Draft proposal for *The International Pharmacopoeia*

**Dexamethasoni phosphatis injectio - Dexamethasone phosphate injection**

(June 2014)

*DRAFT FOR COMMENT*

Should you have any comments on the attached text, please send these to Dr Herbert Schmidt, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidt@who.int; fax: (+41 22) 791 4730) by 30 July 2014.

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/14.580

**Draft proposal for *The International Pharmacopoeia***

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**Dexamethasoni phosphatis injectio - Dexamethasone phosphate injection**

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft received from collaborating laboratory</td>
</tr>
<tr>
<td>Discussion at consultation on specifications for medicines and quality control laboratory issues</td>
</tr>
<tr>
<td>Draft monograph sent out for comment</td>
</tr>
<tr>
<td>Consolidation of comments</td>
</tr>
<tr>
<td>Revision of draft monograph as per comments received</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations for adoption</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
</tr>
</tbody>
</table>

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Dexamethasone phosphate injection

[Note from the Secretariat. To prevent oxidative decomposition of dexamethasone phosphate in aqueous solution sodium metabisulfite is used as an antioxidant. Dijkstra and Dekker\(^1\) reported the addition of bisulfite at the C-1 of the corticosteroid. Comments are in particular sought regarding an appropriate limit for this adduct (impurity I) (see also test for related substances).]

**Description.** A clear, colourless solution

**Category.** Adrenal hormone.

**Storage.** Dexamethasone phosphate injection should be kept in a tightly closed container, protected from light. It should not be allowed to freeze.

**Labelling.** The designation on the container should state the amount of active ingredient as the equivalent quantity of Dexamethasone phosphate in a suitable dose volume.

**Additional information.** Strength in the current WHO Model list of essential medicines for dexamethasone: 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. Strength in the current WHO Model list of essential medicines for children: 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.

4 mg of dexamethasone phosphate is approximately equivalent to 4.37 mg of dexamethasone sodium phosphate.

**Requirements**

Complies with the monograph for *Parenteral Preparations*.

**Definition.** Dexamethasone sodium phosphate injection is a sterile solution of Dexamethasone sodium phosphate in water for injections. It contains not less than 90.0% and not more than 110.0% of the amount of Dexamethasone phosphate \(C_{22}H_{30}FO_8P\) stated on the label.

**Identity tests**

A. Carry out the test as described under *1.14.1 Thin-layer chromatography* using silica gel R2 as the coating substance and a mixture of 60 volumes of 1-butanol R, 20 volumes of acetic acid (~300 g/L) TS and 20 volumes of water R. Apply separately to the plate 5 µL of the following 3 solutions in methanol R. For solution (A) dilute a volume of the injection to obtain a solution containing 1.0 mg of dexamethasone phosphate per mL. For solution (B)

use dexamethasone sodium phosphate RS to obtain a solution containing 1.0 mg of
dexamethasone phosphate per mL. For solution (C) use dexamethasone sodium phosphate
RS and prednisolone sodium phosphate RS to obtain a solution containing 1.0 mg of
dexamethasone phosphate and 1.0 mg of prednisolone phosphate per mL. After removing
the plate from the chromatographic chamber allow it to dry in air and heat at 110 °C for 10
minutes. Spray the hot plate with sulfuric acid/ethanol (20%) TS and heat the plate at 120 °C
for 10 minutes, allow it to cool and examine the chromatogram in daylight and in ultraviolet
light (365 nm).

The test is not valid unless the chromatogram obtained with solution (C) shows 2 spots
which may, however, not be completely separated.

The principal spot obtained with solution (A) corresponds in position, appearance and
intensity with that obtained with solution (B).

B. See the test 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).

**pH value (I.13).** pH of the injection, 7.0–8.5.

**Related substances**

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

Prepare the following solutions in mobile phase A. For solution (1) dilute a volume of the
injection to obtain a concentration equivalent to 1 mg of dexamethasone sodium phosphate per
mL. For solution (2) use a solution containing 20 µg of betamethasone sodium phosphate RS per
mL and 20 µg of dexamethasone sodium phosphate RS per mL. For solution (3) mix equal
volumes of solution (2) and a solution containing 20 µg of dexamethasone RS per mL. For
solution (4) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 µg
dexamethasone sodium phosphate per mL.

Inject 20 µL of solution (2). The test is not valid unless the resolution between the peaks due to
dexamethasone phosphate (retention time about 22 min) and betamethasone sodium phosphate
(with a relative retention time of about 0.95) is not less than 2.0.

Inject alternatively 20 µL each of solutions (1), (3) and (4). In the chromatogram obtained with
solution (3) the following peaks are eluted at the following relative retention with reference to
dexamethasone phosphate (retention time about 22 min): impurity B (betamethasone phosphate):
about 0.95; impurity A (dexamethasone): about 1.37. The chromatogram obtained with solution
(1) may show the following impurities at the following relative retention with reference to
dexamethasone phosphate: impurity I: about 0.13; impurity C: about 0.5; impurity D: about 0.6;
impurity E: about 0.8; impurity F: about 0.92; impurity B: about 0.95; impurity H: about 1.19;
impurity A: about 1.37; impurity G: about 1.41.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor
  of 0.75, is not greater than 0.5 times the area of the principal peak obtained with solution
  (4) (0.5%);
- the area of any peak corresponding to impurity I is not greater than X [to be determined]
  times the area of the principal peak obtained with solution (4) (X %) [to be determined].

[Note from the Secretariat. To prevent oxidative decomposition of dexamethasone phosphate in
aqueous solution sodium metabisulfite is used as an antioxidant. Dijkstra and Dekker\(^1\) reported
the addition of bisulfite at the C-1 of the corticosteroid. Comments are in particular sought
regarding an appropriate limit for this adduct (impurity I).]

**Assay**

Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a
stainless steel column (12.5 cm × 4.6 mm) packed with base-deactivated particles of silica gel
the surface of which has been modified with chemically-bonded octylsilyl gel groups (5 µm) and
end-capped.

Prepare solution (A) by dissolving 7.0 g of ammonium acetate R in 1000 mL of water R.

The mobile phase for the gradient elution consists of a mixture of mobile phase A and mobile
phase B using the following conditions:

<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>0–3.5</td>
<td>90</td>
<td>10</td>
<td>Isocratic</td>
</tr>
<tr>
<td>3.5–23.5</td>
<td>90–60</td>
<td>10–40</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>23.5–34.5</td>
<td>60 to 5</td>
<td>40–95</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>34.5–50</td>
<td>5</td>
<td>95</td>
<td>Isocratic</td>
</tr>
<tr>
<td>50–55</td>
<td>5–90</td>
<td>95–10</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>55–65</td>
<td>90</td>
<td>10</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>
Operate with a flow of 1.0 mL/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature at 30 °C.

Prepare the following solutions in mobile phase A. For solution (1) dilute a volume of the injection to obtain a concentration equivalent to 80 µg dexamethasone phosphate per mL (approximately equivalent to 87 µg dexamethasone sodium phosphate). For solution (2) use a solution containing 87 µg of dexamethasone sodium phosphate RS per mL. For solution (3) use a solution containing 20 µg of betamethasone sodium phosphate RS per mL and 20 µg of dexamethasone sodium phosphate RS per mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dexamethasone phosphate (retention time about 22 min) and betamethasone phosphate (with a relative retention time of about 0.95) is at least 2.0.

Inject alternatively 20 µL each of solutions (1) and (2). Measure the areas of the peak responses corresponding to dexamethasone phosphate and calculate the content of dexamethasone phosphate, \( C_{22H_{30}FO_8P} \), in the injection using the declared content of \( C_{22H_{30}FO_8P} \) in dexamethasone sodium phosphate RS.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains less than 34.2 IU of endotoxin per mg dexamethasone phosphate.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph for Dexamethasone sodium phosphate and the following:

I. Dexamethason bisulfit adduct [chemical name and formula to be added]

**ICRS referred to:**

- betamethasone sodium phosphate RS
  (already established as an ICRS)
- dexamethasone RS
  (already established as an ICRS)
- dexamethasone sodium phosphate RS
  (already established as an ICRS)
- prednisolone sodium phosphate RS
  (already established as an ICRS)
Test solutions to be added

Sulfuric acid/ethanol (20%) TS

Cool separately 20 mL of sulfuric acid (~1760 g/L) TS and 60 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, mix gently and dilute to 100 mL with ethanol.

Note: Sulfuric acid/ethanol (20%) TS must be freshly prepared.

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