Imatinib Capsules

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

<table>
<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 2</th>
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</thead>
<tbody>
<tr>
<td><strong>Contact Details</strong></td>
<td><a href="mailto:helen.corns@mhra.gov.uk">helen.corns@mhra.gov.uk</a></td>
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<td><strong>Deadline for Comment</strong></td>
<td>30th September 2023</td>
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<tr>
<td><strong>Target Publication Date (subject to change)</strong></td>
<td>BP 2025</td>
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<tr>
<td><strong>Notes</strong></td>
<td>New monograph</td>
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<td>If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.</td>
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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, C۱۸H۱۱N۳O**

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 XXX*).
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°C, 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 x 3.9 mm) packed with end-capped octadecylsilica gel for chromatography (5 µm) (Waters 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°C.
(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_{35}N_{7}O_{4}, in the medium from the chromatograms obtained and using the declared content of C_{30}H_{35}N_{7}SO_{4} in imatinib mesilate BPCRS. Each mg of C_{30}H_{35}N_{7}SO_{4} is equivalent to 0.8370 mg of C_{29}H_{35}N_{7}O_{4}.

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 clear 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) 0.096% 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 octadecylsilat silica gel for chromatography (5 μm) (Waters 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°C.
(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 octane sulfonate monohydrate in 1 volume of triethylamine and 500 volumes of water, adjusted to pH 6.2 with orthophosphoric acid.

Mobile phase B methanol.

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>67</td>
<td>33</td>
<td>isocratic</td>
</tr>
<tr>
<td>2-15</td>
<td>67→52</td>
<td>33→48</td>
<td>linear gradient</td>
</tr>
<tr>
<td>15-22</td>
<td>52</td>
<td>48</td>
<td>isocratic</td>
</tr>
<tr>
<td>22-30</td>
<td>52→37</td>
<td>48→63</td>
<td>linear gradient</td>
</tr>
<tr>
<td>30-39</td>
<td>37</td>
<td>63</td>
<td>isocratic</td>
</tr>
<tr>
<td>39-40</td>
<td>37→67</td>
<td>63→33</td>
<td>linear gradient</td>
</tr>
<tr>
<td>40-45</td>
<td>67</td>
<td>33</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

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.

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 factors: 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 clear 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_{7}O, in the capsules from the chromatograms obtained and using the declared content of C_{30}H_{35}N_{7}SO_{4} in imatinib mesilate BPCRS. Each mg of C_{30}H_{35}N_{7}SO_{4} is equivalent to 0.8370 mg of C_{29}H_{31}N_{7}O.

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).

2. 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).