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### DIETHYLCARBAMAZINE DIHYDROGEN CITRATE

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## (Diethylcarbamazini dihydrogenocitras)

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# Draft proposal for inclusion in The International Pharmacopoeia

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(May 2024)

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## DRAFT FOR COMMENTS

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nsp@who.int. For any technical questions, you may contact Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (<a href="mailto:schmidth@who.int">schmidth@who.int</a>), with a copy to Ms Sinéad Jones

(jonessi@who.int, nsp@who.int). Comments should be submitted through the online platform on or by 31 July 2024. Please note that only comments received by this deadline will be considered for the preparation of this document.

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Please send any request for permission to: Ms Sinéad Jones, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications, Department of Health Products Policy and Standards, World Health Organization, CH-1211 Geneva 27, Switzerland, email: jonessi@who.int.

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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/21.896:

### DIETHYLCARBAMAZINE DIHYDROGEN CITRATE

### (DIETHYLCARBAMAZINI DIHYDROGENOCITRAS)

Description	Date
Monograph revision drafted following up on information received from the custodian centre for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines and HealthCare.	July 2021
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications	April 2024
Draft revision sent out for public consultation	June – July 2024
Presentation to the 58 <sup>th</sup> WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2024
Further follow-up action as required.	

40 [Note from the Secretariat. It is proposed to revise the monograph on Diethylcarbamazine

41 dihydrogen citrate to avoid the use of organoleptic tests and of toxic solvents.]

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#### DIETHYLCARBAMAZINE DIHYDROGEN CITRATE

### (DIETHYLCARBAMAZINI DIHYDROGENOCITRAS)

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- 47 **Molecular formula.**  $C_{10}H_{21}N_3O$ ,  $C_6H_8O_7$  or  $C_{16}H_{29}N_3O_8$
- 48 Relative molecular mass. 391.4
- 49 Graphic formula.

- 51 Chemical name. N,N-Diethyl-4-methyl-1-piperazinecarboxamide citrate (1:1); N,N-
- 52 diethyl-4-methyl-1-piperazinecarboxamide 2-hydroxy-1,2,3-propanetricarboxylate
- 53 (1:1).
- 54 **CAS Registry Number.** 1642-54-2.
- **Description.** A white, crystalline powder; odourless or almost odourless.
- Solubility. Very soluble in water  $\underline{R}$ ; soluble in 35 parts of ethanol (~750 g/L) TS;
- 57 practically insoluble in <u>acetone</u> ether R.
- 58 Category. Filaricide.
- 59 **Storage.** Diethylcarbamazine dihydrogen citrate should be kept in a tightly closed
- 60 container, protected from light.
- 61 Additional information. Diethylcarbamazine dihydrogen citrate is hygroscopic; it
- 62 has an acid and bitter taste. Even in the absence of light, Diethylcarbamazine

- 63 dihydrogen citrate is gradually degraded on exposure to a humid atmosphere, the
- decomposition being faster at higher temperatures.

### 65 Requirements

- **Definition.** Diethylcarbamazine dihydrogen citrate contains not less than 98.0% and
- not more than 101.0% of  $C_{10}H_{21}N_3O$ ,  $C_6H_8O_7$ , calculated with reference to the
- anhydrous substance.

### **Identity tests**

- Either tests A and D, or tests B, C and D may be applied.
- Carry out the test as described under 1.7 Spectrophotometry in the infrared A. 71 region. The infrared adsorption spectrum is concordant with the spectrum 72 obtained from diethylcarbamazine dihydrogen citrate RS or with the reference 73 spectrum of diethylcarbamazine dihydrogen citrate. Dissolve 0.05 g in 25 mL 74 of water. Add 1 mL of sodium hydroxide (~80 g/l) TS and 4 mL of carbon 75 disulfide R, and shake for 2 minutes. Separate the aqueous layer. Centrifuge the 76 lower layer if necessary, and filter through a dry filter, collecting the filtrate in 77 a small flask provided with a glass stopper. Carry out the examination of the 78 filtered solution using carbon disulfide R as the blank as described under 1.7 79 Spectrophotometry in the infrared region. The infrared absorption spectrum is 80 concordant with the spectrum obtained from diethylcarbamazine dihydrogen 81 citrate RS treated similarly or with the reference spectrum of 82 diethylcarbamazine base. 83
- B. Carry out the test as described under 1.14.1 Chromatography, Thin-layer
  chromatography, using the conditions given under "Impurities A and B" with
  the following modifications. Use solution (A) as described. For solution (B),
  prepare a solution containing 50 mg of diethylcarbamazine dihydrogen citrate
  RS per mL of methanol R. The principal spot in the chromatogram obtained

89		with solution (A) corresponds in position, appearance and intensity with the
90		spot due to diethylcarbamazine in the chromatogram obtained with solution
91		(B). Dissolve 0.5 g in 10 mL of water, add 10 mL of sodium hydroxide (1
92		mol/l)VS, and extract with 4 successive quantities, each of 5 mL of chloroform
93		R. Retain the aqueous layer for test C. Wash the combined chloroform extracts
94		with water, filter through a plug of cotton wool, and evaporate the chloroform.
95		Add 1 mL of ethyl iodide R to the residue, and heat gently under a reflux
96		condenser for 5 minutes. Cool, separate the viscous yellow oil, and dissolve it
97		in ethanol (~750 g/l) TS. Add, with continuous stirring, sufficient ether R to
98		precipitate the quaternary ammonium salt, and filter. Dissolve the precipitate in
99		ethanol (~750 g/l) TS, reprecipitate with ether R, and dry at 105°C; melting
100		temperature, about 152°C (1-diethylcarbamoyl-4 methylpiperazine ethiodide).
101	C.	Dissolve 0.1 g of the test substance in 5 mL of water R. The solution aqueous
102		layer from test B yields reaction B described under 2.1 General identification
103		<u>tests</u> as characteristic of citrates.
	_	
104	D.	Melting temperature, after drying at 80 °C, about 137 °C.
105	Heavy	w metals. Use 1.0 g for the preparation of the test solution as described under
106		Limit test for heavy metals, Procedure 1: determine the heavy metals content
107		ling to Method A; not more than 20 μg/g.
108	Sulfat	ted ash. Not more than 1.0 mg/g.
109	Clarit	y and colour of solution. Dissolve 2.5 g in carbon-dioxide-free water R and
110	dilute	to 25 mL with the same solvent. The solution not more intensely coloured than
111	refere	nce solution BY6 when compared as described under 1.11.2 Degree of
112	colora	ation of liquids.

113	Water. Determine as described under 2.8 Determination of water by the Karl Fischer
114	method, Method A, using about 1 g of the substance; the water content is not more
115	than 10 mg/g.
116	Loss on drying. Dry 1.000 g of the test substance at 60 °C for 4 hours; it loses not
117	more than 5 mg/g.
118	pH value. pH of a 30 mg/mL solution, 3.5-4.5.
119	N -Methylpiperazine. Carry out the test as described under 1.14.1 Thin layer
120	chromatography, using silica gel R1 as the coating substance and a mixture of 6
121	volumes of ethanol (~750 g/L) TS, 3 volumes of glacial acetic acid R and 1 volume of
122	water as the mobile phase. Apply separately to the plate 5 $\mu$ l of each of 2 solutions in
123	methanol R containing (A) 50 mg of the test substance per mL and (B) 0.050 mg of N
124	methylpiperazine R per mL. After removing the plate from the chromatographic
125	chamber, allow it to dry in air, spray with a mixture of 3 volumes of platinic chloride
126	(60 g/L) TS, 97 volumes of water and 100 volumes of potassium iodide (60 g/L) TS,
127	and examine the chromatogram in daylight. The spot obtained with solution B is
128	more intense than any spot, corresponding in position and appearance, obtained with
129	solution A.
130	Impurities A and B. Carry out the test as described under 1.14.1 Chromatography,
131	Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture
132	of 5 volumes of ammonia (~260 g/L) TS, 30 volumes of methyl ethyl ketone R and 65
133	volumes of methanol R as the mobile phase. Develop the plate for 2/3 of its height.
134	Apply separately to the plate 10 μl of each of 3 solutions in methanol R containing (A)
135	50 mg of the test substance per mL, (B) 0.10 mg of N-methylpiperazine R (impurity
136	A) per mL and (C) 0.10 mg of dimethylpiperazine R (impurity B). After removing the
137	plate from the chromatographic chamber, dry it at 100-105 °C and place it in a
138	chamber with iodine vapour of 30 minutes. Examine the plate in daylight.

In the chromatogram obtained with solution (A)

140	• any spot due to impurity A is not more intense than the corresponding spot in
141	the chromatogram obtained with solution (B) (0.2 per cent);
142	• any spot due to impurity B is not more intense than the corresponding spot in
143	the chromatogram obtained with solution (C) (0.2 per cent).
144	Related substances. Carry out the test as described under 1.14.1 Chromatography,
145	High-performance liquid chromatography, using a stainless steel column (15 cm x 3.9
146	mm) packed with end-capped particles of silica gel, the surface of which has been
147	modified with chemically-bonded octadecylsilyl groups (5 $\mu$ m). As the mobile phase
148	use a mixture of 100 volumes of methanol for chromatography R and 900 volumes of
149	a 10 g/L solution of potassium dihydrogen phosphate R (V/V).
150	Operate with a flow rate of 0.8 mL per minute. As a detector use an ultraviolet
151	spectrophotometer set at a wavelength of 220 nm.
152	Prepare the following solutions:
153	For solution (A), dissolve 31.2 g of potassium dihydrogen phosphate R in water R and
154	dilute to 1000 mL with the same solvent.
155	For solution (1), suspend 0.30 g of the test substance in solution (A) and dilute to 100
156	mL with solution (A). Filter or centrifuge and use the clear filtrate or supernatant.
157	For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with solution (A).
158	For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL with solution (A).
159	For solution (4), dissolve 10 mg of citric acid R in solution (A) and dilute to 10 mL
160	with solution (A).
161	For solution (5), add 0.5 mL of hydrogen peroxide (~330 g/L) TS to 3 mL of solution

(1). Maintain the solution at 80 °C for 3 h. Dilute to 100 mL with solution (A).

163	Inject 20 μL each of solution (1), (2), (3), (4) and (5) and record the chromatograms
164	for about twice the retention time of diethylcarbamazine.
165	Use the chromatogram obtained with solution (4) to identify the peak due to citrate
166	and the chromatogram obtained with solution (5) to identify the peak due to the
167	degradation product. The impurities are eluted, if present, at the following relative
168	retention with reference to diethylcarbamazine (retention time about 7 minutes):
169	citrate about 0.2; degradation product about 1.6.
170	The test is not valid unless in the chromatogram obtained with solution (4) the
171	resolution between the peaks due to diethylcarbamazine and the degradation product
172	is at least 5. Also, the test is not valid unless in the chromatogram obtained with
173	solution (3) the peak due to diethylcarbamazine is detected with a signal-to-noise ratio
174	of at least 10.
175	In the chromatogram obtained with solution (1):
176	• the area of any impurity peak is not greater than 0.1 times the area of the peak
177	due to dimethylcarbamazine in the chromatogram obtained with solution (2)
178	<u>(0.10 %).</u>
179	• The sum of the areas of all impurity peaks is not greater than 0.5 times the area
180	of the peak due to dimethylcarbamazine in the chromatogram obtained with
181	solution (2) (0.5 %). Disregard any peak with an area less than the area of the
182	peak due to dimethylcarbamazine in the chromatogram in the chromatogram
183	obtained with solution (3) (0.05%). Disregard the peak due to citrate.
184	<b>Assay.</b> Dissolve about 0.350 g, accurately weighed, in 30 mL of glacial acetic acid
185	R1, and titrate with perchloric acid (0.1 mol/L) VS as described under <u>2.6 Non-</u>
186	aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is
187	equivalent to 39.14 mg of $C_{10}H_{21}N_3O_{1}C_{6}H_{8}O_{7}$ .

## **Impurities**

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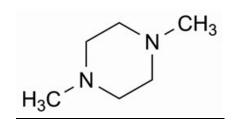
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190 H<sub>3</sub>C NH

191 A. <u>1-methylpiperazine</u>,



193 B. <u>1,4-dimethylpiperazine.</u>

### **Reference substance:**

## Diethylcarbamazine dihydrogen citrate RS

197 Established ICRS. Changes in the intended uses to be verified.

## 198 Infrared reference spectrum:

199 Reference spectrum of diethylcarbamazine dihydrogen citrate to be recorded.

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