Lidocaine and Prilocaine Cream—Revision to Related Compounds Test

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In accordance with the Rules and Procedures of the Council of Experts, this Revision Bulletin removes the two prilocaine process related impurities–Prilocaine related compound B and (RS)–2–Chloro–N–(2–methylphenylenyl)propanamide, as specified impurities in the Related compounds test. The two process related impurities are controlled in the Prilocaine drug substance monograph, which has a requirement of NMT 0.2% for any individual impurity, the same level specified in the Cream monograph for these two process impurities.

This Revision Bulletin is official as of this date. Official text will appear in the Second Supplement to *USP 31–NF 26*.

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(See revised Related compounds test below)

Change to read:

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 ?L) 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:

$$100C(rU / rS)(V / W)(100/L)(1/F)(220.31/256.77)$$

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; rU is the individual peak response of the impurities obtained from the Test solution; rS 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[1]	Relative Response Factor (F)	Limit
o–Toluidine	0.38	2.3 (P)[2]	not more than 2.0%
n–Chloroacetyl–2,6–xylidine	0.54	1.0 (L)[3]	not more than 0.1%
2,6–Dimethylaniline	0.67	3.3 (L)[3]	not more than 0.1%
~~(RS)–2–Chloro–N–(2–methylphenyl)propanamide~~	~~0.83~~	~~1.0 (P)[2]~~	~~not more than 0.2%~~

Prilocaine	1.00	–	–
~~Prilocaine related compound B~~	~~1.09~~	~~1.2 (P)[2]~~	~~not more than 0.2%~~
2–Diethylaminoaceto–2,4–xylidine	1.33	0.8 (L)[3]	not more than 0.1%
Lidocaine	2.14	–	–
n–Dichloroacetyl–2,6–xylidine	2.98	2.2 (L)[3]	not more than 0.1%
Any other individual related compounds	—	1.0 (P)[2]	not more than 0.2%
Total related compounds, excluding o–toluidine	–	–	not more than 1.0%

[1] relative to the prilocaine peaks

[2] P designates a prilocaine related compound

[3] L designates a lidocaine related compound