reagents:**

1-Methyl-2-pyrrolidon

Dimethylformamide (DMF)

Lauric acid methyl ester

**Solutions:**

Internal standard (IS):

Pipette 1.0 ml of lauric acid methyl ester into a 100-ml volumetric flask and fill to the mark with ethanol.

Blank solution:

Pipette 5.0 ml of IS solution into a 50-ml volumetric flask. Inject this solution at least twice.

System suitability solution and reference solution:

Pipette 100 µl 1-methyl-2- pyrrolidon into a 100 ml volumetric flask and fill to the mark with DMF. Pipette 5 ml of the resulting solution and 5.0 ml of IS solution into a 50 ml volumetric flask and fill to the mark with DMF. Inject minimum four times.

Test solution:

Dissolve ca. 500 mg of the test sample, accurately weighed, in DMF using a 10 ml volumetric flask. Add 1.0 ml of IS solution and fill to the mark with DMF. Inject this solution at least four times.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 12 of 13 |  |
|  |  |
|  |  |  |  |

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Chromatographic conditions:** | |  |  |  |
| Apparatus: | gas chromatograph with flame ionisation detector (FID) | | |  |
|  | (e.g. Dani 8610 by Dani) | |  |  |
| Column: | Fused silica capillary |  |  |  |
|  | stationary phase: | DB-WAX |  |  |
|  | length: | 30 m |  |  |
|  | inner diameter: | 0.32 mm |  |  |
|  | film thickness: | 0.5 µm |  |  |
| Gases: | carrier gas: | helium | 0.7 bar |  |
|  | detector: | hydrogen | 40 ml/min |  |
| Injection | 1µl | synth. air | 400 ml/min |  |
|  |  |  |
| : | Split 1:50 |  |  |  |
| Temperatures: | Injector: | 220 °C |  |  |
|  | Detector: | 250 °C |  |  |
| Column temp. | Initial temperature: | 80 °C |  |  |
| programme | Heating rate: | 10 °C/min |  |  |
|  | Final temperature: | 230 °C |  |  |
| Run time | 15 min |  |  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analytical Procedures for the Drug Substance** | Internal Number | Page |  |
| 04/016 | 13 of 13 |  |
|  |  |
|  |  |  |  |

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The following retention times have be determined for the impurities:

|  |  |
| --- | --- |
| Impurity | Retention time |
|  |  |
| 1-Methyl-2-pyrrolidon | 9.8 min |
| Lauric acid methyl ester | 10.7 min |
|  |  |

**System suitability:**

Resolution: The resolution between the 1-methyl-2-pyrrolidon peak and the lauric acid methyl ester peak should be more than 10.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

ABCD

**Validation of Analytical Procedures for the Drug Substance**

|  |  |
| --- | --- |
|  | Internal Number |
| **BEA 2180 BR** | 05/031 |
|  |  |
|  | Document Number |
|  | U05-1365-01 |
|  |  |
|  | Date |
|  | 22 Feb 2007 |
|  |  |
|  | Page |
|  | 1 of 5 |
|  |  |

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The following methods have been validated as detailed below.

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Validation of Analytical Procedures** | Internal Number | Page |  |
| 05/031 | 2 of 5 |  |
| **for the Drug Substance** |  |

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Test: Purity

Test method type: Reversed-phase Gradient HPLC

|  |  |  |  |
| --- | --- | --- | --- |
|  | Selectivity | Separation of the possible impurities | |
|  |  | originating from the route of synthesis from | |
|  |  | each other, from possible degradation | |
|  |  | products and from BEA 2180 BR has been | |
|  |  | verified. A table with the retention times of | |
|  |  | the impurities is given in the document | |
|  |  | “Analytical procedures for the Drug | |
|  |  | Substance”. |  |
|  | Limit of quantitation | <0.05 % (The signal-to-noise ratio for an | |
|  |  | injection of a solution containing 0.05 % | |
|  |  | BEA 2178 was 18:1) | |
|  | Linearity | 0.05 – 0.25 % (BEA 2178) | |
|  | Repeatability | COV, 1.2 % (six injections of 0.06 % BEA | |
|  |  | 2178 |  |
|  | Accuracy | Mean recovery of BEA 2178 | |
|  |  | at 0.05 %: | 122 % |
|  |  | at 0.12 %: | 111 % |
|  |  | at 0.17 %: | 110 % |
|  | Robustness | Stability of test solution: verified over a | |
|  |  | period of 76 hours (brown glass vials, room | |
|  |  | temperature) |  |
|  |  | Column quality: selectivity verified with | |
|  |  | different columns; however, shift of retention | |
|  |  | times |  |
|  |  |  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Validation of Analytical Procedures** | Internal Number | Page |  |
| 05/031 | 3 of 5 |  |
| **for the Drug Substance** |  |

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Test: Purity

Test method type: Normal-phase TLC

|  |  |  |  |
| --- | --- | --- | --- |
|  | Selectivity | Separation of the possible impurities BA 338, | |
|  |  | SCH 731, CDBB 235 from each other and | |
|  |  | from BEA 2180 BR has been validated. A | |
|  |  | table with the Rf-values of the impurities is | |
|  |  | given in the document “Analytical | |
|  |  | procedures for the Drug Substance”. | |
|  | Limit of quantitation | 0.05 % (BA 338, SCH 731 and CDBB 235) | |
|  | Linearity | 0.05 – 0.30 % (BA 338, SCH 731) | |
|  |  | 0.05 – 0.50 % (CDBB 235) | |
|  | Robustness | Stability of test solution: verified over a | |
|  |  | period of 24 hours (volumetric glass flasks, | |
|  |  | room temperature) |  |
|  |  |  |  |
| Test: Residual Solvent – Isopropanol | |  |  |
| Test Method Type: Headspace GC | |  |  |
|  |  |  | |
|  | Selectivity | Separation of isopropanol from toluene is | |
|  |  | verified |  |
|  | Linearity | 0.050 – 1.2 weight% |  |
|  | Limit of quantitation | 0.050 weight% |  |
|  | Limit of detection | 0.025 weight% |  |
|  | Accuracy | Mean recovery at: | 0.050 %: 89.5 % |
|  |  |  | 0.251 %: 97.9 % |
|  |  |  | 0.502 %: 98.3 % |
|  |  |  | 0.754 %: 98.6 % |
|  | Repeatability | COV, 0.9 % (six injections of 0.25 weight% | |
|  |  | isopropanol) |  |
|  | Robustness | Thermostating temperature of headspace | |
|  |  | sampler: comparable results at 60 and 80 °C | |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Validation of Analytical Procedures** | Internal Number | Page |  |
| 05/031 | 4 of 5 |  |
| **for the Drug Substance** |  |

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Test: Residual Solvent – N-Methylpyrrolidone

Test Method Type: GC

|  |  |  |
| --- | --- | --- |
|  | Selectivity | Separation of N-methylpyrrolidone from |
|  |  | lauric acid methyl ester (internal standard) is |
|  |  | verified |
|  | Linearity | 200 – 2100 ppm |
|  | Limit of quantitation | 200 ppm |
|  | Limit of detection | 50 ppm |
|  | Accuracy | Mean recovery at: 413 ppm: 110 % |
|  |  | 2074 ppm: 100 % |
|  |  | 4074 ppm: 100 % |
|  | Repeatability | 200 ppm (n = 6), COV: 1.4 % |
|  |  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Validation of Analytical Procedures** | Internal Number | Page |  |
| 05/031 | 5 of 5 |  |
| **for the Drug Substance** |  |

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Test: Assay

Test method type: Reversed-phase HPLC

|  |  |  |
| --- | --- | --- |
|  | Selectivity | Separation of BEA 2180 from possible |
|  |  | impurities originating from the route of |
|  |  | synthesis and possible degradation products |
|  |  | has been validated. |
|  | Linearity | 60 – 140 %, correlation coefficient, 0.999 |
|  | Repeatability | Mean, 100.0 %, COV, 0.2 %, (n = 6) |
|  | Intermediate | Mean 100,0% ; RSD 0,15% (n=12) |
|  | precision |  |
|  | Accuracy | The recovery is in the range of 99.7 -100.3 % |
|  | Robustness | Stability of test solution: verified over a |
|  |  | period of 2 days. |
|  |  | Column quality: selectivity verified with |
|  |  | different column batches, no significant shift |
|  |  | of retention times observed |
|  |  |  |
| Test: Assay | |  |
| Test method type: AgNO3-Titration | |  |
|  | Linearity | 80 – 120 % (based on 320 mg sample |
|  |  | weight), correlation coefficient, 0.999 |
|  | Repeatability | Mean, 100.4 %, COV, 0.2 %, (n = 6) |
|  |  |  |

**Investigational Medicinal Product Documentation**

**BEA 2180 BR – Version 01 (trial 1205.14)**