Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-May-2021
Document Type: USP Monographs
DocId: GUID-4FCCEA0D-EC0A-4E7F-BAAB-BC25898D43D4_7_en-US
DOI: https://doi.org/10.31003/USPNF_M3728_07_01
DOI Ref: n1j4y

Ropinirole Extended-Release Tablets

DEFINITION

Ropinirole Extended-Release Tablets contain ropinirole hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of ropinirole free base ($C_{16}H_{24}N_2O$).

IDENTIFICATION

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

Buffer: Dissolve 4.5 g of dibasic sodium phosphate dihydrate in 900 mL of water. Adjust with phosphoric acid to a pH of 7.0. Dilute with water to 1 L.

Mobile phase: Methanol and *Buffer* (75:25)

Dilute phosphoric acid: Dissolve 0.7 mL of phosphoric acid in 1 L of water.

Diluent: Acetonitrile and *Dilute phosphoric acid* (80:20)

System suitability solution: 0.1 mg/mL of USP Ropinirole Hydrochloride RS and 0.003 mg/mL of USP Ropinirole Related Compound B RS in *Diluent*. Sonication may be used to aid dissolution.

Standard solution: 0.11 mg/mL of USP Ropinirole Hydrochloride RS in *Diluent*. Sonication may be used to aid dissolution.

Sample solution: Nominally 0.05–0.2 mg/mL of ropinirole prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask containing 75% of the flask volume of *Diluent*. Sonicate for NLT 30 min. Allow to cool to room temperature. Dilute with *Diluent* to volume. Pass a portion of the solution through a nylon filter of 0.45-µm pore size and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 12.5-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of ropinirole

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between ropinirole related compound B and ropinirole, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) 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 ropinirole from the *Sample solution*

r_S = peak response of ropinirole from the *Standard solution*

C_S = concentration of USP Ropinirole Hydrochloride RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of ropinirole free base, 260.37

M_{r2} = molecular weight of ropinirole hydrochloride, 296.84

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Solution A: 121.2 g/L of trishydroxymethylaminomethane in water

Buffer 1: Dissolve 2.1 g of citric acid monohydrate in 900 mL of water. Adjust with *Solution A* to a pH of 4.0. Dilute with water to 1 L.

Buffer 2: Dissolve 3.9 g of ammonium acetate in 900 mL of water. Adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1 L.

Medium: *Buffer 1*; 500 mL. Deaerate as appropriate.

Apparatus 2: 100 rpm with tablet holder. See *Figure 1*.

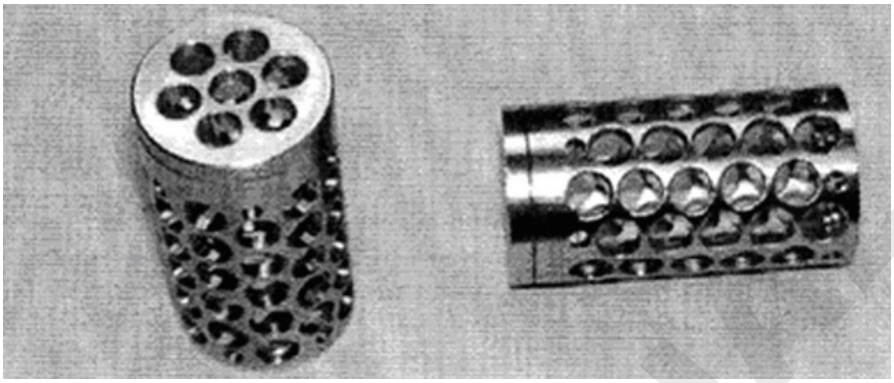

Figure 1. A 37-mm (length) × 19-mm (diameter) stainless steel sinker with screw cap drilled with seven 4-mm holes, bottom drilled with seven 5-mm holes, 12 longitudinal series of 5-mm holes alternately starting and ending with one 3-mm hole, polished electrochemically or with a suitably validated alternative.

Times: 2, 12, and 24 h

Mobile phase: Acetonitrile, methanol, and *Buffer 2* (14:6:80)

Standard solution: (*L*/400) mg/mL of USP Ropinirole Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL for 12-mg Tablets; 100 µL for all other strengths

Run time: NLT 2 times the retention time of ropinirole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at each time point (*i*):

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Ropinirole Hydrochloride RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ropinirole free base, 260.37

M_{r2} = molecular weight of ropinirole hydrochloride, 296.84

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	12	45–65
3	24	NLT 80

The percentages of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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

Solution A: 121.2 g/L of trishydroxymethylaminomethane in water

Buffer 1: Dissolve 2.1 g of citric acid monohydrate and 11.7 mL of *Solution A* in 1000 mL of water. Adjust with *Solution A* to a pH of 4.0.

Buffer 2: Dissolve 4.2 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.5.

Medium: *Buffer 1*; 500 mL

Apparatus 2: 100 rpm

Times: 2, 6, 12, and 24 h

Mobile phase: Acetonitrile and *Buffer 2* (20:80)

Standard solution: (*L*/500) mg/mL of USP Ropinirole Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Centrifuge a portion of the solution under test.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 2 times the retention time of ropinirole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of ropinirole ($C_{16}H_{24}N_2O$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of ropinirole from the *Sample solution*

r_S = peak response of ropinirole from the *Standard solution*

C_S = concentration of USP Ropinirole Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

C_i = concentration of ropinirole in the *Sample solution* at the specified time point (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ropinirole free base, 260.37

M_{r2} = molecular weight of ropinirole hydrochloride, 296.84

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	14–34
2	6	42–62
3	12	68–88
4	24	NLT 85

The percentages of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Buffer: 1.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Medium: 0.1 N hydrochloric acid VS; 500 mL

Apparatus 2: 100 rpm, with sinkers

Times: 1, 6, 12, and 24 h

Mobile phase: Acetonitrile and *Buffer* (10:90)

▲**Standard stock solution:** 0.23 mg/mL of USP Ropinirole Hydrochloride RS prepared as follows. Transfer an appropriate amount of USP Ropinirole Hydrochloride RS to a suitable volumetric flask. Add *Mobile phase* to about 50% of the final volume, and sonicate to dissolve. Dilute with *Mobile phase* to volume.▲ (USP 1-May-2021)

Standard solution: (*L*/500) mg/mL of USP Ropinirole Hydrochloride RS▲from the *Standard stock solution*,▲ (USP 1-May-2021) in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L1

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 2 times the retention time of ropinirole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT ▲2.0▲ (USP 1-May-2021)

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of ropinirole ($C_{16}H_{24}N_2O$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of ropinirole and 3-oxo ropinirole from the *Sample solution*. [NOTE—The relative retention times for ropinirole and 3-oxo ropinirole are 1.0 and ▲0.93,▲ (USP 1-May-2021) respectively.]

r_S = peak response of ropinirole from the *Standard solution*

C_S = concentration of USP Ropinirole Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

C_i = concentration of ropinirole in the *Sample solution* at the specified time point (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ropinirole free base, 260.37

M_{r2} = molecular weight of ropinirole hydrochloride, 296.84

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 25
2	6	40–60

Time Point (*i*)	Time (h)	Amount Dissolved (%)
3	12	65–85
4	24	NLT 80

The percentages of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Solution A: 42 g/L of citric acid in water

Solution B: 59 g/L of sodium citrate dihydrate in water

Solution C: To a 1000-mL volumetric flask containing about 800 mL of water, slowly add 65.7 mL of phosphoric acid. Cool and dilute with water to volume.

Medium: pH 4.0 citrate buffer (transfer 165 mL of *Solution A* and 85 mL of *Solution B* to a 1-L volumetric flask and dilute with water to volume; adjust with 2 N sodium hydroxide TS to a pH of 4.0, if needed); 500 mL

Apparatus 2: 100 rpm, with sinker. See *Dissolution* ⟨711⟩, *Figure 2a*.

Times: 1, 6, 12, and 24 h

Buffer: 8.7 g/L of dibasic potassium phosphate and 5 mL/L triethylamine in water. Adjust with *Solution C* to a pH of 7.2, if needed.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard stock solution: 0.365 mg/mL of USP Ropinirole Hydrochloride RS in water. Sonicate as needed.

Standard solution: 0.018 mg/mL of USP Ropinirole Hydrochloride RS from *Standard stock solution* in *Medium*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

Sample solution: Pass a portion of the solution under test through a suitable filter. Replace the portion of solution removed from the vessel with an equivalent volume of warmed *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 248 nm

Column: 4.6-mm × 10.0-cm; 3-µm packing L1

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 60 µL

Run time: NLT 2 times the retention time of ropinirole

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 concentration (C_i) of ropinirole ($C_{16}H_{24}N_2O$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of ropinirole from the *Sample solution*

r_S = peak response of ropinirole from the *Standard solution*

C_S = concentration of USP Ropinirole Hydrochloride RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of ropinirole free base, 260.37

M_{r2} = molecular weight of ropinirole hydrochloride, 296.84

Calculate the percentage of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of ropinirole in *Medium* in the portion of sample withdrawn at each time point (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	6	40–60
3	12	60–80
4	24	NLT 80

The percentages of the labeled amount of ropinirole ($C_{16}H_{24}N_2O$) dissolved at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: 0.05% (v/v) trifluoroacetic acid in water

Solution B: Acetonitrile and methanol (80:20)

Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	84	16
23	84	16
36	40	60
36.1	84	16
50	84	16

Diluent 1: Acetonitrile and *Solution A* (80:20)

Diluent 2: *Diluent 1* and *Solution A* (20:80)

System suitability solution: 0.03 mg/mL of USP Ropinirole Hydrochloride RS and 0.001 mg/mL of USP Ropinirole Related Compound B RS in *Diluent 2*. Sonication may be used to aid dissolution.

Sensitivity solution: 0.015 µg/mL of USP Ropinirole Hydrochloride RS in *Diluent 2*

Standard solution: 0.15 µg/mL of USP Ropinirole Related Compound B RS in *Diluent 2*

Sample stock solution: Nominally 0.13–0.14 mg/mL of ropinirole from a suitable number of Tablets containing 20–50 mg of ropinirole prepared as follows. Homogenize an appropriate number of Tablets in a suitable volume of *Diluent 1*. Pass a portion of the solution through a nylon filter of 0.45-µm pore size and use the filtrate.

Sample solution: Nominally 26–28 µg/mL of ropinirole from the *Sample stock solution* and *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between ropinirole related compound B and ropinirole, *System suitability solution*

Relative standard deviation: NMT 10% for ropinirole related compound B, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ropinirole related compound B 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 ropinirole related compound B from the *Sample solution*

r_S = peak response of ropinirole related compound B from the *Standard solution*

C_S = concentration of USP Ropinirole Related Compound B RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of ropinirole in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of ropinirole related compound B free base, 274.36

M_{r2} = molecular weight of ropinirole related compound B hydrochloride, 310.82

Calculate the percentage of each degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/F)/[\Sigma(r_U/F) + r_R] \times 100$$

r_U = peak response of each degradation product from the *Sample solution*

F = relative response factor for the corresponding degradation product from *Table 6*

r_R = peak response of ropinirole from the *Sample solution*

Acceptance criteria: See *Table 6*. Disregard peaks less than 0.05%.

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ropinirole monopropyl[a]	0.42	1.0	0.5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ropinirole related compound B	0.89	—	0.5
Ropinirole *N*-hydroxymethyl[b]	0.94	0.71	0.5
Ropinirole	1.00	—	—
Ropinirole *N*-oxide[c]	1.31	1.0	0.5
Ropinirole methylene dimer[d]	1.82	1.0	0.5
Propylidene ropinirole[e,f]	1.96	2.0	—
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	1.5

[a] 4-[2-(Propylamino)ethyl]indolin-2-one.

[b] 4-[2-(Dipropylamino)ethyl]-1-(hydroxymethyl)indolin-2-one.

[c] *N*-[2-(2-Oxoindolin-4-yl)ethyl]-*N*-propylpropan-1-amine oxide.

[d] ▲1,1'-Methylenebis{4-[2-(dipropylamino)ethyl]indolin-2-one}▲ (USP 1-May-2021) ·

[e] (*Z*)-4-[2-(Dipropylamino)ethyl]-3-propylideneindolin-2-one.

[f] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total degradation products for the drug product.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Ropinirole Hydrochloride RS

USP Ropinirole Related Compound B RS

4-[2-(Dipropylamino)ethyl]indoline-2,3-dione hydrochloride.

$C_{16}H_{22}N_2O_2 \cdot HCl$ 310.82

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ROPINIROLE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(1)

Current DocID: GUID-4FCCEA0D-EC0A-4E7F-BAAB-BC25898D43D4_7_en-US

DOI: https://doi.org/10.31003/USPNF_M3728_07_01

DOI ref: n1j4y