Levomethorphan limit test for dextromethorphan containing finished pharmaceutical products

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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 impuritiy 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 investigation. 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 *1.14.1 Chromatography*, High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel coated with cellulose tris(4-methylbenzoate) 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 separating 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 volumetric 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. For solution (3) transfer 2 mg of dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and impurity E (levomethorphan)) in a 25.0 mL volumetric flask, add 20 mL of mobile phase, sonicate for about 5 minutes and make up to volume with mobile phase.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to levomethorphan (retention time about 9 minutes) and 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 *1.14.1 Chromatography*, 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 Dextromethorpan 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 separating 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 volumetric flask, wash the round-bottom flask with further 2.0 mL of 2-propanol 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 peaks due to levomethorphan (retention

time about 9 minutes) and 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%).