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Lidocaine and Prilocaine Cream

» Lidocaine and Prilocaine Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$).

Packaging and storage—Preserve in collapsible tubes or in tight containers. Do not store above 30°. Do not freeze.

USP Reference standards ⟨11⟩—

USP Lidocaine RS
USP Prilocaine Hydrochloride RS
USP Prilocaine Related Compound B RS

(*RS*)-*N*-(4-Methylphenyl)-2-(propylamino)propanamide.

$C_{13}H_{20}N_2O$ 220.31

Identification—The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Microbial enumeration tests ⟨61⟩ and Tests for specified microorganisms ⟨62⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

Minimum fill ⟨755⟩: meets the requirements.

pH ⟨791⟩: between 8.7 and 9.7, determined in a solution (1 in 10) or in the undiluted Cream.

Related compounds—

Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay*.

Standard solution—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.002 mg per mL of each compound. Immediately store this solution at or below 10°.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay*.

Chromatographic system (see *Chromatography ⟨621⟩*)—Proceed as directed in the *Assay*. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are listed in *Table 1;* and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard solution* a minimum of six times, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the portion of the Cream taken by the formula:

$$100C(r_U/r_S)(V/W)(100/L)(1/F)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard solution;* r_U is the individual peak response of the impurities obtained from the *Test solution;* r_S is the individual peak response for either lidocaine or prilocaine obtained from the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of the Cream taken to prepare the *Test solution; L* is the individual label claim, in percent, for either lidocaine or prilocaine; *F* is the relative response factor for each related compound as listed in *Table 1;* and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectively (these are used only for calculation involving prilocaine related compounds). The percentages of lidocaine related compounds and prilocaine related compounds are calculated using the concentration and peak response from USP Lidocaine RS and USP Prilocaine Hydrochloride RS, respectively. The designation of whether an impurity is a lidocaine related compound or prilocaine related compound is specified in *Table 1*. The percentage of any individual unknown related compound is determined using the concentration and peak response from USP Prilocaine Hydrochloride RS in the *Standard solution*.

Table 1

Related Compound	Relative Retention Time[a]	Relative Response Factor (*F*)	Limit
o-Toluidine	0.38	2.3 (P)[b]	not more than 2.0%
n-Chloroacetyl-2,6-xylidine	0.54	1.0 (L)[c]	not more than 0.1%
2,6-Dimethylaniline	0.67	3.3 (L)[c]	not more than 0.1%
Prilocaine	1.00	—	—
2-Diethylaminoaceto-2,4-xylidine	1.33	0.8 (L)[c]	not more than 0.1%
Lidocaine	2.14	—	—
n-Dichloroacetyl-2,6-xylidine	2.98	2.2 (L)[c]	not more than 0.1%
Any other individual related compounds	—	1.0 (P)[b]	not more than 0.2%
Total related compounds, excluding *o*-toluidine	—	—	not more than 1.0%

[a] Relative to the prilocaine peak.

[b] P designates a prilocaine related compound.

[c] L designates a lidocaine related compound.

Assay—

Solution A—Dissolve about 2.73 g of monobasic potassium phosphate in 630 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

Solution B—Dissolve about 2.73 g of monobasic potassium phosphate in 900 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

Mobile phase—Use variable mixtures of filtered and degassed *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.2 mg per mL of each compound. Immediately store this solution at or below 10°.

System suitability solution—Dissolve an accurately weighed quantity of USP Prilocaine Related Compound B RS in the *Standard preparation,* and dilute quantitatively, and stepwise if necessary, with the *Standard preparation,* to obtain a solution having a known concentration of about 0.08 mg per mL of prilocaine related compound B.

Assay preparation—Transfer a portion of the Cream, equivalent to about 20 mg each of lidocaine and prilocaine, accurately weighed, to a 100-mL volumetric flask. Add 5 mL of 5 N sodium hydroxide to disperse the Cream, and mix. Add 5 mL of 5 N hydrochloric acid, and dilute with *Solution A* to volume, and mix. Pass a portion through a nylon filter having a 0.2-µm or finer porosity, discarding the first 1 mL, and use the filtrate. Immediately store this solution at or below 10°.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 232-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. The samples are maintained at or below 10°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	67	33	equilibration

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–11.0	67	33	isocratic
11.0–22.0	67→100	33→0	linear gradient
22.0–32.0	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.00 for prilocaine, 1.09 for prilocaine related compound B, and 2.14 for lidocaine; and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard preparation* a minimum of five times, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates, based on the prilocaine peak; the tailing factor is not more than 1.5, based on the prilocaine peak; and the relative standard deviation for replicate injections is not more than 2.0%.
Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the lidocaine and prilocaine peaks. Calculate the percentage of the label claim of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$) in the portion of Cream taken by the formula:

$$100C(r_U/r_S)(V/W)(100/L)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard preparation;* r_U and r_S are either the individual peak responses of lidocaine or prilocaine obtained from the *Assay preparation* and the *Standard preparation,* respectively; V is the volume, in mL, of the *Assay preparation; W* is the weight, in mg, of the Cream taken to prepare the *Assay preparation; L* is the individual label claim, in percent, for either lidocaine or prilocaine; and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectively (these are used only for calculating the percentage of prilocaine in the Cream).

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

Topic/Question	Contact	Expert Committee
LIDOCAINE AND PRILOCAINE CREAM	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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