Mobile phase: Tetrahydrofuran and *Buffer* (30:70)
Diluent: Tetrahydrofuran and water (30:70)
System suitability solution: In a 250-mL separator, mix 100 mL of water, 100 mL of dichloromethane, 30 mg of USP Ketorolac Tromethamine RS, and 1 mL of 1 N hydrochloric acid. Insert the stopper, shake, and allow the layers to separate. Transfer the lower dichloromethane layer to a stoppered borosilicate glass flask, and discard the upper layer. Expose the dichloromethane solution to direct sunlight for 10–15 min. Transfer 1.0 mL of the solution to a vial, evaporate in a current of air or in a stream of nitrogen to dryness, add 1.0 mL of *Diluent*, and swirl to dissolve. [NOTE—This solution may be stored under refrigeration and used as long as the chromatogram obtained as directed for *Analysis* is suitable for identifying the peaks due to the ketorolac 1-keto analog and ketorolac 1-hydroxy analog, and for the measurement of the resolution between the ketorolac 1-keto analog and ketorolac.]
Standard solution: 0.4 mg/mL of USP Ketorolac Tromethamine RS in *Diluent*
Sample solution: 0.4 mg/mL of Ketorolac Tromethamine in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 313 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for the ketorolac 1-hydroxy analog, the ketorolac 1-keto analog, and ketorolac are about 0.63, 0.89, and 1.0, respectively. Make adjustments if necessary to achieve a retention time for ketorolac of about 8–12 min.]
Suitability requirements
Resolution: NLT 1.5 between ketorolac 1-keto analog and ketorolac, *System suitability solution*
Column efficiency: NLT 5500 theoretical plates, *Standard solution*
Relative standard deviation: NMT 1.5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of keterolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$) in the portion of Keterolac Tromethamine taken:

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

r_U = peak area from the *Sample solution*
r_S = peak area from the *Standard solution*
C_S = concentration of USP Ketorolac Tromethamine RS in the *Standard solution* (mg/mL)
C_U = concentration of Ketorolac Tromethamine in the *Sample solution* (mg/mL)
Acceptance criteria: 98.5%–101.5% on the dried basis

IMPURITIES
- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

Delete the following:

- **HEAVY METALS,** *Method II* ⟨231⟩: 20 ppm (Official 1-Dec-2015)
- **ORGANIC IMPURITIES**
Mobile phase, Diluent, System suitability solution, Standard solution, and **Sample solution:** Prepare as directed in the *Assay*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 313 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: 3 times the retention time of ketorolac
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Ketorolac Tromethamine taken:

$$\text{Result} = (r_U/r_T) \times F \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*
r_T = sum of all the peak responses from the *Sample solution*
F = relative response factor (see *Table 1*)
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Impurity having a 0.54 relative retention time	0.54	2.2	0.5
Ketorolac 1-hydroxy analog	0.63	0.67	0.1
Impurity having a 0.66 relative retention time	0.66	0.91	0.5
Ketorolac 1-keto analog	0.89	0.52	0.1
Ketorolac tromethamine	1.0	1.0	—
Total impurities	—	—	1.0

SPECIFIC TESTS
- **pH** ⟨791⟩
Sample solution: 10 mg/mL
Acceptance criteria: 5.7–6.7
- **LOSS ON DRYING** ⟨731⟩
Analysis: Dry under vacuum at 60° for 3 h.
Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.
- **USP REFERENCE STANDARDS** ⟨11⟩
USP Ketorolac Tromethamine RS

Ketorolac Tromethamine Injection

DEFINITION
Ketorolac Tromethamine Injection is a sterile solution of Ketorolac Tromethamine. It contains NLT 90.0% and NMT 110.0% of the labeled amount of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$).

IDENTIFICATION
- **A.**
Sample: *Standard solution* and *Sample solution* (1:1), prepared as directed in the *Assay*
Analysis: Chromatograph the *Sample* as directed in the *Assay*

Acceptance criteria: The chromatogram obtained exhibits two main peaks corresponding to ketorolac and the internal standard.

ASSAY

- **PROCEDURE**

[NOTE—Protect all the solutions from light.]

Mobile phase: Methanol, water, and glacial acetic acid (55:44:1)

Diluent: Methanol and water (1:1). [NOTE—Resolution may be increased by increasing the proportion of water in the *Mobile phase*.]

Internal standard solution: 0.3 mg/mL of naproxen in methanol

Standard stock solution: 0.24 mg/mL of USP Ketorolac Tromethamine RS in methanol

Standard solution: 0.024 mg/mL of USP Ketorolac Tromethamine RS from the *Standard stock solution* and 0.03 mg/mL of *Internal standard solution* in *Diluent*

Sample stock solution: Nominally 0.24 mg/mL of ketorolac tromethamine in methanol, from an equivalent volume of Injection.

Sample solution: Transfer 5.0 mL of the *Sample stock solution* and 5.0 mL of the *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for ketorolac and naproxen are 0.7 and 1.0, respectively.]

Resolution: NLT 5.4 between ketorolac and naproxen

Column efficiency: NLT 2700 theoretical plates for the ketorolac peak

Tailing factor: NMT 1.5 for the ketorolac peak

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$) in each mL of Injection taken:

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

R_U = peak response ratio of ketorolac to naproxen from the *Sample solution*

R_S = peak response ratio of ketorolac to naproxen from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

SPECIFIC TESTS

- **pH** ⟨**791**⟩**:** 6.9–7.9
- **BACTERIAL ENDOTOXINS TEST** ⟨**85**⟩**:** It contains NMT 5.8 USP Endotoxin Units/mg of ketorolac tromethamine.
- **STERILITY TESTS** ⟨**71**⟩**:** Meets the requirements for *Test for Sterility of the Product to Be Examined, Membrane Filtration*
- **PARTICULATE MATTER IN INJECTIONS** ⟨**788**⟩**:** Meets the requirements for small-volume injections
- **OTHER REQUIREMENTS:** Meets the requirements for *Injections* ⟨1⟩

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose containers, preferably of Type I glass, protected from light, and

- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Endotoxin RS

USP Ketorolac Tromethamine RS

Ketorolac Tromethamine Tablets

DEFINITION

Ketorolac Tromethamine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$).

IDENTIFICATION

- 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**

Mobile phase: Methanol, water, and glacial acetic acid (55:44:1)

Diluent: Methanol and water (1:1). [NOTE—Protect all volumetric solutions from light.]

Standard stock solution: 0.24 mg/mL of USP Ketorolac Tromethamine RS in methanol

Standard solution: 24 µg/mL of USP Ketorolac Tromethamine RS in *Diluent* from *Standard stock solution*

System suitability stock solution: 25 µg/mL each of USP Ketorolac Tromethamine RS, USP Ketorolac Related Compound A RS, USP Ketorolac Related Compound B RS, USP Ketorolac Related Compound C RS, and USP Ketorolac Related Compound D RS in methanol

System suitability solution: 0.25 µg/mL each of USP Ketorolac Tromethamine RS, USP Ketorolac Related Compound A RS, USP Ketorolac Related Compound B RS, USP Ketorolac Related Compound C RS, and USP Ketorolac Related Compound D RS in *Standard solution* from *System suitability stock solution*

Sample stock solution: 0.2 mg/mL of ketorolac tromethamine prepared as follows. Transfer 10 Tablets to a suitable volumetric flask. Add a quantity of water equivalent to about 10% of the volume of the flask, and sonicate until the Tablets are disintegrated. Add a quantity of methanol equivalent to 40% of the volume of the flask, and sonicate for 10 min to dissolve the ketorolac tromethamine. Cool to ambient temperature, dilute with methanol to volume, and mix. Centrifuge, or allow to settle.

Sample solution: 0.02 mg/mL of ketorolac tromethamine in *Diluent* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 100 µL

Run time: 3.8 times the retention time of ketorolac peak

System suitability

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

[NOTE—The relative retention times are 0.8 for ketorolac related compound B and 1.0 for the ketorolac peaks.]

Suitability requirements

Resolution: NLT 1.5 each between the keterolac and ketorolac related compound B and ketotolac and ketorolac related compound C peaks, *System suitability solution*

Column efficiency: NLT 2700 theoretical plates, *Standard solution*