# Entecavir Oral Solution

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

**Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.**



## Document History and Schedule for the Adoption Process

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|---|---|
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| Further follow-up action as required. | |

# Entecavir Oral Solution

Entecavir Oral Solution is a solution of Entecavir in a suitable vehicle.

Entecavir Oral Solution contains not less than 90.0 per cent and not more than 105.0 per cent of the stated amount of entecavir, $C_{12}H_{15}N_5O_3$.

**Usual strength**. 0.05 mg per ml.

## Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

## Tests

**Related substances**. Determine by liquid chromatography (2.4.14).
*Solvent mixture*. 20 volumes of *methanol* and 80 volumes of *water*.
*Test solution.* Use the oral solution, dilute if necessary with the solvent mixture.

*Reference solution (a).* Dissolve 20 mg of *entecavir monohydrate IPRS* in 4 ml of *methanol* with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 20.0 ml with the solvent mixture.

*Reference solution (b).* Dissolve 20 mg of *entecavir monohydrate IPRS* and 0.6 g of *methylparaben* in 5 ml of *methanol* with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 20.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- column temperature: 30°,
- mobile phase: A. a buffer solution prepared by dissolving 19.1 g of *disodium tetraborate decahydrate* in 900 ml of *water*, add 35 ml of *methanol* and dilute to 1000 ml with *water*,
  B. *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

| Time (in min.) | Mobile phase A (per cent v/v) | Mobile phase B (per cent v/v) |
|---|---|---|
| 0 | 100 | 0 |
| 12 | 100 | 0 |
| 30 | 68.5 | 31.5 |
| 31 | 50 | 50 |
| 34 | 50 | 50 |

| | | |
|---|---|---|
| 35 | 100 | 0 |
| 43 | 100 | 0 |

| Name | Relative retention time |
|---|---|
| Entecavir | 1.0 |
| Epimer-1* | 1.5 |
| Epimer-2* | 1.6 |

*2-({9-[(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6-oxo-6,9-dihydro-1*H*-purin-2-yl}amino)propanoic acid. Configuration of epimers may be interchangeable.

The relative retention time with reference to entecavir for methylparaben is about 1.2.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to entecavir and methylparaben is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to epimer-1 and epimer-2, each of, is not more than 1.0 per cent, the area of any other secondary peak is not more than 0.5 per cent, and the sum of areas of all the secondary peaks is not more than 2.2 per cent, calculated by area normalization.

**Other tests**. Comply with the tests stated under Oral liquids.

**Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to entecavir and methylparaben is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{12}H_{15}N_5O_3$ in the solution.

**Microbial contamination** (2.2.9). The total microbial count is not more than $10^2$ CFU per ml, total fungal count is not more than $10^1$ CFU per ml. 1 ml free from *Escherichia coli*.

**Storage**. Store protected from light, at a temperature not exceeding 30°.