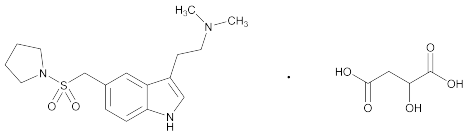
# Almotriptan Malate



$C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$ 469.55

Pyrrolidine, 1-[[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]sulfonyl]-, 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 almotriptan malate ($C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$), calculated on the anhydrous and solvent-free 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

***Change to read:***

- **Procedure**

**Buffer:** 2.72 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
**Mobile phase:** Methanol and *Buffer* (40:60)
**System suitability solution:** 0.14 mg/mL each of USP Almotriptan Malate RS and USP Almotriptan Related Compound B RS in *Mobile phase*. Sonication may be used to promote dissolution.
**Standard solution:** 0.14 mg/mL of USP Almotriptan Malate RS in *Mobile phase*. Sonication may be used to promote dissolution.
**Sample solution:** 0.14 mg/mL of Almotriptan Malate in *Mobile phase*. Sonication may be used to promote dissolution.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 230 nm
**Column:** 4.6-mm × 15-cm; 5-µm packing L10
**Flow rate:** 1 mL/min
**Injection volume:** 10 µL
**Run time:** •NLT• (IRA 1-May-2017) 2 times the retention time of almotriptan
**System suitability**
**Samples:** *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for almotriptan related compound B and almotriptan are 0.7 and 1.0, respectively.]
**Suitability requirements**
**Resolution:** NLT 2.0 between almotriptan and almotriptan related compound B, *System suitability solution*
**Tailing factor:** NMT 2.0, *Standard solution*
**Relative standard deviation:** NMT 0.85% for six injections, *Standard solution*
**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 of almotriptan 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* (mg/mL)
$C_U$ = concentration of Almotriptan Malate in the *Sample solution* (mg/mL)

**Acceptance criteria:** 98.0%–102.0% on the anhydrous and solvent-free basis

## IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.10%

***Change to read:***

- **Limit of Almotriptan Related Compound D and Almotriptan *N*-Dimer**

**Run buffer:** 23.5 g/L of phosphoric acid in water. Adjust with triethanolamine to a pH of 3.0 and pass through a suitable filter of 0.45-µm pore size.
**Diluent:** Methanol and water (50:50)
**Internal standard solution:** 0.01 mg/mL of 4-hydroxy-4-phenylpiperidine in *Diluent*
**System suitability solution:** 0.005 mg/mL each of USP Almotriptan Related Compound B RS, •• (IRA 1-May-2017) USP Almotriptan Related Compound D RS, and USP Almotriptan Malate RS in the *Internal standard solution*. Pass through a suitable filter of 0.45-µm pore size.
**Standard stock solution:** 0.5 mg/mL of USP Almotriptan Malate RS in *Diluent*
**Standard solution:** 0.005 mg/mL of USP Almotriptan Malate RS from the *Standard stock solution* in the *Internal standard solution*. Pass through a suitable filter of 0.45-µm pore size.
**Sample solution:** 2.5 mg/mL of Almotriptan Malate in the *Internal standard solution*. Sonication may be used to promote dissolution. Pass the solution through a suitable filter of 0.45-µm pore size.
•**Capillary rinsing procedure:** Use separate *Run buffer* vials for the capillary rinse and sample analysis. Condition the capillary by rinsing with water, 0.1 N sodium hydroxide, water, and the *Run buffer* before each injection. [NOTE—It may be suitable to rinse with water, 0.1 N sodium hydroxide, and water using a pressure of 20 psi for NLT 2 min each and then to rinse with the *Run buffer* using a pressure of 20 psi for NLT 5 min.]
**Instrumental conditions**
**Mode:** CE
**Detector:** UV 214 nm
**Capillary, Capillary effective length, Capillary temperature,** and **Voltage:** Use parameters described under *A* or *B* as indicated in *Table 1*.

**Table 1**

| Parameter | A | B |
|---|---|---|
| Capillary | 75-µm × 48.5-cm; uncoated fused silica | 75-µm × 60-cm; uncoated fused silica |
| Capillary effective length | 40 cm | 47 cm |

**Table 1** *(Continued)*

| Parameter | A | B |
|---|---|---|
| Capillary temperature | 15° | 25° |
| Voltage | A voltage of 15.5 kV may be suitable. | A voltage of 15.0 kV may be suitable. |

**Injection sequence:** 0.5 psi for 8 s for the *Sample solution*, followed by 0.5 psi for 1 s for the *Run buffer*
**Run time:** NLT 2.5 times the migration time of almotriptan● (IRA 1-May-2017)
**System suitability**
**Samples:** *System suitability solution* and *Standard solution*
[NOTE—See ●*Table 2*● (IRA 1-May-2017) for the relative migration times.]
**Suitability requirements**
**Resolution:** NLT 2.0 between almotriptan related compound B and almotriptan; NLT 2.0 between ●almotriptan● (IRA 1-May-2017) and almotriptan related compound D, *System suitability solution*
**Relative standard deviation:** NMT 5.0% for the ratio of the peak response of almotriptan to the peak response of the internal standard, *Standard solution*
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the corrected peak response:

$$\text{Result} = (r/m)$$

$r$ = peak response
$m$ = migration time of the peak (min)
Calculate the percentage of almotriptan related compound D, almotriptan *N*-dimer, and other impurities in the portion of Almotriptan Malate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

$R_U$ = corrected peak response ratio of the impurity to the internal standard from the *Sample solution*
$R_S$ = corrected peak response ratio of almotriptan to the internal standard 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:** See ●*Table 2*.

**Table 2●** (IRA 1-May-2017)

| Name | Relative Migration Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Almotriptan *N*-dimer[a] | 0.71 | 0.3 |
| Internal standard[b] | 0.78 | — |
| Almotriptan related compound B[c] | 0.92 | — |
| Almotriptan●● (IRA 1-May-2017) | 1.0 | — |
| Almotriptan related compound C[c]●● (IRA 1-May-2017) | 1.02 | — |
| Almotriptan related compound D | 1.22 | 0.1 |
| Any individual unspecified impurities | — | 0.1 |

[a] 2-{1-({3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}-*N*,*N*-dimethylethan-1-amine.
[b] 4-Hydroxy-4-phenylpiperidine.
[c] ●If present, this impurity may not be fully resolved from almotriptan. It is quantified using the test for *Organic Impurities*.● (IRA 1-May-2017)

***Change to read:***

- **ORGANIC IMPURITIES**

**Buffer:** Add 10 mL of triethylamine to every 1000 mL of 0.01 M phosphoric acid. Adjust with phosphoric acid to a pH of 6.5.
**Mobile phase:** Acetonitrile and *Buffer* (15:85)
**System suitability stock solution:** 0.5 mg/mL each of USP Almotriptan Related Compound B RS, USP Almotriptan Related Compound C RS, and USP Almotriptan Related Compound D RS in methanol
**System suitability solution:** 0.005 mg/mL each of USP Almotriptan Related Compound B RS, USP Almotriptan Related Compound C RS, and USP Almotriptan Related Compound D RS from the *System suitability stock solution* in water
**Standard solution:** 0.007 mg/mL of USP Almotriptan Malate RS in water
**Sample solution:** 3.5 mg/mL of Almotriptan Malate in water. Sonication may be used to promote dissolution.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 210 nm
**Column:** 4.6-mm × 30-cm; 5-µm packing L1
**Flow rate:** 1 mL/min
**Injection volume:** 20 µL
**Run time:** ●NLT● (IRA 1-May-2017) 3 times the retention time of almotriptan
**System suitability**
**Samples:** *System suitability solution* and *Standard solution*
[NOTE—See ●*Table 3*● (IRA 1-May-2017) for the relative retention times.]
**Suitability requirements**
**Resolution:** NLT 1.0 between almotriptan related compound C and almotriptan related compound D, *System suitability solution*
**Relative standard deviation:** NMT 5.0% for six replicate injections, *Standard solution*
**Analysis**
**Samples:** *System suitability solution*, *Standard solution*, and *Sample solution*
Chromatograph the *System suitability solution* and identify the components on the basis of their relative retention times, as shown in ●*Table 3*.● (IRA 1-May-2017)
Calculate the percentage of each impurity in the portion of Almotriptan Malate taken:

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

$r_U$ = peak response of each 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* (mg/mL)
$C_U$ = concentration of Almotriptan Malate in the *Sample solution* (mg/mL)

**Acceptance criteria:** See *Table 3*.

**Table 3** (IRA 1-May-2017)

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Malic acid[a] | 0.10 | — |
| Almotriptan related compound B | 0.62 | 0.1 |
| Almotriptan related compound C | 0.77 | 0.5 |
| Almotriptan related compound D[b] | 0.92 | — |
| Almotriptan | 1.00 | — |
| Any other individual impurity | — | 0.1 |
| Total impurities[c] | — | 1.0 (IRA 1-May-2017) |

[a] This peak is due to the malate counterion; hence it is not an impurity. It is not to be reported or included in the total impurities. (IRA 1-May-2017)
[b] This impurity is quantified using the *Limit of Almotriptan Related Compound D and Almotriptan N-Dimer* test.
[c] The sum of all impurities from the test for *Organic Impurities* and the *Limit of Almotriptan Related Compound D and Almotriptan N-Dimer* test.

***Change to read:***

- **LIMIT OF FUMARIC ACID**

**Buffer:** 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.8.
**Mobile phase:** Methanol and *Buffer* (5:95)
**Standard solution:** 0.0085 mg/mL of USP Fumaric Acid RS and 0.0017 mg/mL of USP Maleic Acid RS in water. Sonication may be used to promote dissolution.
**Sample solution:** 2.8 mg/mL of Almotriptan Malate in water. Sonication may be used to promote dissolution.
**Chromatographic system**
(See *Chromatography* ⟨621⟩*, System Suitability*.)
**Mode:** LC
**Detector:** UV 220 nm
**Column:** 4.6-mm × 25-cm; 5-µm packing L7
**Flow rate:** 0.7 mL/min
**Injection volume:** 10 µL
**Run time:** NLT 1.6 times the retention time of fumaric acid
**System suitability**
**Sample:** *Standard solution*
[NOTE—See *Table 4* (IRA 1-May-2017) for the relative retention times.]
**Suitability requirements**
**Resolution:** NLT 2.0 between fumaric acid and maleic acid
**Relative standard deviation:** NMT 5.0% for fumaric acid from six injections
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of fumaric acid ($C_4H_4O_4$) in the portion of Almotriptan Malate taken:

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

$r_U$ = peak response of fumaric acid from the *Sample solution*
$r_S$ = peak response of fumaric acid from the *Standard solution*
$C_S$ = concentration of USP Fumaric Acid RS in the *Standard solution* (mg/mL)
$C_U$ = concentration of Almotriptan Malate in the *Sample solution* (mg/mL)

**Acceptance criteria:** See *Table 4*.

**Table 4** (IRA 1-May-2017)

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Malic acid[a] | 0.60 | — |
| Maleic acid[a] | 0.80 | — |
| Fumaric acid | 1.0 | 0.2 |

[a] Included for identification purposes only.

## SPECIFIC TESTS

***Change to read:***

- **WATER DETERMINATION** ⟨921⟩*, Method I, Method Ia*: (IRA 1-May-2017) NMT 0.5%

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

***Change to read:***

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Almotriptan Malate RS
USP Almotriptan Related Compound B RS
2-{5-[(Pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine hemifumarate.
$C_{15}H_{21}N_3O_2S \cdot {}^1/_2C_4H_4O_4$ (IRA 1-May-2017) 365.46
USP Almotriptan Related Compound C RS
*N*-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.
$C_{16}H_{23}N_3O_2S$ 321.44
USP Almotriptan Related Compound D RS
1-[({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl) sulfonyl]pyrrolidine *N*-oxide.
$C_{17}H_{25}N_3O_3S$ 351.46
USP Fumaric Acid RS
USP Maleic Acid RS