Abiraterone Acetate Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	25–Jan–2019
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Abiraterone Acetate Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph.

- *Dissolution Test 2* was validated using an Acquity UPLC CSH Fluoro-Phenyl brand of L43 column. The typical retention time for abiraterone acetate is about 0.6 min.

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.[1]

Should you have any questions, please contact Feiwen Mao, Senior Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8320 or fm@usp.org).

[1] 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*.

Abiraterone Acetate Tablets

DEFINITION

Abiraterone Acetate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$).

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: 10 mM of ammonium acetate in water
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Acetonitrile (%)	Ethanol (%)
0	50	20	30
40	15	55	30
47	0	20	80
58	0	20	80
60	50	20	30
70	50	20	30

[NOTE—Protect solutions from light.]
System suitability solution: 0.625 mg/mL of USP Abiraterone System Suitability Mixture RS in acetonitrile. [NOTE—See *Table 2* for relative retention times of the main components of the mixture.]

Table 2

Name	Relative Retention Time
7-Ketoabiraterone acetate	0.42
α-Epoxyabiraterone acetate	0.62
β-Epoxyabiraterone acetate	0.66
Abiraterone	0.69
3-Deoxy-3-acetyl abiraterone-3-ene	0.85
Abiraterone acetate	1.0
Abiraterone ethyl ether	1.18
Abiraterone isopropyl ether	1.26
Anhydro abiraterone	1.29
3-Deoxy 3-chloroabiraterone	1.31
O-Chlorobutylabiraterone	1.33

Standard solution: 0.625 mg/mL of USP Abiraterone Acetate RS in acetonitrile
Sample solution: Nominally equivalent to 0.625 mg/mL of abiraterone acetate in acetonitrile, prepared from NLT 20 powdered Tablets as follows. Transfer the powder to a suitable volumetric flask. Add 50% of the flask volume of acetonitrile, shake by mechanical means for 30 min, and dilute with acetonitrile to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, and use the clear solution for analysis.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm or diode array. [NOTE—Use diode array detector to perform *Identification* test *B*.]
Column: 3-mm × 15-cm; 3-µm packing L1
Column temperature: 15°
Flow rate: 0.45 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.0 between anhydro abiraterone and 3-deoxy 3-chloroabiraterone peaks, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Abiraterone Acetate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of abiraterone acetate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲Test 1▲ (TBD)
[NOTE—Protect solutions from light.]
Buffer: 56.5 mM of monobasic sodium phosphate in water. Adjust with 5 N sodium hydroxide or phosphoric acid to a pH of 4.5.
Medium: 0.25% of sodium lauryl sulfate in *Buffer*; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Standard solution: 0.3 mg/mL of USP Abiraterone Acetate RS in *Medium* prepared as follows. Transfer USP Abiraterone Acetate RS into a suitable volumetric flask. Add 4% of the flask volume of acetonitrile to dissolve, and dilute with *Medium* to volume.
Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size. Use the filtrate.
Mobile phase: Acetonitrile, formic acid, and water (55: 0.05: 45)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 252 nm
Column: 4.6-mm × 3-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
System suitability
Sample: *Standard solution*

Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$) dissolved:

$$(r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
[NOTE—Protect solutions from light.]
Buffer: 56.5 mM of monobasic sodium phosphate in water. Adjust with 5 N sodium hydroxide or phosphoric acid to a pH of 4.5.
Medium: 0.25% of sodium lauryl sulfate in *Buffer*; 900 mL
Apparatus 2: 75 rpm
Time: 30 min
Standard solution: 0.28 mg/mL of USP Abiraterone Acetate RS in *Medium* prepared as follows. Transfer USP Abiraterone Acetate RS into a suitable volumetric flask. Add 4% of the flask volume of acetonitrile to dissolve, and dilute with *Medium* to volume.
Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size. Use the filtrate.
Mobile phase: Acetonitrile and water (90:10)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 2.1-mm × 7.5-cm; 1.7-µm packing L43
Column temperature: 35°
Flow rate: 0.5 mL/min
Injection volume: 0.5 µL
Run time: NLT 1.7 times the retention time of abiraterone acetate
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of abiraterone acetate from the *Sample solution*
r_S = peak response of USP Abiraterone Acetate RS from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of abiraterone acetate ($C_{26}H_{33}NO_2$) is dissolved.▲ (TBD)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**
[NOTE—Protect solutions from light.]
Solution A, Mobile phase, System suitability solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Sensitivity solution: 0.3 µg/mL of USP Abiraterone Acetate RS in acetonitrile from *Standard solution*
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 1.0 between anhydro abiraterone and 3-deoxy 3-chloroabiraterone peaks, *System suitability solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak area of each impurity from the *Sample solution*
r_S = peak area of abiraterone acetate from the *Standard solution*
C_S = concentration of USP Abiraterone Acetate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of abiraterone acetate in the *Sample solution* (mg/mL)
F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any peak less than 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
7-Ketoabiraterone acetate	0.42	1.4	0.50
α-Epoxyabiraterone acetate	0.62	0.26	0.80
β-Epoxyabiraterone acetate	0.66	0.26	0.80
Abiraterone	0.69	1.0	0.40
Abiraterone acetate	1.0	—	—
Abiraterone ethyl ether[a]	1.18	—	—
Abiraterone isopropyl ether[a]	1.26	—	—
Unspecified impurity	—	1.0	0.20

Table 3 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities	—	—	2.0

[a] This is a process impurity and is controlled in the drug substance monograph. It is included in the table for identification only, and it is not to be reported in the total impurities.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

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

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Abiraterone Acetate RS
  USP Abiraterone System Suitability Mixture RS
  It contains Abiraterone Acetate and small amounts of the following:
  Abiraterone
  17-(Pyridin-3-yl)androsta-5,16-dien-3β-ol.
  $C_{24}H_{31}NO$ 349.52
  Abiraterone ethyl ether
  3β-Ethoxy-17-(pyridin-3-yl)androsta-5,16-diene.
  $C_{26}H_{35}NO$ 377.57
  Abiraterone isopropyl ether
  3β-Isopropoxy-17-(pyridin-3-yl)androsta-5,16-diene.
  $C_{27}H_{37}NO$ 391.60
  Anhydro abiraterone
  17-(Pyridin-3-yl)androsta-3,5,16-triene.
  $C_{24}H_{29}N$ 331.50
  O-Chlorobutylabiraterone
  3β-(4-Chlorobutoxy)-17-(pyridin-3-yl)androsta-5,16-diene.
  $C_{28}H_{38}ClNO$ 440.07
  3-Deoxy-3-acetyl abiraterone-3-ene
  1-[17-(Pyridin-3-yl)androsta-3,5,16-trien-3-yl]ethanone.
  $C_{26}H_{31}NO$ 373.53
  3-Deoxy 3-chloroabiraterone
  3β-Chloro-17-(pyridin-3-yl)androsta-5,16-diene.
  $C_{24}H_{30}ClN$ 367.96
  α-Epoxyabiraterone acetate
  17-(Pyridin-3-yl)-16α,17α-epoxyandrost-5-en-3β-yl acetate.
  $C_{26}H_{33}NO_3$ 407.55
  β-Epoxyabiraterone acetate
  17-(Pyridin-3-yl)-16β,17β-epoxyandrost-5-en-3β-yl acetate.
  $C_{26}H_{33}NO_3$ 407.55
  7-Ketoabiraterone acetate
  7-Oxo-17-(pyridin-3-yl)androsta-5,16-dien-3β-yl acetate.
  $C_{26}H_{31}NO_3$