

BRIEFING

Almotriptan Malate. This monograph was posted on the USP Website as Draft 2 on February 25, 2011. The SM4 Expert Committee received and considered the following comments, and has approved the monograph as an Authorized USP Pending Monograph, Version 2.

- **Comment 1:** During the testing of USP Almotriptan System Suitability RS, the commenter observed a peak eluting in the second injection of the *System suitability solution* at about 40 min. This peak is clearly a late eluting peak from the first injection. It appears the peak at about 40 min is reproducible in solutions made from USP Almotriptan System Suitability RS. To minimize the impact from this observed carryover, the commenter requested the inclusion of the following *Note* in the *Chromatographic system* of the *Organic Impurities* test: [NOTE—It is recommended to inject a blank after every injection of the *System suitability solution/Standard solution* and before the sample injection.]
- **Response 1:** Comment incorporated.
- **Comment 2:** The commenter requested to change the proposed *Diluent* from a 20:80 mixture of acetonitrile and water to a 20:80 mixture of acetonitrile and 1 M hydrochloric acid to enhance the stability of the almotriptan hydrazine precursor impurity.
- **Response 2:** Comment not incorporated at this time. The Expert Committee is willing to consider this change upon receipt of additional supporting data.
- **Comment 3:** The RRFs for impurities at an RRT of 0.47 for the hydrazine precursor and 0.63 for the aniline precursor are very low; therefore, it is advisable to quantify these impurities against respective standards.
- **Response 3:** Comment not incorporated. The Expert Committee will consider this request when suitable reference standard materials become available.
- **Comment 4:** The area counts for the almotriptan aniline precursor are very low; and therefore, it is better to quantify this impurity at a different wavelength (i.e., at 245 nm or 210 nm).
- **Response 4:** Comment not incorporated at this time. The Expert Committee is willing to consider this change upon receipt of additional supporting data.

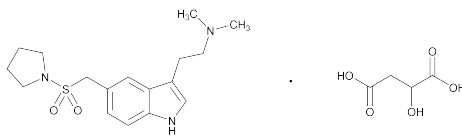
The liquid chromatographic procedure used in the *Assay* is based on analyses performed with the Inertsil C8–3 brand of L7 column. The typical retention time for almotriptan is about 8.1 min.

The liquid chromatographic procedure used in the *Organic Impurities* test is based on analyses performed with the Inertsil C8 brand of L7 column. The typical retention time for almotriptan is about 25 min.

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Almotriptan Malate

v. 2 Authorized November 1, 2011



$C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$ 469.55
1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine, hydroxybutanedioate (1:1);
1-[[[3-[2-(Dimethylamino)ethyl]indol-5-yl]methyl]sulfonyl]pyrrolidine malate (1:1) [181183-52-8].

DEFINITION

Almotriptan Malate contains NLT 98.0% and NMT 102.0% of $C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$, calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION (197K)**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
Protect all volumetric solutions from light, and use amber glassware.

Buffer: To 0.5 g of octanesulfonic acid sodium salt, monohydrate, add 5 mL of phosphoric acid, and dissolve in 1 L of water. Adjust with 10 N sodium hydroxide solution to a pH of 3.0.

Diluent: Acetonitrile and water (20:80)

Solution A: Acetonitrile and *Buffer* (10:90)

Solution B: Acetonitrile and *Buffer* (70:30)

Mobile phase: *Solution A* and *Solution B* (72:28)

Standard solution: 0.05 mg/mL of USP Almotriptan Malate RS in *Diluent*. Sonication may be used to aid dissolution.

Sample solution: 0.05 mg/mL of Almotriptan Malate in *Diluent*. Sonication may be used to aid dissolution.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 228 nm

Column: 4.6-mm × 25-cm; 5-μm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 10 μL

Run time: 2.5 times the retention time of the almotriptan peak

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 3000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of almotriptan malate ($C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$) in the portion of Almotriptan Malate 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 Almotriptan Malate RS in the *Standard solution* (mg/mL)

C_U = concentration of Almotriptan Malate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION (281):** NMT 0.1%

• **ORGANIC IMPURITIES**

Protect all volumetric solutions from light, and use amber glassware.

Buffer, Diluent, Solution A, and Solution B: Proceed as directed in the *Assay*.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
5.0	85	15
20.0	78	22
30.0	70	30
40.0	70	30

2 / Almotriptan

Table 1 (Continued)

Time (min)	Solution A (%)	Solution B (%)
40.5	85	15
48.0	85	15

System suitability solution: 1 mg/mL of USP Almotriptan System Suitability RS and 0.01 mg/mL of USP Almotriptan Related Compound A RS in *Diluent*

Standard solution: 1 µg/mL of USP Almotriptan Malate RS in *Diluent*

Sample solution: 1 mg/mL of Almotriptan Malate in *Diluent*

Chromatographic system: Proceed as directed in the Assay, except to use an injection size of 5 µL.

[NOTE—It is recommended to inject a blank after every injection of the *System suitability solution/Standard solution* and before the sample injection.]

System suitability

Samples: *System suitability solution* and *Standard solution* [NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between the almotriptan monomethyl analog and almotriptan peaks, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Almotriptan Malate taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

r_u = peak response of each individual impurity from the *Sample solution*

r_s = peak response of almotriptan from the *Standard solution*

C_s = concentration of USP Almotriptan Malate RS in the *Standard solution* (µg/mL)

C_u = concentration of Almotriptan Malate in the *Sample solution* (µg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Malic acid ^a	0.10	—	—
Almotriptan hydrazine precursor ^b	0.47	0.15	0.15

^a For identification purposes only. It is not included in the calculation of total impurities.

^b 1-(4-Hydrazinylbenzylsulfonyl)pyrrolidine.

^c 1-(4-Aminobenzylsulfonyl)pyrrolidine.

^d (3-[2-(Dimethylamino)ethyl]-5-[(pyrrolidin-1-yl)sulfonylmethyl]-1*H*-indol-1-yl)methanol.

^e 2-{5-[(Pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.

^f *N*-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.

^g 1-[(3-[2-(Dimethylamino)ethyl]indol-5-yl)methyl]sulfonylpyrrolidine *N*-oxide.

^h *N*-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}propan-2-amine.

ⁱ 2-{2-[(3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl)methyl]-5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl]-*N,N*-dimethylethanamine.

* Used in the *System suitability solution* for identification purposes.

Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Almotriptan aniline precursor ^c	0.63	0.13	0.15
Almotriptan related compound A ^{d,*}	0.82	1.0	0.15
Almotriptan triptamine ^e	0.88	1.3	0.15
Almotriptan monomethyl analog ^f	0.96	1.0	0.15
Almotriptan	1.0	—	—
Almotriptan <i>N</i> -oxide ^g	1.1	1.0	0.15
Almotriptan isopropyl analog ^h	1.3	1.0	0.15
Almotriptan dimer ⁱ	1.4	1.0	0.15
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	1.0

^a For identification purposes only. It is not included in the calculation of total impurities.

^b 1-(4-Hydrazinylbenzylsulfonyl)pyrrolidine.

^c 1-(4-Aminobenzylsulfonyl)pyrrolidine.

^d (3-[2-(Dimethylamino)ethyl]-5-[(pyrrolidin-1-yl)sulfonylmethyl]-1*H*-indol-1-yl)methanol.

^e 2-{5-[(Pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.

^f *N*-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.

^g 1-[(3-[2-(Dimethylamino)ethyl]indol-5-yl)methyl]sulfonylpyrrolidine *N*-oxide.

^h *N*-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}propan-2-amine.

ⁱ 2-{2-[(3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl)methyl]-5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl]-*N,N*-dimethylethanamine.

* Used in the *System suitability solution* for identification purposes.

SPECIFIC TESTS

- **LOSS ON DRYING (731):** Dry a sample in vacuum at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**
USP Almotriptan Malate RS
USP Almotriptan Related Compound A RS
(3-[2-(Dimethylamino)ethyl]-5-[(pyrrolidin-1-yl)sulfonylmethyl]-1*H*-indol-1-yl)methanol.
C₁₈H₂₇N₃O₃S 365.49
USP Almotriptan System Suitability RS
[It contains at least 94% of almotriptan malate and at least 5% of the almotriptan monomethyl analog.]