

## Sorafenib Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	28-Jan-2022
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	Small Molecules 3

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 3 Expert Committee intends to revise the Sorafenib Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution test. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.<sup>1</sup>

Should you have any questions, please contact Robyn Fales, Scientist IV (240-221-2047 or [rfp@usp.org](mailto:rfp@usp.org)).

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<sup>1</sup> This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

## Sorafenib Tablets

### DEFINITION

Sorafenib Tablets contain an amount of Sorafenib Tosylate equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ).

### IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

### ASSAY

#### • PROCEDURE

**Solution A:** 1 g/L of [monobasic potassium phosphate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 2.4.

**Solution B:** [Absolute alcohol](#), [acetonitrile](#), and *Solution A* (16:24:60)

**Solution C:** [Absolute alcohol](#) and [acetonitrile](#) (40:60)

**Solution D:** [Water](#). Adjust with [phosphoric acid](#) to a pH of 2.4.

**Mobile phase:** See [Table 1](#). Return to original conditions and re-equilibrate the system.

**Table 1**

Time (min)	Solution B (%)	Solution C (%)
0	100	0
2	100	0
14	33	67

**Diluent:** *Solution C* and *Solution D* (75:25)

**Standard solution:** 0.22 mg/mL of [USP Sorafenib Tosylate RS](#) in *Diluent*. Sonicate to aid the dissolution. [NOTE—It is equivalent to 0.16 mg/mL of sorafenib in *Diluent*.]

**Sample stock solution:** Nominally equivalent to 4 mg/mL of sorafenib in *Diluent*, prepared as follows.

Cut 5 Tablets into small pieces and transfer into a 250-mL volumetric flask. Add 150 mL of *Diluent*, shake for NLT 5 h until completely disintegrated and dispersed, and dilute with *Diluent* to volume.

Sonicate for 30 min, and centrifuge a portion of this solution for 5 min or pass a portion of this solution through a polytetrafluoroethylene (PTFE) [or equivalent] filter of 0.45- $\mu$ m pore size. Use the clear supernatant for the *Sample solution* preparation.

**Sample solution:** Nominally equivalent to 0.16 mg/mL of sorafenib in *Diluent*, from *Sample stock solution*

### Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 235 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

**Column:** 4.6-mm × 10-cm; 3.5-μm packing [L1](#)

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10 μL

### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** 0.8–2.0

**Relative standard deviation:** NMT 1.5%

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib (C<sub>21</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>3</sub>) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

$r_U$  = peak response from the *Sample solution*

$r_S$  = peak response from the *Standard solution*

$C_S$  = concentration of [USP Sorafenib Tosylate RS](#) in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of sorafenib in the *Sample solution* (mg/mL)

$M_{r1}$  = molecular weight of sorafenib, 464.83

$M_{r2}$  = molecular weight of sorafenib tosylate, 637.03

**Acceptance criteria:** 95.0%–105.0%

## PERFORMANCE TESTS

### Change to read:

- [DISSOLUTION](#) (711).

#### ▲Test 1▲ (TBD)

**Medium:** 0.1 N hydrochloric acid containing 1% [sodium lauryl sulfate](#); 900 mL

**Apparatus 2:** 100 rpm

**Time:** 15 min

Determine the percentage of the labeled amount of sorafenib (C<sub>21</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>3</sub>) dissolved by using one of the following procedures.

#### Chromatographic procedure

**Buffer:** 1.0 g/L of [monobasic potassium phosphate](#) in [water](#). Adjust with [phosphoric acid](#) to a pH of 2.5.

**Mobile phase:** [Acetonitrile](#) and *Buffer* (45:55) for *Column A*, or [acetonitrile](#) and *Buffer* (50:50) for *Column B*

**Standard stock solution:** 1.54 mg/mL of [USP Sorafenib Tosylate RS](#) in [methanol](#)

**Standard solution:** 0.3 mg/mL of [USP Sorafenib Tosylate RS](#), prepared as follows. Transfer 20 mL of *Standard stock solution* into a 100-mL volumetric flask and dilute with *Medium* to volume. [NOTE—It is equivalent to 0.22 mg/mL of sorafenib.]

**Sample solution:** Pass a portion of the solution under test through a filter of 10- $\mu$ m pore size.

### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 266 nm

#### Columns

**Column A:** 2-mm  $\times$  5-cm; 5- $\mu$ m packing [L1](#)

**Column B:** 3-mm  $\times$  5-cm; 5- $\mu$ m packing [L1](#)

**Column temperature:** 40°

**Flow rate:** 2.5 mL/min for *Column A* or 3.0 mL/min for *Column B*

**Injection volume:** 5  $\mu$ L

### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** 0.8–2.0

**Relative standard deviation:** NMT 1.5%

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

$r_U$  = peak response from the *Sample solution*

$r_S$  = peak response from the *Standard solution*

$C_S$  = concentration of [USP Sorafenib Tosylate RS](#) in the *Standard solution* (mg/mL)

$L$  = label claim (mg/Tablet)

$V$  = volume of *Medium*, 900 mL

$M_{r1}$  = molecular weight of sorafenib, 464.83

$M_{r2}$  = molecular weight of sorafenib tosylate, 637.03

### Spectrophotometric procedure

**Standard solution:** 0.3 mg/mL of [USP Sorafenib Tosylate RS](#), prepared as follows. Transfer an amount of [USP Sorafenib Tosylate RS](#) into a suitable volumetric flask, add [methanol](#) equivalent to 2.5% of the final volume, and dilute with *Medium* to volume. [NOTE—It is equivalent to 0.22 mg/mL of sorafenib.]

**Sample solution:** Centrifuge portions of the solution under test or pass through a suitable glass fiber filter of 1- $\mu$ m pore size.

### Instrumental conditions

**Mode:** UV

**Analytical wavelength:** 280 nm

**Cell path length:** 1 mm

**Blank:** *Medium*

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Sorafenib Tosylate RS](#) in the *Standard solution* (mg/mL)

$L$  = label claim (mg/Tablet)

$V$  = volume of *Medium*, 900 mL

$M_{r1}$  = molecular weight of sorafenib, 464.83

$M_{r2}$  = molecular weight of sorafenib tosylate, 637.03

**Tolerances:** NLT 75 (Q) of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ) is dissolved.

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

**Medium:** 0.1 N hydrochloric acid containing 1% (w/v) [sodium lauryl sulfate](#); 900 mL

**Apparatus 2:** 75 rpm

**Time:** 20 min

**Diluent:** [Acetonitrile](#) and *Medium* (50:50). Dilute 3 mL of this solution with *Medium* to 50 mL.

**Standard stock solution:** 0.15 mg/mL of [USP Sorafenib Tosylate RS](#) prepared as follows. Transfer a suitable amount of [USP Sorafenib Tosylate RS](#) to an appropriate volumetric flask. Add 50% of the flask volume of [acetonitrile](#) and 30% of the flask volume of *Medium* and sonicate for 5 min to dissolve. Dilute with *Medium* to volume.

**Standard solution:** 0.009 mg/mL of [USP Sorafenib Tosylate RS](#) from *Standard stock solution* in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter. Discard the first 2 mL of the filtrate and dilute a portion of the filtrate with *Medium* to obtain a concentration that is similar to that of the *Standard solution*.

### Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

**Mode:** UV

**Analytical wavelength:** 266 nm, with background correction at 490 nm

**Cell:** 1 cm

**Blanks:** *Medium* and *Diluent*

### Analysis:

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$	= concentration of <a href="#">USP Sorafenib Tosylate RS</a> in the <i>Standard solution</i> (mg/mL)
$V$	= volume of <i>Medium</i> , 900 mL
$D$	= dilution factor of the <i>Sample solution</i>
$M_{r1}$	= molecular weight of sorafenib, 464.83
$M_{r2}$	= molecular weight of sorafenib tosylate, 637.03
$L$	= label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of sorafenib ( $C_{21}H_{16}ClF_3N_4O_3$ ) is dissolved. ▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

## IMPURITIES

### ● ORGANIC IMPURITIES

**Mobile phase, Diluent, Sample solution, and Chromatographic system:** Proceed as directed in the *Assay*.

**Standard stock solution:** Use the *Standard solution* from the *Assay*.

**Standard solution:** 0.44 µg/mL of [USP Sorafenib Tosylate RS](#) in *Diluent*, from the *Standard stock solution*

**System suitability solution:** 0.44 µg/mL of [USP Sorafenib Related Compound H RS](#) in *Standard stock solution*

**Sensitivity solution:** 0.22 µg/mL of [USP Sorafenib Tosylate RS](#) in *Diluent*, from the *Standard solution*

#### System suitability

**Samples:** *System suitability solution* and *Sensitivity solution*

#### Suitability requirements

**Resolution:** NLT 1.5 between the sorafenib related compound H and sorafenib peaks, *System suitability solution*

**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*

#### Analysis

**Samples:** *Sample solution* and *Standard solution*

Disregard the process impurity peaks listed in [Table 2](#).

**Table 2**

Name	Relative Retention Time
Sorafenib impurity A <sup>a</sup>	0.12
Toluenesulphonic acid <sup>b</sup>	0.15
PAPE-ethyl carbamate <sup>c</sup>	0.34
Sorafenib impurity E <sup>d</sup>	0.46
Sorafenib impurity D <sup>e</sup>	0.47
Sorafenib impurity C <sup>f</sup>	0.58

Name	Relative Retention Time
Sorafenib impurity F <sup>g</sup>	0.82
Sorafenib impurity G <sup>h</sup>	0.93
Sorafenib related compound H	0.97
Sorafenib	1.00
Di(chlorotrifluoromethyl)phenylurea <sup>i</sup>	1.48

<sup>a</sup> 4-(4-Aminophenoxy)-*N*-methylpicolinamide.

<sup>b</sup> It is the counter ion of sorafenib and is present in the chromatogram of the *Sample solution*.

<sup>c</sup> Ethyl (4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)carbamate.

<sup>d</sup> *N,N'*-Bis{4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl}urea.

<sup>e</sup> Isopropyl {4-[2-(methylcarbamoyl)pyridin-4-yl]oxyphenyl}carbamate.

<sup>f</sup> 4-Chloro-3-(trifluoromethyl)aniline.

<sup>g</sup> *N*-Methyl-4-{4-[3-(3-trifluoromethylphenyl)ureido]phenoxy}picolinamide.

<sup>h</sup> Ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate.

<sup>i</sup> 1,3-Bis[4-chloro-3-(trifluoromethyl)phenyl]urea.

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

$r_U$  = peak response of each impurity from the *Sample solution*

$r_S$  = peak response of sorafenib from the *Standard solution*

$C_S$  = concentration of [USP Sorafenib Tosylate RS](#) in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of sorafenib in the *Sample solution* (mg/mL)

$M_{r1}$  = molecular weight of sorafenib, 464.83

$M_{r2}$  = molecular weight of sorafenib tosylate, 637.03

**Acceptance criteria:** See [Table 3](#). The reporting threshold is 0.1%.

**Table 3**

Name	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	0.2
Total impurities	0.5

## SPECIFIC TESTS

• **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count is NMT  $10^3$  cfu/g, and the total combined molds and yeasts count is NMT  $10^2$  cfu/g. It meets the requirements of the tests for the absence of *Escherichia coli*.

## ADDITIONAL REQUIREMENTS

● **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature between 15° and 30° in a dry place.

### **Add the following:**

▲● **LABELING:** When more than one *Dissolution Test* is given, the labeling states the test used only if *Test 1* is not used. ▲ (TBD)

● **USP REFERENCE STANDARDS** (11)

[USP Sorafenib Tosylate RS](#)

[USP Sorafenib Related Compound H RS](#)

4-(4-{3-[2-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*-methylpicolinamide.

$C_{21}H_{16}ClF_3N_4O_3$                       464.83

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### Page Information:

Not Applicable

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