Aciclovir Oral Suspension

General Notices

Details for the public consultation of this monograph are as follows:

<table>
<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Details</td>
<td><a href="mailto:helen.coms@mhra.gov.uk">helen.coms@mhra.gov.uk</a></td>
</tr>
<tr>
<td></td>
<td><a href="mailto:laxsaan.elanganathan@mhra.gov.uk">laxsaan.elanganathan@mhra.gov.uk</a></td>
</tr>
<tr>
<td>Deadline for Comment</td>
<td>31 March 2021</td>
</tr>
<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
</tr>
<tr>
<td>Notes</td>
<td>Revised monograph</td>
</tr>
<tr>
<td></td>
<td>If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.</td>
</tr>
<tr>
<td>Related substances</td>
<td>Specified impurities, solutions (3) to (5), system suitability, and correction factor revised as per European Pharmacopoeia monograph</td>
</tr>
</tbody>
</table>

Action and use

Purine nucleoside analogue; antiviral (herpesviruses).

DEFINITION

Aciclovir Oral Suspension is a suspension of Aciclovir in a suitable flavoured vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements.

Content of aciclovir, C8H11N5O3

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. The light absorption, Appendix II B, in the range 230 to 250 nm of the solution prepared in the Assay before the final dilution exhibits a maximum at 255 nm and a broad shoulder at about 274 nm.

B. In the Related substances test, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak due to aciclovir in the chromatogram obtained with a solution prepared as follows. Dissolve 25 mg of aciclovir
**BPCRS** in 10 mL of *dimethyl sulfoxide* and dilute 2 volumes of the resulting solution to 5 volumes with the solvent mixture used in the Related substances test.

## TESTS

### Acidity

pH, 4.0 to 7.0, *Appendix V L.*

### Related substances

Carry out the method for *liquid chromatography*, *Appendix III D*, using the following solutions, in a solvent mixture of 1 volume of *dimethyl sulfoxide* and 4 volumes of *water* unless otherwise indicated.

1. To a quantity of the oral suspension containing 0.5 g of Aciclovir add 20 mL of *dimethyl sulfoxide*, shake to disperse and add sufficient solvent mixture to produce 100 mL and filter through a 0.2-µm nylon filter. Dilute 1 volume of the filtrate to 5 volumes with the solvent mixture.
2. Dilute 1 volume of solution (1) to 100 volumes and further dilute 1 volume of this solution to 5 volumes.
3. Dissolve 5 mg of *aciclovir for system suitability A EPCRS* in 1 mL of *dimethyl sulfoxide* and dilute to 5 mL with *water*.
4. Dissolve the contents of a vial of *aciclovir for impurity C identification EPCRS* in 200 µL of *dimethyl sulfoxide* and dilute to 1 mL with *water*. Prepare the solution immediately before use.
5. Dissolve the contents of a vial of *aciclovir for impurity G identification EPCRS* in 1 mL of solution (3).

### CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Supelcosil LC-18-DB is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 10 µL of each solution.

### MOBILE PHASE

**Phosphate buffer solution pH 3.1** Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 3.1 with *orthophosphoric acid*.

**Phosphate buffer solution pH 2.5** Dissolve 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 mL of *water* and adjust to pH 2.5 with *orthophosphoric acid*.

**Mobile phase A** 1 volume of *acetonitrile* and 99 volumes of phosphate buffer solution pH 3.1.

**Mobile phase B** 50 volumes of *acetonitrile* and 50 volumes of phosphate buffer solution pH 2.5.

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Time (Minutes) | Mobile phase A (% v/v) | Mobile phase B (% v/v) | Comment
--- | --- | --- | ---
0-5 | 100 | 0 | isocratic
5-27 | 100→80 | 0→20 | linear gradient
27-40 | 80 | 20 | isocratic
40-46 | 80→100 | 20→0 | linear gradient

**SYSTEM SUITABILITY**

The test is not valid unless:

- in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and aciclovir is at least 1.5.
- in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity K and impurity G is at least 1.5.

**LIMITS**

Identify any peak in solution (1) corresponding to impurity C using the chromatogram obtained with solution (4) and multiply the area of this peak by a correction factor of 2.2.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the area of any other secondary 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 any secondary peaks 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%).

**ASSAY**

To a weighed quantity containing 0.4 g of Aciclovir add 400 mL of water and 25 mL of 1M sulfuric acid, shake well, disperse with the aid of ultrasound for 10 minutes and add sufficient water to produce 500 mL. Filter the resulting solution, discard the first few mL of filtrate and dilute 5 mL of the filtrate to 200 mL with 0.05M sulfuric acid. Add 10 mL of the resulting solution to 5 mL of a 0.01% w/v solution of cetrimide in 0.05M sulfuric acid, add sufficient 0.05M sulfuric acid to produce 100 mL and measure the fluorescence, Appendix II E, using an excitation wavelength of 308 nm and an emission wavelength of 415 nm. Set the instrument to zero using a 0.0005% w/v solution of cetrimide in 0.05M sulfuric acid. Calculate the content of C8H11N5O3 in the oral suspension from the fluorescence obtained by carrying out the operation at the same time using a mixture prepared by adding 10 mL of a 0.002% w/v solution of aciclovir BPCRS in 0.05M sulfuric acid and beginning at the words ‘… to 5 mL of a 0.01% w/v solution of cetrimide…’. Determine the weight per mL of the...
oral suspension, Appendix V G, and calculate the content of C₈H₁₁N₅O₃, weight in volume, using the declared content of C₈H₁₁N₅O₃ in aciclovir BPCRS.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Aciclovir.