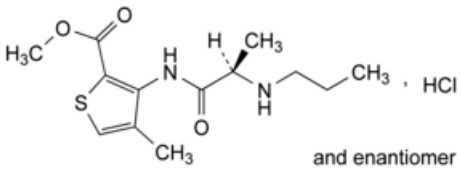
Edition: BP 2025 (Ph. Eur. 11.6 update)

Articaine Hydrochloride

General Notices

(Ph. Eur. monograph 1688)



$C_{13}H_{21}ClN_2O_3S$ 320.8 *23964-57-0*

Action and use

Local anaesthetic.

Ph Eur

DEFINITION

Methyl 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylate hydrochloride.

Content

98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Dissolve 50.0 mg in a 1 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with the same acid. Dilute 5.0 mL of the solution to 100.0 mL with a 1 g/L solution of *hydrochloric acid R*. Examined between 200 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 272 nm. The specific absorbance at the maximum is 290 to 320.

B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Place dropwise 20 µL of the test solution on 300 mg discs.

Test solution Dissolve 0.1 g in 5 mL of *water R*, add 3 mL of a saturated solution of *sodium hydrogen carbonate R* and shake twice with 2 mL of *methylene chloride R*. Combine the methylene chloride layers, dilute to 5.0 mL with *methylene chloride R* and dry over *anhydrous sodium sulfate R*.

Comparison *articaine hydrochloride CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution Dissolve 20 mg of the substance to be examined in 5 mL of *ethanol (96 per cent) R*.

Reference solution Dissolve 20 mg of *articaine hydrochloride CRS* in 5 mL of *ethanol (96 per cent) R*.

Plate *TLC silica gel F_{254} plate R*.

Mobile phase *triethylamine R*, *ethyl acetate R*, *heptane R* (10:35:65 *V/V/V*).

Application 5 µL.

Development Over a path of 15 cm.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Results The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 0.50 g in *water R* and dilute to 10 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method I*).

pH (*2.2.3*)

4.2 to 5.2.

Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20.0 mL with the same solvent.

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 5.0 mg of *articaine impurity A CRS* and 2.5 mg of *articaine impurity E CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 45 °C.

Mobile phase Mix 25 volumes of *acetonitrile R* and 75 volumes of a solution prepared as follows: dissolve 2.02 g of *sodium heptanesulfonate R* and 4.08 g of *potassium dihydrogen phosphate R* in *water R* and dilute to 1000 mL with the same solvent. Adjust to pH 2.0 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 10 µL.

Run time 5 times the retention time of articaine.

Relative retention With reference to articaine (retention time = about 9 min): impurity A = about 0.8; impurity E = about 0.86.

System suitability Reference solution (b):

— *resolution*: minimum 1.2 between the peaks due to impurities A and E.

Limits:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *sum of impurities other than A*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 32.08 mg of $C_{13}H_{21}ClN_2O_3S$.

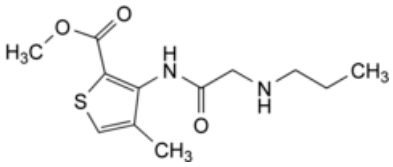
STORAGE

Protected from light.

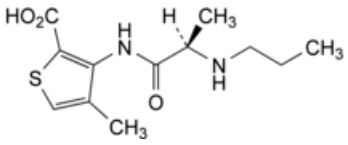
IMPURITIES

Specified impurities A.

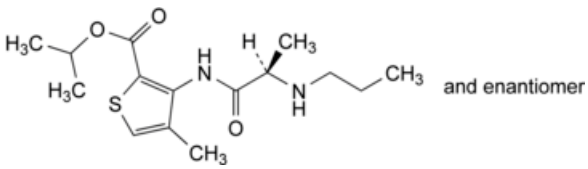
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C, D, E, F, G, H, I, J.



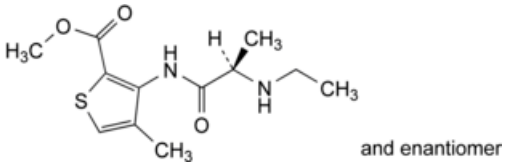
A. methyl 4-methyl-3-[[2-(propylamino)acetyl]amino]thiophene-2-carboxylate (acetamidoarticaine),



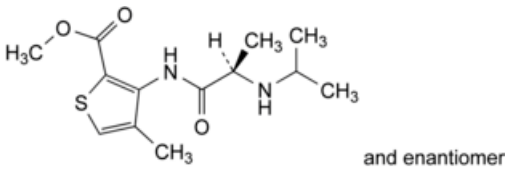
B. 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylic acid (articaine acid),



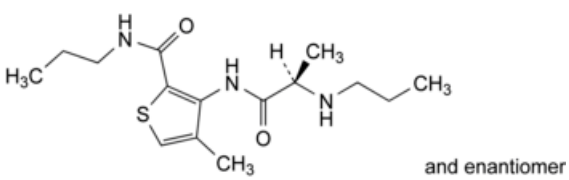
C. 1-methylethyl 4-methyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxylate (articaine isopropyl ester),



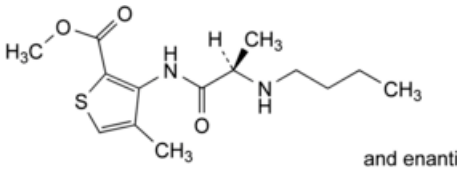
D. methyl 3-[[(2*RS*)-2-(ethylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (ethylarticaine),



E. methyl 4-methyl-3-[[(2*RS*)-2-[(1-methylethyl)amino]propanoyl]amino]thiophene-2-carboxylate (isopropylarticaine),

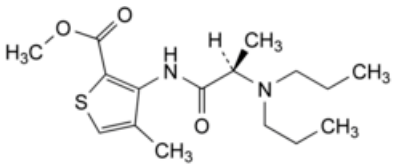


F. 4-methyl-*N*-propyl-3-[[(2*RS*)-2-(propylamino)propanoyl]amino]thiophene-2-carboxamide (articaine acid propionamide),



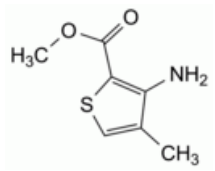
and enantiomer

G. methyl 3-[[(2*RS*)-2-(butylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (butylarticaine),

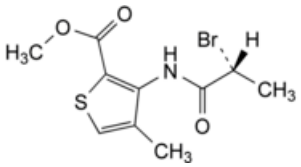


and enantiomer

H. methyl 3-[[(2*RS*)-2-(dipropylamino)propanoyl]amino]-4-methylthiophene-2-carboxylate (dipropylarticaine),



I. methyl 3-amino-4-methylthiophene-2-carboxylate (3-aminoarticaine),



and enantiomer

J. methyl 3-[[(2*RS*)-2-bromopropanoyl]amino]-4-methylthiophene-2-carboxylate (bromo compound).

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