Edition: BP 2025 (Ph. Eur. 11.6 update)

# Imatinib Capsules

General Notices

**Action and use**

Tyrosine kinase (BCR-ABL) inhibitor; antineoplastic.

## DEFINITION

Imatinib Capsules contain Imatinib Mesilate.

*The capsules comply with the requirements stated under Capsules and with the following requirements.*

## PRODUCTION

Risk assessment should be used to evaluate the potential for mutagenic methanesulfonate esters to be formed in the presence of low molecular weight alcohols. If a risk of methanesulfonate ester formation is identified through risk assessment, these impurities should not exceed the threshold of toxicological concern.

**Content of imatinib, $C_{29}H_{31}N_7O$**

95.0 to 105.0% of the stated amount.

## IDENTIFICATION

Shake a quantity of the mixed capsule contents containing the equivalent of 50 mg of imatinib with 10 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the reference spectrum of imatinib mesilate *(RS 514)*.

## TESTS

**Dissolution**

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

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.05M *potassium dihydrogen orthophosphate*, adjusted to pH 4.5 with 0.1M *sodium hydroxide*, if necessary, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and filter (a 0.45-µm PTFE membrane filter is suitable). Dilute the filtered medium, if necessary, with sufficient dissolution medium to produce a solution expected to contain the equivalent of 0.0056% w/v of imatinib.
(2) 0.0066% w/v of *imatinib mesilate BPCRS* in the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 269 nm.
(f) Inject 5 µL of each solution.

MOBILE PHASE

42 volumes of a solution containing 0.75% w/v of *sodium octanesulfonate monohydrate* in a mixture of 1 volume of *triethylamine* and 500 volumes of *water*, adjusted to pH 6.2 with *orthophosphoric acid*, and 58 volumes of *methanol*.

When the chromatograms are recorded under the prescribed conditions the retention time of imatinib is about 5 minutes.

DETERMINATION OF CONTENT

Calculate the total content of imatinib, $C_{29}H_{31}N_7O$, in the medium from the chromatograms obtained and using the declared content of $C_{30}H_{35}N_7SO_4$ in *imatinib mesilate BPCRS*. Each mg of $C_{30}H_{35}N_7SO_4$ is equivalent to 0.8370 mg of $C_{29}H_{31}N_7O$.

LIMITS

The amount of imatinib 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 mixed capsule contents containing the equivalent of 0.2 g of imatinib in 50 mL of *methanol (80%)* and centrifuge. Dilute 1 volume of the supernatant liquid to 5 volumes with *methanol (50%)* and filter (a 0.45-µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 20 volumes with *methanol (50%)* and further dilute 1 volume to 10 volumes with *methanol (50%)*.
(3) 0.1% w/v of *imatinib impurity standard BPCRS* in *methanol (50%)*.
(4) Dilute 1 volume of solution (2) to 5 volumes with *methanol (50%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Symmetry C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 269 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

*Mobile phase A* 2 volumes of *methanol* and 98 volumes of a solution containing 0.75% w/v of *sodium octanesulfonate monohydrate* in 1 volume of *triethylamine* and 500 volumes of *water*, adjusted to pH 6.2 with *orthophosphoric acid*.

*Mobile phase B* *methanol*.

| Time (Minutes) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comment |
|---|---|---|---|
| 0-2 | 67 | 33 | isocratic |
| 2-15 | 67→52 | 33→48 | linear gradient |
| 15-22 | 52 | 48 | isocratic |

| Time (Minutes) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comment |
|---|---|---|---|
| 22-30 | 52→37 | 48→63 | linear gradient |
| 30-39 | 37 | 63 | isocratic |
| 39-40 | 37→67 | 63→33 | linear gradient |
| 40-45 | 67 | 33 | re-equilibration |

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 1.5, where *Hp* is the height above the baseline of the peak due to imatinib and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* of the peak due to imatinib is at least 15.

.

**CALCULATION OF IMPURITIES**

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

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

For peak identification, use solution (3).

Imatinib retention time: about 27 minutes.

Relative retention: impurity 1, about 0.3; impurity J, about 0.5; and impurity C, about 1.2.

Correction factor: impurity 1, multiply by 1.3.

LIMITS

— impurity C: not more than 0.3%;

— unspecified impurities: for each impurity, not more than 0.2%;

— total impurities: not more than 1.0%;

— reporting threshold: 0.1%.

## ASSAY

Weigh the contents of 20 capsules. Mix and powder if necessary. 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 mixed capsule contents containing the equivalent of 0.2 g of imatinib in 80 mL of 0.05M *potassium dihydrogen orthophosphate*, dilute to produce 100 mL and centrifuge. Dilute 1 volume of the supernatant liquid to 20 volumes with *methanol (50%)* and filter (a 0.45-µm PTFE filter is suitable).
(2) 0.012% w/v of *imatinib mesilate BPCRS* in 0.05M *potassium dihydrogen orthophosphate*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

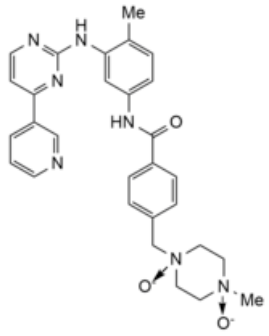
Calculate the content of imatinib, $C_{29}H_{31}N_7O$, in the capsules from the chromatograms obtained and using the declared content of $C_{30}H_{35}N_7SO_4$ in *imatinib mesilate BPCRS*. Each mg of $C_{30}H_{35}N_7SO_4$ is equivalent to 0.8370 mg of $C_{29}H_{31}N_7O$.

## LABELLING

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

## IMPURITIES

The impurities limited by the requirements of this monograph include impurities C and J listed under Imatinib Mesilate and:




1. 4-[(4-methyl-1,4-dioxido-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (imatinib (piperidine)-*N*,*N*-dioxide).