Consultation documents

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The International Pharmacopoeia

**Misoprostolum**

**Misoprostol**

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.602, January 2015).

The working document with line numbers 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, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidtth@who.int.

Molecular formula. $\text{C}_{22}\text{H}_{38}\text{O}_5$

Relative molecular mass. 382.5

Graphic formula

![Graphic formula](image)

**Chemical name.** Mixture of methyl 7-([(1RS, 2RS, 3RS)-3-hydroxy-2-[(1E, 4RS)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate and methyl 7-[(1RS, 2RS, 3RS)-3-hydroxy-2-[(1E, 4SR)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate; CAS Reg. No. 59122-46-2.

**Description.** Clear, colourless or yellowish, oily liquid.

**Solubility.** Practically insoluble in water R, soluble in dehydrated ethanol R, sparingly soluble in acetonitrile R.

**Category.** Prostaglandin (PGE) analogue.

**Storage.** Misoprostol neat oil should be kept in a tightly sealed container and stored at a temperature between -25 and -10°C.

**Additional information.** Misoprostol is hygroscopic. It is gradually degraded at room temperature, the degradation being faster at higher temperatures.
Requirements

Definition. Misoprostol contains not less than 96.0% and not more than 102.0% of C\textsubscript{22}H\textsubscript{38}O\textsubscript{5} with reference to the anhydrous substance.

Identity tests

Either test A or tests B and C 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 misoprostol RS or with the reference spectrum of misoprostol.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 μL of each of the following two solutions in dehydrated ethanol R. For solution (1) use 0.1 mg of the test substance per mL. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).

C. See the test described under “Assay”. The retention time of the principal peak in the chromatogram obtained from solution (1) is similar to that in the chromatogram obtained from solution (2).

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 1.0 mL of a 10 mg per mL solution of the test substance in methanol R; the water content is not more than 10 mg/g.

Related substances

Prepare fresh solutions and perform the tests without delay.

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 octadecylsilyl silica gel (5 μm).\textsuperscript{1}

Use the following conditions for gradient elution:

- mobile phase A: mix 28 volumes of acetonitrile R with 69 volumes of water R and 3 volumes of methanol R;
- mobile phase B: mix 47 volumes of acetonitrile R with 50 volumes of water R and 3 volumes of methanol R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>0–5</td>
<td>100</td>
<td>0</td>
<td>equilibration</td>
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<tr>
<td>5–15</td>
<td>100 to 65</td>
<td>0 to 35</td>
<td>linear gradient</td>
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<td>15–22</td>
<td>65</td>
<td>35</td>
<td>isocratic</td>
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<td>22–25</td>
<td>65 to 0</td>
<td>35 to 100</td>
<td>linear gradient</td>
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<td>25–30</td>
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<tr>
<td>32–35</td>
<td>100</td>
<td>0</td>
<td>re-equilibration</td>
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</tbody>
</table>

\textsuperscript{1} An Ascentis Express C18 column was found suitable.
Maintain the column temperature at 35°C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water R as solvent. For solution (1) dissolve 50 mg of the test substance in 10 mL and sonicate for about 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 μg of misoprostol per mL. For solution (3) heat 5 mL of solution (1) in a water bath at 75°C for 1 hour.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 20 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes)) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol. Inject alternately 20 μL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the sum of the areas of peaks eluting with a relative retention between 0.80 and 0.98 with reference to misoprostol is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%). The area of any other impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%). The sum of the areas of all peaks, other than the principal peak, is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Diastereoisomers

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 2.1 mm) packed with silica gel for chromatography R (3.5 μm). As the mobile phase use a mixture of 4 volumes of 2-propanol R, 96 volumes of heptane R and 0.1 volume of trifluoroacetic acid R.

As the test solution use 1.0 mg of the test substance per mL of a mixture of 4 volumes of 2-propanol R and 96 volumes of heptane R.

Maintain the column temperature at 25°C.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 205 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 10 μL of the test solution.

The chromatogram shows two principal peaks due to misoprostol at retention times of about 14 and 16 minutes. The test is not valid unless the resolution between these two peaks is at least 2.0.

Measure the areas of the two peaks corresponding to misoprostol. The first peak of misoprostol is 45% –55% of the sum of the areas of the two peaks due to misoprostol.

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2 An Xbridge HILIC column was found suitable.
Assay

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 octadecylsilyl silica gel (5 μm)\(^3\). As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water.

Prepare the following solutions in the mobile phase. For solution (1) use 0.1 mg of misoprostol per mL. For solution (2) use 0.1 mg of misoprostol RS per mL.

Maintain the column temperature at 35°C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject alternately 20 μL each of solutions (1) and (2). The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of \(C_{22}H_{38}O_5\) with reference to the anhydrous substance.

**Impurities**

A. [chemical name to be added] (8-epimisoprostol) and its epimer at C* and their enantiomers

D. [chemical name to be added] (misoprostol B) and enantiomer

C. [chemical name to be added] (misoprostol A) and its epimer at C* and their enantiomers

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\(^3\) An Ascentis Express C18 column was found suitable.
**Clindamycini hydrochloridum**  
Clindamycin hydrochloride

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.603, January 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: schmidt@who.int.

![Chemical structure of Clindamycin hydrochloride]

C₁₈H₃₃ClN₂O₅S, HCl

**Relative molecular mass.** 461.5

**Chemical name**

**Description.** A white or almost white, crystalline powder.

**Solubility.** Very soluble in water, freely soluble in methanol R, and slightly soluble in ethanol (~750 g/L) TS.

**Category.** Antibacterial.

**Storage.** Clindamycin hydrochloride should be kept in a tightly closed container.

**Requirements**

**Definition.** Clindamycin hydrochloride contains not less than 91.0% and not more than 102.0% of C₁₈H₃₃ClN₂O₅S, HCl, calculated with reference to the anhydrous substance.

**Identity test**
• Either tests A and E or 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 clindamycin hydrochloride RS or with the *reference spectrum* of clindamycin hydrochloride.

B. Carry out the test as described under [1.14.1. Thin layer chromatography](#) using silica gel R1 as the coating substance and the upper layer of a mixture of 19 volumes of 2-propanol R, 38 volumes of a solution of ammonium acetate (~150 g/L) TS adjusted to pH 9.6 with ammonia (~260 g/L) TS and 43 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 5 μL of each of the following three solutions in methanol R. For solution (A) use 1 mg of test substance per mL. For solution (B) use 1 mg of Clindamycin hydrochloride RS per mL. For solution (C) use 1 mg of Clindamycin hydrochloride...
RS and 1 mg of lincomycin hydrochloride RS per mL. After removing the plate from the chromatographic chamber dry the plate in air and spray with potassium permanganate (~1 g/L) TS. 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 2 clearly separated spots.

C. See the test described under “Assay”. The principal peak in the chromatogram obtained with solution (1) is similar in retention time to the principal peak in the chromatogram obtained with solution (2).

D. Dissolve about 10 mg in 2 mL of hydrochloric acid (~200 g/L) TS and heat on a water-bath for 3 minutes. Add 3 mL of sodium carbonate (106 g/L) TS and 1 mL of sodium nitroprusside (20 g/L) TS. A violet-red colour develops.

E. A 0.01 g/mL solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

Specific optical rotation. Use a 40.0 mg/mL solution and calculate with reference to the anhydrous substance: \( [\alpha]_{D}^{20\circ} = +135^\circ \text{ to } +150^\circ \).

Sulfated ash. Not more than 5.0 mg/g.

Water. Determine as described under 2.8 Determination of water by Karl Fischer Method, Method A, using 0.5 g of the substance. The water content is not less than 30 mg/g and not more than 60 mg/g.

pH value. pH of a 100 mg/mL solution in carbon-dioxide-free water R, 3.0–5.0.

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

Prepare the following solutions in the mobile phase. For solution (1) dissolve 100 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 100 mg of clindamycin hydrochloride RS in a 25 mL volumetric flask.

Inject alternately 20 μL each of solution (1), (2) and (3). Record the chromatograms for about 2 times the retention time of clindamycin (retention time about 10 minutes).

In the chromatogram obtained with solution (3) the peaks are eluted at the following relative retention with reference to clindamycin (retention time about 10 minutes): impurity A (lincomycin) about 0.4; impurity B (clindamycin B) about 0.65; impurity C (7-epiclindamycin) about 0.8. The test is not valid unless the resolutions between the peaks due to impurities B and C and impurity C and clindamycin are at least 3.0.

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to either impurity B or impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
• the area of any other peak, other than the principal peak, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
• the sum of the areas of all peaks, other than the principal peak, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%).

Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay. 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).\(^1\) As the mobile phase

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\(^1\) Hypersil BDS 5 μm was found to be suitable.
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phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of potassium dihydrogen phosphate (6.8 g/L) TS adjusted to pH 7.5 with potassium hydroxide (~400 g/L) TS.

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) use a solution containing 1.0 mg of clindamycin hydrochloride 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 210 nm. Inject alternately 20 μL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to clindamycin obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of clindamycin hydrochloride \( \text{C}_{18}\text{H}_{33}\text{ClN}_2\text{O}_5\text{S}, \text{HCl} \) using the declared content of \( \text{C}_{18}\text{H}_{33}\text{ClN}_2\text{O}_5\text{S}, \text{HCl} \) in clindamycin hydrochloride RS.

**Impurities**

A. R1=CH2-CH2-CH3, R2=OH, R3=H: methyl 6,8-dideoxy-6-\[\{(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl\}carbonyl]amino]-1-thio-\( \alpha \)-d-galacto-octopyranoside (lincomycin)

B. R1=C2H5, R2=H, R3=Cl: methyl 7-chloro-6,7,8-trideoxy-6-\[\{(2S,4R)-4-ethyl-1-methylpyrrolidin-2-yl\}carbonyl]amino]-1-thio-\( \alpha \)-d-galacto-octopyranoside (clindamycin B)

C. R1=CH2-CH2-CH3, R2=Cl, R3=H: methyl 7-chloro-6,7,8-trideoxy-6-\[\{(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl\}carbonyl]amino]-1-thio-d-erythro-\( \alpha \)-d-galacto-octopyranoside (7-epiclindamycin)

**Reagents to be established**

**Hydrochloric acid (~200 g/L) TS**

Procedure. Dilute hydrochloric acid (~250 g/L) TS with water to contain approximately 200 g of HCl in 1000 mL (approximately 5.5 mol/L).

**Sodium carbonate (106 g/L) TS**

A solution of sodium carbonate R containing about 106 g of Na\textsubscript{2}CO\textsubscript{3} per litre (approximately 1 mol/L).

**Sodium nitroprusside (20 g/L) TS**

A solution of sodium nitroprusside R containing about 20 g of Na\textsubscript{2}Fe(NO)(CN)\textsubscript{6} per litre. Note: Sodium nitroprusside (20 g/L) TS must be freshly prepared.

**Potassium dihydrogen phosphate (6.8 g/L) TS**

A solution of potassium dihydrogen phosphate R containing 6.8 g of KH\textsubscript{2}PO\textsubscript{4} per litre (0.1 mol/L).

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**Clindamycini hydrochloridi capsulae**  
Clindamycin hydrochloride capsules

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.604, January 2015).

The working document with line numbers 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, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

**Category.** Antibacterial.

**Storage.** Clindamycin hydrochloride capsules should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model list of essential medicines (EML): 150 mg (as hydrochloride). Strengths in the current EML for Children: 150 mg (as hydrochloride).

**Labelling.** The designation on the container should state the quantity of clindamycin hydrochloride in terms of the equivalent amount of clindamycin. 150 mg of clindamycin is approximately equivalent to 162.9 mg of clindamycin hydrochloride.

**Requirements**

Comply with the monograph for Capsules.

**Definition.** Clindamycin hydrochloride capsules contain clindamycin hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of \( \text{C}_{18}\text{H}_{33}\text{ClN}_2\text{O}_5\text{S} \) stated on the label.

**Identity tests**

- Either tests A and D or B and D or C and D may be applied.

A. Shake a quantity of the contents of the capsules containing the equivalent of 30 mg of clindamycin with 15 mL of dichlormethane R, filter and evaporate the filtrate to dryness. 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 clindamycin hydrochloride RS, treated in the same way as the test substance, or with the reference spectrum of clindamycin hydrochloride.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R1 as the coating substance and the upper layer of a mixture of 19 volumes of 2-propanol R, 38 volumes of a solution of ammonium acetate (150 g/L) TS adjusted to pH 9.6 with ammonia (260 g/L) TS and 43 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 5 μL of each of the following three solutions. For solution (A) shake a quantity of the contents of the capsules equivalent to 10 mg of Clindamycin with 10 mL of methanol R, filter and use the clear filtrate. For solution (B) use 1 mg of clindamycin hydrochloride RS per mL of methanol R. For solution (C) use 1 mg of clindamycin hydrochloride RS and 1 mg of lincomycin hydrochloride RS per mL of methanol R. After removing the plate from the chromatographic chamber allow it to dry in air and spray with potassium permanganate (~1 g/L) TS. 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.

D. See the method 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).

E. Shake a quantity of the contents of the capsules containing 50 mg of Clindamycin with 5 mL of water and filter. The clear filtrate yields the reactions described under 2.1 General identification tests as characteristic of chlorides.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using a quantity of the contents of the capsules equivalent to 0.5 g of Clindamycin; the water content is not more than 70 mg/g.

**Dissolution/Disintegration**

Either test A or test B may be applied.

A. **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 water and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 15 mL of the medium from each vessel and filter, discarding the first 10 mL of the filtrate. Prepare standard solution as follows: dissolve a suitable amount of clindamycin hydrochloride RS, then add a suitable volume of the dissolution medium to obtain a concentration of 167 µg per mL. Determine the content of clindamycin (C\textsubscript{18}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{5}S) in the filtrate according to the method below. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions as described under “Assay”.

For each of the capsules tested calculate the amount of clindamycin (C\textsubscript{18}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{5}S) in the medium using the declared content of C\textsubscript{18}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{5}SHCl in clindamycin hydrochloride RS. Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria. The amount in solution for each capsule is not less than 80% (Q) of the amount declared on the label.

B. **Disintegration.** Comply with 5.3 Disintegration test for tablets and capsules operating the apparatus for 15 minutes. If the capsules do not comply carry out test A (Dissolution) above.

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

Prepare the following solutions in the mobile phase. For solution (1) transfer a quantity of the contents of the capsules equivalent to about 100 mg of Clindamycin into a 25 mL volumetric flask. Add about 20 mL of mobile phase and sonicate for 10 minutes. Dilute to volume with mobile phase, mix and filter. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 100 mg of clindamycin hydrochloride RS in a 25 mL volumetric flask. Inject alternately 20 μL each of solutions (1), (2) and (3). Record the chromatograms for 2 times the retention time of clindamycin (retention time about 10 minutes).

In the chromatogram obtained with solution (3) the peaks are eluted at the following relative retention with reference to clindamycin (retention time about 10 minutes): impurity A (lincomycin) about 0.4; impurity B (clindamycin B) about 0.65; impurity C (7-epiclindamycin) about 0.8. The test is not valid unless the resolutions between the peaks due to impurities B and C and impurity C and clindamycin are at least 3.0.
In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity B or impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the area of any peak, corresponding to impurity A is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25cm × 4.6mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm). ¹ As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R adjusted to pH 7.5 with potassium hydroxide (~400 g/L) TS.

Prepare the following solutions in mobile phase. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity of the mixed contents equivalent to about 100 mg of clindamycin, accurately weighed, into a 100 mL volumetric flask. Add about 80 mL of the mobile phase, sonicate for 10 minutes, make up to volume with the mobile phase, mix and filter. For solution (2) use a solution containing 1.1 mg of clindamycin hydrochloride 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 210 nm.

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

Measure the areas of the peaks corresponding to clindamycin obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of clindamycin (C₁₈H₃₃ClN₂O₅S) in the capsules using the declared content of C₁₈H₃₃ClN₂O₅S,HCl in clindamycin hydrochloride RS. Each mg of C₁₈H₃₃ClN₂O₅S,HCl is equivalent to 0.9209 mg of C₁₈H₃₃ClN₂O₅S.

**Impurities.** The impurities limited by the requirements of this monograph are impurity A, B and C listed in the monograph for Clindamycin hydrochloride.

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¹ Hypersil BDS 5 μm is suitable.
Dextromethophani hydrobromidum
Dextromethorphan hydrobromide

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.605, January 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 Dextromethorphan hydrobromide.]

[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. \( \text{C}_{18}\text{H}_{25}\text{NO},\text{HBr},\text{H}_2\text{O} \)
Relative molecular mass. 370.3

Graphic formula.

Chemical name. (+)-3-Methoxy-17-methyl-9α,13α-14α-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.

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

Category. Antitussive.

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 \( \text{C}_{18}\text{H}_{25}\text{NO},\text{HBr} \), calculated with reference to the anhydrous substance.

Identity tests

• Either tests A, F and E or tests B, F, G 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. [deleted as part of the proposed revision]

D. [deleted as part of the proposed revision]

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.

F. Determine the specific optical rotation using a 20 mg/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.** 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.

**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-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 about 120 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 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 %).

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).

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/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.

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; 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 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) (0.5%);

- the area or the corrected area of not more than one peak corresponding to either impurity A, impurity B, impurity C or impurity D 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 $C_{18}H_{25}NO,HBr$.

Impurities

A. ent-3-methoxymorphinan,

B. ent-17-methylmorphinan-3-ol,

C. ent-3-methoxy-17-methylmorphinan-10-one,
D. *ent-*(14S)-3-methoxy-17-methylmorphinan.

Reagents to be established

**Potassium iodobismuthate/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 brown 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.

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