



DEXTROMETHORPHAN HYDROBROMIDE

Proposed text for revision of

The International Pharmacopoeia

(May 2014)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr Herbert Schmidt, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidt@who.int; fax: (+41 22) 791 4730) by 7 July 2014.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

© World Health Organization 2014

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of the World Health Organization. The draft should not be displayed on any website.

Please send any request for permission to:

Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland.

Fax: (41-22) 791 4730; email: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/14.585

Draft revision for The International Pharmacopoeia:

DEXTROMETHORPHAN HYDROBROMIDE

	Date
Revision of draft monograph sent out for comment following a scientific assessment on behalf of the WHO Prequalification Team	May 2014
Collation of comments received	August–September 2014
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion	October 2014
Further follow-up action as required	

[Note from the Secretariat. Following consumption of dextromethorphan cough syrups contaminated with levomethorphan approximately 50 persons died in Pakistan in January 2013. A further suspected drug intoxication involving 11 patients was reported several months later, in September 2013, in Paraguay. Investigations revealed that the medicines administered were manufactured using adulterated dextromethorphan hydrobromide, which contained levomethorphan at levels varying between 9.5% to 22.6%. Following these incidents the World Health Organization issued Drug Alerts Nos 126 and 129 and called on all Member States to increase vigilance against adulterated Dextromethorphan/Dextromethorphan hydrobromide API.]

It is proposed to revise the monograph on Dextromethorphan hydrobromide in The International Pharmacopoeia with a view to add a statement under the section “Manufacture” requiring that the production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide. This limit was deemed appropriate following a scientific assessment on behalf of the WHO Prequalification Team.

A chiral method, selective for levomethorphan, is currently under development and shall be included in the “Supplementary Information Section” of The International Pharmacopoeia once elaborated.

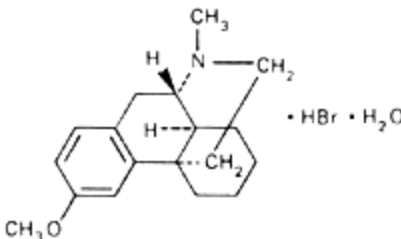
Changes from the current monograph are indicated in the text by insert or delete.]

DEXTROMETHORPHANI HYDROBROMIDUM
DEXTROMETHORPHAN HYDROBROMIDE

Molecular formula. $C_{18}H_{25}NO, HBr, H_2O$

Relative molecular mass. 370.3

Graphic formula.



Chemical name.

(+)-3-Methoxy-17-methyl-9 α ,13 α -14 α -morphinan hydrobromide monohydrate; (+)-*cis*-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2*H*-10,4a-iminoethanophenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

Description. A white or almost white, crystalline powder; ~~odourless or almost odourless.~~

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antitussive drug.

Storage. Dextromethorphan hydrobromide should be kept in a well-closed container.

Requirements

Definition. Dextromethorphan hydrobromide contains not less than 98.0% and not more than 101.0% of $C_{18}H_{25}NO, HBr$, calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide using a suitable chiral method.

Identity tests

- Either tests A and E or tests B, C, D and E may be applied.
 - A. Dry a small quantity of the test substance for 4 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R and carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from dextromethorphan hydrobromide RS similarly prepared or with the *reference spectrum* of dextromethorphan hydrobromide.
 - B. The absorption spectrum of a 0.10 mg/ml solution in sodium hydroxide (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a maximum at 280 nm; the absorbance of a 1 cm layer at this wavelength is about 0.59.
 - C. Dissolve 0.05 g in 2 ml of sulfuric acid (~100 g/l) TS. Add 1 ml of mercury/nitric acid TS drop by drop while shaking; a white, crystalline precipitate in the form of platelets is produced and the solution does not immediately turn red. Heat on a water-bath for about 10 minutes; a yellow to red colour develops.
 - D. Melting temperature, about 125 °C with decomposition.
 - E. To a 5 mg/ml solution add 0.25 ml of nitric acid (~130 g/l) TS; this test yields reaction B described under 2.1 General identification tests as characteristic of bromides.

Specific optical rotation. Use a 20 mg/ml solution in hydrochloric acid (0.1 mol/l) VS and calculated with reference to the anhydrous substance; $[\alpha]_D^{20^\circ} = +28.0^\circ$ to $+30.0^\circ$.

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under [2.8 Determination of water by the Karl Fischer method](#), Method A, using about 0.2 g of the substance; the water content is not less than 35 mg/g and not more than 55 mg/g.

pH value. Dissolve 0.4 g in carbon-dioxide-free water R using gentle heat, dilute to 20 ml with the same solvent and measure the pH at 20 °C; the value lies between 5.2 and 6.5.

Dimethylaniline. Dissolve 0.5 g in 15 ml of water using gentle heat, cool and add 4 ml of acetic acid (~60 g/l) TS, 1 ml of sodium nitrite (10 g/l) TS and sufficient water to produce 25 ml. Prepare similarly a reference solution containing 5 µg of *N,N*-dimethylaniline R in 25 ml. The colour produced in the test solution is not more intense than that produced in the reference solution when compared as described under [1.11 Colour of liquids](#); the dimethylaniline content is not more than 10 µg/g.

Phenolic substances. To 5 mg add 1 drop of hydrochloric acid (~70 g/l) TS, 1 ml of water and 0.2 ml of ferric chloride (50 g/l) TS. Mix, add 0.2 ml of potassium ferricyanide (50 g/l) TS, dilute to 5 ml with water, shake well and allow to stand for 15 minutes; the solution is yellowish brown and shows no greenish or blue colour.

Assay

Dissolve about 0.5 g, accurately weighed, in 40 ml of glacial acetic acid R1 and add 10 ml of mercuric acetate/acetic acid TS, warming slightly if necessary to effect solution. Titrate with perchloric acid (0.1 mol/l) VS as described under [2.6 Non-aqueous titration](#), Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 35.23 mg of $C_{18}H_{25}NO, HBr$.
