



## RETINOL ORAL SOLUTION

### Adopted text for addition to *The International Pharmacopoeia*

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**Other name.** Paediatric vitamin A oral solution; vitamin A oral solution.

**Category.** Vitamin.

**Storage.** Paediatric retinol oral solution should be kept in a tightly-closed container, protected from light.

**Labelling.** The labelling should state the name of the retinol ester or esters present, the content of vitamin A expressed in International Units (IU) for single doses or IU/ml for multidose containers, and the names and quantities of any stabilizing agents added.

#### **Additional information.**

Strength in the current WHO Model list of essential medicines:

Oral oily solution in multidose container: 100 000 IU/ml.

Oral oily solution as single doses (“capsules”): 50 000 IU; 100 000 IU; 200 000 IU.

Strength in the current WHO Model list of essential medicines for children:

Oral oily solution in multidose container: 100 000 IU/ml.

Oral oily solution as single doses (“capsules”): 100 000 IU; 200 000 IU.

#### **Requirements**

Complies with the monograph for [“Liquid preparations for oral use”](#).

**Definition.** Retinol oral solution contains Retinol concentrate, oily form diluted in a suitable vegetable oil. It may contain suitable antimicrobial agents and stabilizing agents (such as vitamin E or other antioxidants). The oral solution contains not less than 90.0% and not more than 120.0% of the amount of vitamin A stated on the label.

Retinol oral solution may be presented either in a multidose container with a suitable administration device or as single doses, each encapsulated in a soft gelatin shell. The “capsule” shell is designed so that it may be broached (for example, with a nipple which may be cut) and so that the oral solution may be administered easily by mouth when the broached shell is squeezed gently. The capsule shell constitutes the single unit container.

**Manufacture.** For an oral solution presented as single doses, each encapsulated in a soft gelatin shell, the composition and method of manufacture of the soft gelatin shell and the packaging of the final product is chosen and validated to ensure that the contents can be adequately expressed with use of only gentle pressure.

*Carry out the analytical procedures as rapidly as possible, avoiding exposure to actinic light and oxidizing agents, oxidizing catalysts (e.g. copper, iron, etc.), acids, heat and maintaining whenever possible an atmosphere of nitrogen above the solutions.*

### Identity tests

- Either tests A and B or tests A and C may be applied.
- A. 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 12 volumes of cyclohexane R and 1 volume of ether R as the mobile phase. Apply separately to the plate 2  $\mu$ l of each of the following solutions in cyclohexane R. For solution (A) dissolve a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A in 10 ml. For solution (B) prepare a solution of retinol esters RS containing the equivalent of 5000 IU of vitamin A per ml of each ester (retinol acetate, retinol propionate, and retinol palmitate). 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 or spots obtained with solution (A) corresponds or correspond in position and appearance to one or more of the spots obtained with solution (B) in accordance with the ester content stated on the label. The test is not valid unless the chromatogram obtained with solution (B) shows three clearly separated spots. The  $R_f$  values of the esters increase in the following order: retinol acetate, retinol propionate, retinol palmitate.
- B. See the test described below under Assay method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).
- C. To a quantity of the oral solution containing the equivalent of 50 000 IU of vitamin A, add 100 ml of ethanol (~750 g/l) TS. Dilute 1 ml of the resulting solution to 50 ml with a mixture of 100 volumes of ethanol (~750 g/l) TS and 1 volume of hydrochloric acid (~420 g/l) TS. Immediately after preparation measure the absorbance (1.6) in the range 300 to 400 nm. The solution exhibits a single maximum at 326 nm. Heat the solution in a water bath for 30 seconds and cool rapidly. The absorption spectrum of the resulting solution, when observed

between 300 and 400 nm, exhibits a shoulder at 332 nm and maxima at 348, 367 and 389 nm

**Uniformity of deliverable dose (single-dose containers).** For an oral solution presented in single-dose containers the individual mass of the expressed contents of at least 18 of the single-dose containers as weighed under Assay is within  $\pm 10\%$  of the average mass and no individual mass is outside  $\pm 20\%$ .

**Assay.** For an oral solution presented in single-dose containers express the contents of 20 single-dose containers, following the directions for use as stated on the label. Weigh directly the individual contents delivered from each single-dose container and calculate the average mass. [Do not weigh the contents delivered by difference between full and empty containers.] Carry out the assay using the mixed oral solution from the 20 containers.

- Either method A, where valid, or method B may be applied.
- A. Immediately dissolve a quantity of the oral solution containing the equivalent of about 200 000 IU of vitamin A, accurately weighed, in 5 ml of n-pentane R and dilute with 2-propanol R to a presumed concentration of 10-15 IU per ml. Verify that the absorption maximum of the solution to be examined, against 2-propanol R as blank, lies between 325 nm and 327 nm. Measure the absorbances at 300 nm, 326 nm, 350 nm and 370 nm. Calculate the ratio  $A_\lambda/A_{326}$  for each wavelength. If the ratios do not exceed 0.60 at 300 nm, 0.54 at 350 nm and 0.14 at 370 nm, calculate the content of vitamin A in IU:

For an oral solution presented in a multidose container calculate the content of vitamin A in IU per ml from the expression:  $A_{326} \times V \times d \times 1900 / (100 \times m)$ , where  $A_{326}$  is the absorbance at 326 nm,  $V$  is the dilution factor used to give 10-15 IU per ml,  $m$  is the mass of sample used in g,  $d$  is the weight per ml (1.3.1) of the oral solution and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

For an oral solution presented as single doses calculate the deliverable content of vitamin A in IU per “capsule” from the expression:  $A_{326} \times V \times AM \times 1900 / (100 \times m)$ , where  $A_{326}$  is the absorbance at 326 nm,  $V$  is the dilution factor used to give 10-15 IU per ml,  $m$  is the mass of sample used in g,  $AM$  is the average mass of the expressed contents in g per “capsule” and 1900 is the factor to convert the specific absorbances of esters of retinol into IU per g.

If one or more of the ratios  $A_\lambda/A_{326}$  exceeds the values given, or if the wavelength of the absorption maximum does not lie between 325 nm and 327 nm, use Method B.

- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#), using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with octadecylsilyl groups (5  $\mu\text{m}$ ). As the mobile phase, use a mixture of 95 volumes of methanol R and 5 volumes of water R.

Prepare the following solutions. For solution (1) transfer a quantity of the oral solution containing the equivalent of about 100 000 IU of vitamin A, accurately weighed, into a 100 ml volumetric flask. Dissolve immediately in 5 ml of n-pentane R. Add 40 ml of 0.1 M tetrabutylammonium hydroxide TS in 2-propanol R. Swirl gently and allow the mixture to stand for 10 minutes at a temperature between 60 °C and 65 °C, swirling occasionally. Allow to cool to room temperature, dilute to volume with 2-propanol R containing 1 g/l butylated hydroxytoluene R, and homogenise carefully to avoid air bubbles. Dilute 5 ml of the resulting solution to 50 ml with 2-propanol R. For solution (2) transfer an amount of retinol acetate RS containing the equivalent of about 100 000 IU of vitamin A, accurately weighed, into a 100 ml volumetric flask. Proceed as described for solution (1).

Operate with a flow rate of 1 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 325 nm.

Inject alternately 10 µl each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of retinol.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per ml (1.3.1) and calculate the content of vitamin A in IU per ml of the oral solution or, where appropriate, in IU delivered per “capsule”.

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