Consultation documents

To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), specifying that you wish to be added to the electronic mailing list.

The International Pharmacopoeia

Carbamazepinum

Carbamazepine

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.608, July 2015).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Carbamazepine in The International Pharmacopoeia.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. $C_{15}H_{12}N_{2}O$

Relative molecular mass. 236.3

Graphic formula.

Chemical name. 5H-Dibenz[b,f]azepine-5-carboxamide; CAS Reg. No. 298-46-4.

Description. A white to almost white, crystalline powder.

Solubility. Practically insoluble in water; sparingly soluble in acetone; soluble in ethanol (~750 g/L) TS; freely soluble in dichloromethane.

Category. Antiepileptic.
**Additional information.** Carbamazepine exhibits polymorphism. The acceptable crystalline form is anhydrous polymorph form III\(^1\). It corresponds to carbamazepine RS.

**Storage.** Carbamazepine should be kept in a tightly closed container.

**Requirements**

**Definition.** Carbamazepine contains not less than 98.0% and not more than 102.0% of C\(_{15}\)H\(_{12}\)N\(_2\)O, calculated with reference to the dried substance.

**Identity tests**

- Either test A or any two of tests B, C and D may be applied.
- **A.** Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum obtained from the test substance without pretreatment is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.
- **B.** Carry out test B.1 or, where UV detection is not available, test B.2.

**B.1.** Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the test substance per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.

**B.2** Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3, then heat it at 105°C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.

**C.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

---

D. Heat 0.1 g with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**Melting range.** 189–193°C.

**Chlorides.** For the preparation of the test solution boil 3.57 g in 50 mL of water for 10 minutes, cool, again adjust the volume, filter. To 25 mL of the filtrate add 10 mL of nitric acid (~130 g/L) TS and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 0.14 mg/g.

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 μg/g.

**Sulfated ash.** Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant weight at 105°C; it loses not more than 5.0 mg/g.

**Acidity or alkalinity.** Stir 1.0 g with 20 mL of carbon-dioxide-free water R for 15 minutes and filter. To 10 mL of the filtrate add 0.1 mL of phenolphthalein/ethanol TS and titrate with carbonate-free sodium hydroxide (0.01 mol/L) VS; not more than 0.5 mL is required to obtain a pink colour. Add 0.15 mL of methyl red/ethanol TS and titrate with hydrochloric acid (0.01 mol/L) VS; not more than 1.0 mL is required to obtain a red colour.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions given under “Assay, method B”.

Prepare the following solutions. For solution (1) dissolve about 75 mg of the test substance in 25 mL of methanol R, sonicate and dilute to 50 mL with water R. For solution (2) dilute 1 volume of solution (1) to 1000 volumes with a mixture of equal volumes of methanol R and water R. For solution (3) use a solution containing 10 μg of carbamazepine RS and 10 μg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 μL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 μL each of solution (1) and solution (2). Record the chromatograms for eight times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%).
• the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);

• the sum of the corrected areas of the peaks corresponding to impurity A, impurity D and impurity E and the areas of all other peaks, other than the principal peak, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%).

Assay
• Either method A or B may be applied.

A.  Dissolve about 0.1 g, accurately weighed, in sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL with the same solvent, and again dilute 10.0 mL of this dilution to 100.0 mL with ethanol (~750 g/L) TS. Measure the absorbance \((1.6)\) of a 1 cm layer of the resulting solution at the maximum at about 285 nm. Calculate the percentage content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) in the substance being tested, using the absorptivity value of 49.0 (\(A_{1cm}^{1\%} = 490\)).

B.  Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 μm).\(^2\) As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) dissolve about 10 mg of the test substance, accurately weighed, in 25 mL of methanol R, sonicate and dilute to 50.0 mL with water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 μL each of solution (1) and (2). The assay is not valid unless the efficiency (N) is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of carbamazepine \((\text{C}_{15}\text{H}_{12}\text{N}_2\text{O})\) in the samples using the declared content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) in carbamazepine RS.

Impurities

\[\text{A. 10,11-dihydro-dibenzo[b,f]azepine-5-carboxamide (10,11-dihydrocarbamazepine)}\]

\(^2\) A Nucleosil 100-10 CN column was found suitable.
B. 9-methylacridine

C. (5\textit{H}-dibenzo[\textit{b,f}]azepin-5-ylcarbonyl)urea (\textit{N}-carbamoylcarbamazepine)

D. 5\textit{H}-dibenzo[\textit{b,f}]azepine (iminostilbene)

E. 10,11-dihydro-5\textit{H}-dibenzo[\textit{b,f}]azepine (iminodibenzyl)

***
Carbamazepine tablets

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.632, July 2015).


Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

**Category.** Antiepileptic.

**Storage.** Carbamazepine tablets should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 100 mg, 200 mg. Strength in the current WHO EML for children: 100 mg, 200 mg.

**Requirements**

Complies with the monograph for Tablets.

**Definition.** Carbamazepine tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine (C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O) stated on the label.

**Identity tests**

- Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

A. Carry out the examination with the crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.
B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).
Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.

For each of the tablets tested calculate the amount of carbamazepine \((\text{C}_{15}\text{H}_{12}\text{N}_2\text{O})\) in the medium using the absorptivity value of 49.0 \((A_{1\%c}=490)\). Evaluate the results as described under 5.5 Dissolution test for solid dosage forms, Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

Assay

• Either method A or B may be applied.

A. Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol (~750 g/L) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol (~750 g/L) TS, filter and dilute the cooled filtrate with sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Calculate the content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) using the absorptivity value of 49.0 \((A_{1\%c}=490)\).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 μm). As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine \((\text{C}_{15}\text{H}_{12}\text{N}_2\text{O})\) in the tablets using the declared content of \(\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}\) in carbamazepine RS.

Impurities. The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

---

1 A Nucleosil 100-10 CN column was found suitable.
Carbamazepini compressi manducabili
Carbamazepine chewable tablets

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.609, July 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Category. Antiepileptic.

Storage. Carbamazepine chewable tablets should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 100 mg, 200 mg. Strengths in the current WHO EML for children: 100 mg, 200 mg.

Requirements

Complies with the monograph for Tablets.

Definition. Carbamazepine chewable tablets contain Carbamazepine in a suitable basis that may contain suitable flavouring agents. Carbamazepine chewable tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine (C_{15}H_{12}N_{2}O) stated on the label.

Identity tests

• Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

A. Carry out the examination with the crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.
B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with reference solution (C) shows 2 clearly separated spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under Assay B. Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature.

• the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
• the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
• the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).
temperature. Measure the absorbance (1.6) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.

For each of the tablets tested calculate the amount of carbamazepine (C₁₅H₁₂N₂O) in the medium using the absorptivity value of 49.0 (A₁cm = 490). Evaluate the results as described under 5.5 Dissolution test for solid dosage forms, Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

**Assay**

- Either method A or B may be applied.

**A.** Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol (~750 g/L) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol (~750 g/L) TS, filter and dilute the cooled filtrate with sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

  Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Calculate the content of C₁₅H₁₂N₂O using the absorptivity value of 49.0 (A₁cm = 490).

**B.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 µm).¹ As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

  Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

  Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

  Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

  Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine (C₁₅H₁₂N₂O) in the tablets using the declared content of C₁₅H₁₂N₂O in carbamazepine RS.

**Impurities.** The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

---

¹ A Nucleosil 100-10 CN column was found suitable.
Carbamazepini suspensionum peroralum  
Carbamazepine oral suspension

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.610, July 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Category. Antiepileptic.

Storage. Carbamazepine oral suspension should be kept in tightly closed, light-resistant containers, protected from freezing and from excessive heat.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 100 mg per 5 mL. Strength in the current WHO EML for children: 100 mg per 5 mL.

Requirements

Complies with the monograph for Liquid preparations for oral use.

Definition. Carbamazepine oral suspension is a suspension of Carbamazepine in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of carbamazepine (C_{15}H_{12}N_{2}O) stated on the label.

Identity tests

• Either test A alone or any two of tests B, C and D may be applied.

Transfer a quantity of the oral suspension equivalent to about 0.25 g of carbamazepine to a centrifuge tube, centrifuge and wash the precipitate with two quantities of 10 mL of water R. Dissolve the precipitate as completely as possible in 10 mL of dichloromethane R, filter and evaporate the filtrate to dryness in air, dry the residue at 105°C for 30 minutes and use it for the following tests.

A. Carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 μL of each of the following three solutions, prepared using as a solvent in a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the residue per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).
The principal spot obtained with solution (A) corresponds in position, appearance
and intensity with that obtained with solution (B). The test is not valid unless the
chromatogram obtained with reference solution (C) shows 2 clearly separated
spots.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the
conditions described under test B.1 but using a plate containing silica gel R5 as the
coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air.
Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for
15 minutes. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance
and intensity with that obtained with solution (B). The test is not valid unless the
chromatogram obtained with reference solution (C) shows 2 clearly separated
spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography,
using the conditions given under “Assay”, Method B. The retention time of the principal
peak in the chromatogram obtained with solution (1) corresponds to the retention time
of the peak due to carbamazepine in the chromatogram obtained with solution (2).

D. Heat 0.1 g of the residue with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for
3 minutes; an orange-red colour is produced.

pH value (1.13). pH of the oral suspension, 3.5–4.5.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid
chromatography using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) shake the oral solution and transfer a quantity
of it, containing about 0.2 g of Carbamazepine, into a 100 mL volumetric flask, add 50 mL
of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room
temperature and dilute to volume with water R. Centrifuge 10 mL of the suspension. Transfer
5.0 mL of the supernatant to a 10 mL volumetric flask and dilute to volume with equal volumes
of methanol R and water R. For solution (2) dilute 1 volume of solution (1) to 500 volumes with
equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg
of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal
volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine
and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for
times the retention time of carbamazepine. In the chromatogram obtained with solution (1)
the following impurities, if present, are eluted at the following relative retention with reference
to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1;
and impurity E about 2.5.

In the chromatogram obtained with solution (1):
• the area of any peak corresponding to impurity A, when multiplied by a correction factor of
2.8, is not greater than the area of the principal peak in the chromatogram obtained with
solution (2) (0.2%);
• the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

• the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

Assay

• Either method A or B may be applied.

A. Shake the oral solution and transfer an accurately weighed quantity of it, containing about 0.1 g of Carbamazepine, to a 100 mL volumetric flask, add about 50 mL of ethanol (~750 g/L) TS and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute with the same solvent to volume and filtrate the solution. Dilute 1.0 mL of the filtrate to a 100.0 mL with ethanol (~750 g/L) TS.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent containing ethanol (~750 g/L) TS. Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of \( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O} \), weight in volume, of the oral suspension using the absorptivity value of 49.0 \( (A_{1\text{cm}}^1 = 490) \).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded cyanopropyl groups (10 μm).\(^1\) As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) shake the oral solution and transfer an accurately weighed quantity of it, containing about 200 mg of Carbamazepine, to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute to volume with water R and filtrate the solution. Dilute 5.0 mL of the filtrate to 50.0 mL with equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 μL each solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of carbamazepine (\( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O} \)), weight in volume, of the oral suspension using the declared content of \( \text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O} \) in carbamazepine RS.

Impurities. The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

\(^1\) A Nucleosil 100-10 CN column was found suitable.
Consultation documents

WHO Drug Information Vol. 29, No. 3, 2015

Norethisteronum
Norethisterone

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.628, July 2015).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Norethisterone in The International Pharmacopoeia.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. $C_{20}H_{26}O_2$

Relative molecular mass. 298.4

Graphic formula.

Chemical name. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one; CAS Reg. No. 68-22-4.

Description. A white or almost white, crystalline powder.

Solubility. Practically insoluble in water; soluble in methylene chloride, sparingly soluble in acetone and in anhydrous ethanol.

Category. Progestational steroid.

Storage. Norethisterone should be kept in a well-closed container, protected from light.

Requirements

Definition. Norethisterone contains not less than 98.0% and not more than 101.0% of $C_{20}H_{26}O_2$, calculated with reference to the dried substance.

Identity tests

Either test A alone or the tests B, D and E or C, D and E may be applied.

A. 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 norethisterone RS or with the reference spectrum of norethisterone.
B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R1 as the coating substance and a mixture of 95 volumes of dichloromethane R and 5 volumes of methanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 3 solutions in dehydrated ethanol containing (A) 0.2 mg of the test substance per mL, (B) 0.2 mg of norethisterone RS per mL and (C) 0.2 mg of norethisterone RS and 0.2 mg levonorgestrel RS per mL. Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air and spray the plate with sulfuric acid/ethanol (10%) TS. Heat the plate to 105°C for 10 minutes, allow it to cool and examine the chromatogram in ultraviolet light (365nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Related substances”. The retention time of the principal peak in the chromatogram obtained from solution (1) is similar to the principal peak in the chromatogram obtained from solution (3).

D. Dissolve about 10 mg in 1 mL of dehydrated ethanol R. Add silver nitrate (100 g/L) TS and shake; a white precipitate is produced.

E. Dissolve about 10 mg of the sample in 50 mL of dehydrated alcohol R and dilute to 100.0 mL with the same solvent, dilute 5.0 mL of this solution to 50.0 mL with dehydrated alcohol R. The absorption spectrum (1.6) of the solution, when observed between 200 nm and 400 nm, exhibits a maximum at about 240 nm; the specific absorbance A \text{cm}^{-1}\text{%} at 240 nm is between 510 and 630.

**Specific optical rotation** (1.4). Use a 10 mg per mL solution in acetone R and calculate with reference to the anhydrous substance; \[ \left[\alpha\right]_{D}^{20°C} = -32° \text{ to } -37°. \]

**Sulfated ash** (2.3). Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant weight at 105°C; it loses not more than 5.0 mg/g.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm)\(^1\).

Use the following conditions for gradient elution:

- **Mobile phase A:** water R;
- **Mobile phase B:** acetonitrile R

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20</td>
<td>63</td>
<td>37</td>
<td>Isocratic</td>
</tr>
<tr>
<td>20–25</td>
<td>63 to 20</td>
<td>37 to 80</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>25–35</td>
<td>20</td>
<td>80</td>
<td>Isocratic</td>
</tr>
<tr>
<td>35–36</td>
<td>20 to 63</td>
<td>80 to 37</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>36–45</td>
<td>63</td>
<td>37</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

\(^1\) The Agilent ZORBAX Eclipse XDB-C8 column has been found suitable.
Operate with a flow rate of 1.0 mL per minute. As a detector use a variable wavelength spectrophotometer set at a wavelength of 254 nm and, for impurity C, D and I, at 210 nm.

Prepare the following solutions using as the diluent a mixture of 40 volumes of water R and 60 volumes of acetonitrile R. For solution (1) dissolve about 25 mg of the test substance and dilute to 10.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 5.0 mg of norethisterone for system suitability RS (containing the impurities A, B, C, D, E, F, G and H) and dilute to 2.0 mL. For solution (4) use a solution containing 2.5 µg of ethinylestradiol RS (impurity I) per mL.

Inject solution 20 µL of solution (3). The assay is not valid unless in the chromatogram recorded at the wavelength of 254 nm the peaks due to impurity B (with a relative retention of about 0.9) and due to norethisterone (retention time about 10 minutes) are baseline separated and the peak-to-valley ratio (Hp/Hv) is at least 1.2, where Hp = height above the baseline of the peak due to impurity A (with a relative retention of about 0.8) and Hv = the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Inject alternately 20µL each of solution (1), (2) and (4)

Use the chromatogram obtained with solution (3) and the chromatogram supplied with norethisterone for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F, G and H. If present, the impurities are eluted at the following relative retention with reference to norethisterone (retention time about 10 minutes): impurity H about 0.3; impurity A about 0.8; impurity B about 0.9; impurity I about 1.1 (at 210 nm); impurity G about 1.5; impurity C about 1.6 (at 210 nm); impurity D about 1.7 (at 210 nm); impurity E about 2.3 and impurity F about 2.4.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.5, is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity B is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.7, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.4, is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity H, when multiplied by a correction factor of 1.7, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity G is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity C or D, recorded at 210 nm, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity I, recorded at 210 nm, is not greater than the area of the principal peak obtained with solution (4) (0.1%)
- the area of any other peak, other than the principal peak due to norethisterone, is not greater than the area of the principal peak obtained with solution (2) (0.1%).
• the sum of the corrected areas of any peak corresponding to impurity A, E, F and H and the areas of all other peaks recorded at 254 nm, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with the solution (2) (0.3 %). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

Assay
Dissolve about 0.20 g, accurately weighed, in 40 mL of tetrahydrofuran R. Add 10 mL of silver nitrate (100 g/L) TS and titrate with sodium hydroxide (0.1 mol/L) VS, determining the endpoint potentiometrically. Rinse the electrode with acetone R after each titration. Perform a blank determination and make any necessary correction. 1 mL of 0.1 M sodium hydroxide is equivalent to 29.84 mg of C20H26O2.

Impurities

A. 17-hydroxy-19-nor-17α-pregna-4,6-dien-20-yn-3-one

B. estr-4-ene-3,17-dione (norandrostenedione)

C. 17-hydroxy-19-nor-17α-pregn-5-en-20-yn-3-one

D. 17-hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one (synthesis impurity)

---

E. 3-ethynyl-19-nor-17α-pregna-3,5-dien-20-yn-17-ol

F. 3-ethoxy-19-nor-17α-pregna-3,5-dien-20-yn-17-ol

G. 17-hydroxy-19-norpregn-4-en-20-yn-3-one (17-epi-norethisterone) (degradation product2)

H. 6β,17-dihydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (6β-hydroxynorethisterone) (degradation product2)

I. 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol; 17-ethynyl-estro-1,3,5,(10)-triene-3,17β-diol (ethinylestradiol)

Reagent to be added:
Sulfuric acid/ethanol (10%) TS:

Procedure. Cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 90 mL of ethanol (~750 g/L) TS to about –5°C. Carefully add the acid to the ethanol keeping the solution as cool as possible and mix gently.

***
WHO Drug Information Vol. 29, No. 3, 2015

Consultation documents

Norethisteroni compressi
Norethisterone tablets

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.229, June 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Category. Progestational steroid.

Storage. Norethisterone tablets should be kept in a well-closed container, protected from light.

Additional information. Strengths on the 6th invitation to manufacturers of reproductive health products to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Team - Medicines: 0.35 mg. Additional strengths available 0.625 and 5 mg.

Requirements

Complies with the monograph on Tablets.

Definition. Norethisterone tablets contain not less than 90.0% and not more than 110.0% of the amount of Norethisterone (C_{20}H_{26}O_{2}) stated on the label.

Identity tests

- Either test A alone or tests B and C may be applied.
  
  A. Mix a portion of powdered tablets, containing about 50 mg of norethisterone, with 15 mL of hexane R and shake for 15 minutes. Centrifuge the mixture then decant and discard the hexane R. Extract the residue with two 10 mL portions of hexane R, centrifuging, decanting and discarding the supernatant as before. Add 25 mL of dichloromethane to the residue, shake and filter. Evaporate the filtrate to about 3 mL, add a few mL of hexane R to induce crystallization and evaporate to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from norethisterone RS, treated in the same way as the test substance, or with the reference spectrum of norethisterone.

  B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”, method A. The retention time of the peak due to norethisterone in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

  C. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R1 as the coating substance and a mixture of 95 volumes of dichloromethane R and 5 volumes of methanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 3 solutions in dehydrated ethanol R. For solution (A) dissolve a quality of the powdered tablets, equivalent to about 2 mg of norethisterone, in 10 mL, centrifuge for 10 minutes and use the supernatant liquid. For solution (B) use a solution containing 0.2 mg of norethisterone RS per mL. For solution (C) use a solution containing 0.2 mg of norethisterone RS and 0.2 mg of levonorgestrel RS per mL. Develop the plate. After removing the plate from the chromatographic chamber
allow it to dry in air or in a current of air and spray with sulfuric acid/ethanol (10%) TS. Heat the plate to 105°C for 10 minutes, allow to cool and examine the chromatogram in ultraviolet light (365 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

Dissolution

For 0.625 mg tablets. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of a solution of 0.09% sodium lauryl sulfate R in hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of 10 mL of the medium through an in-line filter and use the filtrate as solution (1). For solution (2) dissolve a suitable amount of norethisterone RS in 10 mL of ethanol (~750 g/L) TS and dilute to a suitable volume with dissolution medium to obtain a solution containing 0.7 µg per mL.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions as described under “Assay” but injecting alternately 50 µL each of the solutions (1) and (2).

For each of the six tablets calculate the total amount of norethisterone (C₂₀H₂₆O₂), in the medium, using the declared content of (C₂₀H₂₆O₂) in norethisterone RS. The amount of norethisterone in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

For 0.35 mg tablets. Carry out the test as described above for 0.65 mg tablets but using 500 mL of a solution of 0.09% sodium lauryl sulfate R in hydrochloric acid (~3.65 g/L) TS as the dissolution medium.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm).¹

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20</td>
<td>63</td>
<td>37</td>
<td>Isocratic</td>
</tr>
<tr>
<td>20–25</td>
<td>63 to 20</td>
<td>37 to 80</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>25–35</td>
<td>20</td>
<td>80</td>
<td>Isocratic</td>
</tr>
<tr>
<td>35–36</td>
<td>20 to 63</td>
<td>80 to 37</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>36–45</td>
<td>63</td>
<td>37</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.0 mL per minute. As a detector use a variable wavelength spectrophotometer set at a wavelength of 254 nm and, for impurity C, D and I at 210 nm.

Prepare the following solutions using as the diluent a mixture of 40 volumes of water R and 60 volumes of acetonitrile R. For solution (1) transfer a quantity of the powdered tablets, containing the equivalent of about 10 mg of norethisterone, in 10 mL and sonicate for

¹ The Agilent ZORBAX Eclipse XDB-C8 column has been found suitable.
15 minutes. Stir vigorously for 15 minutes, centrifuge and use the supernatant. For solution (2) dilute a suitable volume of solution (1) to obtain a solution containing 1.0 µg of norethisterone per mL. For solution (3) dissolve 5.0 mg of norethisterone for system suitability RS (containing the impurities A, B, C, D, E, F, G and H) in the solvent and dilute to 2.0 mL. For solution (4) use a solution containing 2.5 µg of ethinylestradiol RS (impurity I) per mL.

Inject solution 20 µL of solution (3). The assay is not valid unless in the chromatogram recorded at the wavelength of 254 nm the peaks due to impurity B (with a relative retention of about 0.9) and due to norethisterone (retention time about 10 minutes) are baseline separated and the peak-to-valley ratio (Hp/Hv) is at least 1.2, where Hp is the height above the baseline of the peak due to impurity A (with a relative retention of about 0.8) and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Inject alternately 50 µL each of solution (1), (2) and (4).

Use the chromatogram obtained with solution (3) and the chromatogram supplied with norethisterone for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F, G and H. If present the impurities are eluted at the following relative retention with reference to norethisterone (retention time about 10 minutes): impurity H about 0.3; impurity A about 0.8; impurity B about 0.9; impurity I about 1.1 (at 210 nm); impurity G about 1.5; impurity C about 1.6 (at 210 nm); impurity D about 1.7 (at 210 nm); impurity E about 2.3 and impurity F about 2.4.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.5, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.7, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.4, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity H, when multiplied by a correction factor of 1.7, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity I, recorded at 210 nm, is not greater than 2 times the area of the principal peak obtained with solution (4) (0.5%);
- the area of any other peak, other than the principal peak due to norethisterone, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);

Assay

Either method A or B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl
group (5 µm). As the mobile phase use a mixture of 65 volumes of methanol R and 35 volumes of water R.

Prepare the following solutions using the mobile phase as the diluent. Weigh and powder 20 tablets. For solution (1) transfer a quantity of the powdered tablets, containing about 1.25 mg of norethisterone, accurately weighed, to a 50 mL volumetric flask, add 30 mL mobile phase and sonicate for 15 minutes. Cool to room temperature, dilute to volume and mix. Centrifuge the suspension and use the supernatant. For solution (2) use a solution containing 25 µg of norethisterone RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 244 nm.

Inject alternately 20 µL each of the solutions (1) and (2). Record the chromatograms for about 20 minutes.

Measure the areas of the peak responses obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of norethisterone \( \text{C}_{20}\text{H}_{26}\text{O}_{2} \) in the tablets, using the declared content of \( \text{C}_{20}\text{H}_{26}\text{O}_{2} \) in norethisterone RS.

B. Use the average of the 10 individual results obtained in the test for “Uniformity of content”.

**Uniformity of content**

The tablets comply with the test for **5.1 Uniformity of content for single-dose preparations** using the following method of analysis.

Carry out the test as described under **1.14.4 High-performance liquid chromatography** using the chromatographic conditions as described under “Assay”, method A.

Prepare the following solutions using the mobile phase as diluent. For solution (1) transfer one tablet to a 25 mL volumetric flask. Add about 15 mL of the diluent, sonicate to disintegrate and shake for 10 minutes and dilute to volume. Centrifuge the suspension and use the clear supernatant liquid. For solution (2) use a solution containing 25 µg of norethisterone RS per mL (for 0.625 mg tablets) or 14 µg of norethisterone RS per mL (for 0.35 mg tablets).

Inject alternately 20 µL each of solution (1) and (2). Measure the areas of the peaks corresponding to norethisterone obtained in the chromatograms and calculate the content of norethisterone \( \text{C}_{20}\text{H}_{26}\text{O}_{2} \) in each tablet, using the declared content of \( \text{C}_{20}\text{H}_{26}\text{O}_{2} \) in norethisterone RS.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph on Norethisterone.

**Reagent to be added:**

Sulfuric acid/ethanol (10%) TS

**Procedure.** Cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 90 mL of ethanol (~750 g/L) TS to about –5°C. Carefully add the acid to the ethanol keeping the solution as cool as possible and mix gently.

### Impurities

The JADE-PAKODS-AQ (5 Micron 250×4.6mm) column has been found suitable.

---

2 The JADE-PAKODS-AQ (5 Micron 250×4.6mm) column has been found suitable.
This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.605/Rev.1, August 2015).

The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed the revise the monograph on Dextromethorphan hydrobromide.

In investigations leading to the proposed test for related substances it was found that impurity F may co-elute with impurity D. Manufacturers are invited to submit a reference substance of impurity D and to propose a chromatographic methods that is capable to separate also the two mentioned impurities.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. $\text{C}_{18}\text{H}_{25}\text{NO, HBr, H}_2\text{O}$

Relative molecular mass. 370.3

Graphic formula

![Graphic formula](image)

Chemical name
Monohydrate of ent-3-methoxy-17-methylmorphan hydrobromide; (9α,13α,14α)-3-methoxy-17-methylmorphan, hydrobromide, hydrate (1:1:1); (+)-cis-6-methoxy-11-methyl-1,3,4,9,10,10a-hexahydro-2$H$-10,4a-(iminoethano)phenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

Description. A white or almost white, crystalline powder.

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/L) TS.

Category. Antitussive.

Storage. Dextromethorphan hydrobromide should be kept in a well-closed container, protected from light.
Requirements

Definition. Dextromethorphan hydrobromide contains not less than 99.0% and not more than 101.0% of C_{18}H_{25}NO.HBr, calculated with reference to the anhydrous substance.

Identity tests

[Note from the Secretariat. In the final version of the monograph the order of the different identity tests will be aligned to the style of The International Pharmacopoeia.]

- Either tests A, E and F or tests B, E, F and G 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 per 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.

E. To a 5 mg per 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.

F. Determine the specific optical rotation using a 20 mg per mL solution of the test substance in hydrochloric acid (0.1 mol/L) VS. Calculated with reference to the anhydrous substance; the specific optical rotation is between +28.0° to +30.0°.

G. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R1 as the coating substance and a freshly prepared mixture of 2 volumes of ammonia (~260 g/L) TS, 10 volumes of dichloromethane R, 13 volumes of methanol R, 20 volumes of ethyl acetate R and 55 volumes of toluene R as the mobile phase. Apply separately to the plate 5 μL of each of the following 2 solutions in methanol R containing (A) 2.5 mg of the test substance per mL and (B) 2.5 mg of dextromethorphan hydrobromide RS per mL. Develop the plate for a distance of about 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air, spray it with potassium iodobismuthate/tartaric acid TS and examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

Sulfated ash (2.3). 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 46 mg/g and not more than 51 mg/g.

pH value (1.13). 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.

**Impurity E (Levomethorphan).** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cellulose tris(4-methylenzoate) groups (5 μm).¹ As the mobile phase use a mixture of 940 volumes of n-hexane R, 60 volumes of 2-propanol R and 1 volume of diethylamine R.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 285 nm. Maintain the column at 30°C.

Prepare the following solutions. For solution (1) transfer about 100 mg of the test substance in a 10.0 mL flask. Add 4 mL 2-propanol R, sonicate for about 5 minutes, allow to cool at room temperature and make up to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and impurity E (levomethorphan)).

Inject 20 μL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to impurity E (levomethorphan) (retention time about 9 minutes) and due to dextromethorphan (relative retention of about 1.3) is at least 3.

Inject alternately 20 μL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity E (levomethorphan) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).²

As the mobile phase use a solution prepared as follows: dissolve 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R, add 0.56 g of ammonium nitrate R and adjust to apparent pH 2.0 with glacial acid R.

Operate with a flow of 1.0 mL per min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Prepare the following solutions in mobile phase. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) dilute 1.0 mL of solution (1) to 200.0 mL. For solution (3) dissolve 2 mg of dextromethorphan impurity A RS in 2 mL of solution (1) and dilute to 25.0 mL.

Inject 20 μL of solution (3). The test is not valid unless the resolution between the peaks due to dextromethorphan (retention time about 22 min) and impurity A (with a relative retention of about 1.1) is at least 1.5.

Inject alternately 20 μL each of solutions (1) and (2). Record the chromatograms for about twice the retention time of dextromethorphan.

---

¹ A Chiralcel OJ-H column was found suitable.
² A Waters Symmetry C18 column was found suitable.
In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to dextromethorphan (retention time about 22 minutes): impurity B about 0.4; impurity C about 0.8; impurity D about 0.9; impurity F about 0.9 and impurity A about 1.1.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, impurity B or impurity D/F is not greater than the area of the principal peak obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.2, is not greater than the area of the principal peak obtained with solution (2) (0.05 %);
- the area or the corrected area of not more than one peak corresponding to either impurity A, impurity B, impurity C or impurity D/F is greater than 0.5 times the area of the principal peak obtained with solution (2) (0.25 %);
- the area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.10 %);
- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with the solution (2) (1.0 %). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.05 %).

**Assay**

Dissolve about 0.3 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.1 mol/L) VS and 20 mL of dehydrated ethanol R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added between the 2 points of inflexion. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.23 mg of \( \text{C}_{18}\text{H}_{25}\text{NO,HBr} \).

**Impurities**

A. *ent*-3-methoxymorphinan (nordextromethorphan) (degradation product),

B. *ent*-17-methylmorphinan-3-ol (dextrorphan) (degradation product),
C. ent-3-methoxy-17-methylmorphinan-10-one (degradation product),

D. ent-3-methoxy-17-methyl-14α-morphinan (14-epi-dextromethorphan).

[Note from the Secretariat. Graphic formula to be added.]

E. Levomethorphan

F. Dextromethorphan N-Oxide (degradation product)

Reference substances to be established

Dextromethorphan for system suitability RS
Dextromethorphan impurity A RS

Reagents to be established

Potassium iodo(bismuthate/tartaric acid TS

Stock solution. Suspend 1.7 g of bismuth subnitrate R and 20 g of tartaric acid R in 40 mL of water R. To the suspension add 40 mL of potassium iodide (400 g/L) TS and stir for 1 hour. Filter. The solution may be kept for several days in amber glass bottles.

Spray solution. Mix immediately before use 5 mL of the stock solution with 15 mL of water R.

Docusate sodium R

Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.

A commercially available reagent of suitable grade.
Dextromethorphan oral solution

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.635, August 2015).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to include the monograph on Dextromethorphan oral solution in The International Pharmacopoeia. In investigations leading to the proposed test for related substances it was found that impurity F may co-elute with impurity D. Manufacturers are invited to submit a reference substance of impurity D and to propose a chromatographic methods that is capable to separate also the two mentioned impurities.]

Category. Antitussive.

Storage. Dextromethorphan oral solution should be kept in well-closed container, protected from light.

Additional information. Strength usually available: 15 mg per 10 mL.

Requirements

Complies with the monograph for Liquid preparations for oral use.

Definition. Dextromethorphan oral solution is a solution of Dextromethorphan hydrobromide in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of Dextromethorphan hydrobromide (C_{18}H_{25}NO,HBr,H_{2}O) stated on the label.

Manufacture. The selection of the active ingredient ensures that the oral solution, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide. A suitable levomethorphan limit test for dextromethorphan oral solutions (and other dextromethorphan finished pharmaceutical products) is published in the Supplementary Information section.

Identity tests

• Either tests A and B or test B together with any one of tests C or D may be applied.

Transfer a quantity of the oral solution containing about 75 mg of Dextromethorphan hydrobromide to a 250 mL separating funnel, add 20 mL of water R, 5 mL of sodium hydroxide (~100 g/L) TS, 40 mL of hexane R and shake thoroughly. Remove the hexane layer and filter through anhydrous sodium sulfate R into a beaker. Repeat the extraction using two 40 mL portions of hexane R and collecting the extracts in the beaker after filtering. Evaporate the combined extracts and dissolve the residue in 30 mL of dichloromethane R. Use the test solution for “Identity tests” A, B and D.

A. Evaporate 10 mL of the test solution to dryness and carry out the examination with the dried residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from
dextromethorphan hydrobromide RS treated similarly or with the reference spectrum of dextromethorphan.

B. Use 10 mL of the test solution to determine the optical rotation (1.4); the substance is dextrorotatory.

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the same chromatographic conditions as described under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

D. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 2 volumes of ammonia (~260 g/L) TS, 10 volumes of dichloromethane R, 13 volumes of methanol R, 20 volumes of ethyl acetate R and 55 volumes of toluene R as the mobile phase. Apply separately to the plate 5 µL of each of the following three solutions. For solution (A) use the test solution. For solution (B) use about 2.5 mg of dextromethorphan hydrobromide RS per mL of methanol R. For solution (C) use about 2.5 mg of dextromethorphan hydrobromide RS and 2.5 mg of pentoxyverine citrate R per mL of methanol R. After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium iodobismuthate TS1 and examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

**pH value** (1.13). pH of the oral solution, 4.0–6.0.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the same chromatographic conditions as described under “Assay”.

Prepare the following solutions in mobile phase. For solution (1) transfer a volume of the oral solution, equivalent to about 210 mg of Dextromethorphan hydrobromide, into a 200 mL volumetric flask, make up to volume, shake and filter. For solution (2) dilute 2.0 mL of solution (1) to 200.0 mL. For solution (3) use a solution containing about 40 µg of dextromethorphan hydrobromide RS and about 40 µg of dextromethorphan impurity A RS per mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dextromethorphan (retention time about 15 min) and impurity A (with a relative retention of about 1.1) is at least 1.5.

Inject alternately 20 µL each of solutions (1) and (2) and record the chromatograms for twice the retention time of dextromethorphan.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to dextromethorphan (retention time about 22 minutes): impurity B about 0.4; impurity C about 0.8; impurity D/F about 0.9; and impurity A about 1.1.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, impurity B or impurity D/F is not greater than the 0.5 times the area of the principal peak obtained with solution (2) (0.5 %);
• the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.2, is not greater than 0.5 times the area of the principal peak obtained with solution (2) (0.5%);

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl group (5 µm)\(^1\).

Prepare the mobile phase by dissolving 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R. Add 0.56 g of ammonium nitrate R and adjust to an apparent pH 2.0 with glacial acetic acid R.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 280 nm.

Prepare the following solutions in mobile phase.

For solution (1) transfer a weighed quantity of the oral solution, containing the equivalent of about 37.5 mg of Dextromethorphan hydrobromide, into a 50 mL volumetric flask, make up to volume, shake and filter. For solution (2) use 0.75 mg of dextromethorphan hydrobromide RS per mL.

Inject alternatively 20 µL each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to dextromethorphan obtained in the chromatograms. Determine the weight per mL (1.3.1) of the oral solution and calculate the percentage content of Dextromethorphan hydrobromide (C\(_{18}\)H\(_{25}\)NO,HBr,H\(_2\)O), weight in volume, of the oral solution, using the declared content of C\(_{18}\)H\(_{25}\)NO,HBr in dextromethorphan hydrobromide RS. Each mg of C\(_{18}\)H\(_{25}\)NO,HBr is equivalent to 1.0511 mg of C\(_{18}\)H\(_{25}\)NO,HBr,H\(_2\)O.

Impurities
The impurities limited by the requirements of this monograph include impurities A, B, C, D and F listed in the monograph for Dextromethorphan hydrobromide.

Reagents to be established:

**Pentoxyverine citrate R**
A commercially available reagent of suitable grade.

**Docusate sodium R**
Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.
A commercially available reagent of suitable grade.

---

\(^1\) Shiseido ACR column and Phenomenex Luna column and have been found suitable.
Levomethorphan limit test for dextromethorphan-containing finished pharmaceutical products

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.636, August 2015).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/.
Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to include in the supplementary information section of The International Pharmacopoeia a levomethorphan limit test for dextromethorphan containing finished pharmaceutical products.]

Dextromethorphan-containing medicines shall contain Dextromethorphan hydrobromide which complies with all the requirements of the respective monograph and other applicable chapters of The International Pharmacopoeia. In particular, the concentration of impurity E (levomethorphan) shall not exceed the limit of 0.1% (see monograph on Dextromethorphan hydrobromide).

The following tests allow control laboratories (e.g. national quality control laboratories) to test suspicious dextromethorphan-containing medicines to establish whether or not an active pharmaceutical ingredient (API) meeting the limit for impurity E (levomethorphan) had been used to manufacture the product under examination.

In many cold and cough medicines dextromethorphan is used in combination with other active ingredients, for example, chlorpheniramine, doxylamine, ephedrine, paracetamol, phenylpropanolamine, pseudoephedrine, promethazine or triprolidine. Due to the diversity of these substances the selectivity of the test procedures described below may not be sufficient for all products under investigations. If the chromatogram obtained provides evidence that other active ingredients or excipients interfere with the levomethorphan determination the analyst shall modify the analytical procedure, e.g. by adding further extraction steps.

Also depending on the additional active ingredients or the excipients in the product to be examined it may be necessary to flush the column with a mobile phase consisting of 950 volumes of 2-propanol R, 50 volumes of n-hexane R and 1 volume of diethylamine R after each run.

**Limit test for levomethorphan in dextromethorphan containing oral solutions**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cellulose tris(4-methybenzoate) groups (5 μm). As the mobile phase use a mixture of 940 volumes of n-hexane R, 60 volumes of 2-propanol R and 1 volume of diethylamine R.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 285 nm. Maintain the column at 30°C.

Prepare the following solutions. For solution (1) transfer a quantity of the oral solution containing the equivalent of 50 mg of Dextromethorphan hydrobromide to a separation

---

1 A Chiralcel OJ-H column was found suitable.
funnel. Add sodium hydroxide (~40 g/L) TS until the solution has a pH value greater than 11 (check the value using pH-indicator paper). Extract the solution with three 50 mL volumes of hexane R. Dry the combined extracts over 3 g anhydrous sodium sulphate R, filter, wash the residue with 30 mL of hexane R, combine the hexane extracts in a round-bottom flask and evaporate to dryness. Add 2.0 mL of 2-propanol R to dissolve the residue and transfer the solution to a 10.0 mL flask, wash the round-bottom flask with further 2.0 mL of 2-propanol R and also transfer the solution to the 10.0 mL flask. Dilute to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of Dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and levomethorphan).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to levomethorphan (retention time about 9 minutes) and due to dextromethorphan (retention time of about 12 minutes) is at least 3.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to levomethorphan is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**Limit test for levomethorphan in dextromethorphan containing capsules and lozenges**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions given under Limit test for levomethorphan in dextromethorphan oral solutions.

For solution (1) transfer a quantity of the contents of the capsules (hard gelatin capsules)/transfer a number of capsules (soft gelatin capsules) or lozenges, containing the equivalent of about 50 mg of Dextromethorphan hydrobromide to a 100 mL conical flask, add about 50 mL of water and heat and shake on a steam bath for about 15 minutes. Allow to cool, filter and transfer the eluate to a separation funnel. Wash the flask and the filtrate with 2 times 10 mL of water. Combine the aqueous solutions and add sodium hydroxide (~40 g/L) TS until the solution has a pH value greater than 11 (check the value using pH-indicator paper). Extract with three 50 mL volumes of hexane R. Dry the combined extracts over 3 g anhydrous sodium sulphate R, filter, wash the residue with 30 mL of hexane R, combine the hexane extracts in a round-bottom flask and evaporate to dryness. Add 2.0 mL of 2-propanol R to dissolve the residue and transfer the solution to a 10.0 mL flask, wash the round-bottom flask with further 2.0 mL of 2-propanol R and also transfer the solution to the 10.0 mL flask. Dilute to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of Dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and levomethorphan).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to levomethorphan (retention time about 9 minutes) and due to dextromethorphan (retention time of about 12 minutes) is at least 3.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to levomethorphan is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).