

## Entecavir

*2-Amino-1,9-dihydro-9-[(1S,3R,4S)-4hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6H-purin-6-one, monohydrate*

Entecavir is an antiviral drug for hepatitis B treatment in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. It is in the drug class of nucleoside reverse transcriptase inhibitors (NRTIs), available by prescription only.

Entecavir passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

### Epidemiological data

No cancer epidemiology studies were identified.

### Animal carcinogenicity data

- Two-year gavage studies in rats:
  - Male and female Sprague-Dawley rats treated by daily gavage: FDA (2004, pp. 4 & 123-125); FDA (2010, pp. 21-22)
    - *Increase in brain glioma (by pairwise comparison) in males*
    - *Increase in hepatocellular adenoma and carcinoma combined, brain glioma, and skin fibroma (by pairwise comparison) in females*
  
- Two-year gavage studies in mice
  - Male and female CD-1 mice administered by daily gavage: FDA (2004, pp. 5 & 113-115); FDA (2010, p. 22)
    - *Increase in hepatocellular carcinoma, hepatocellular adenoma and carcinoma combined, lung carcinoma (by pairwise comparison), and lung adenoma and carcinoma combined (by pairwise comparison and trend) in males*
    - *Increase in lung carcinoma, lung adenoma and carcinoma combined, spleen hamangiosarcoma, spleen hemangioma and hemangiosarcoma combined, ovarian hemangioma, uterine hemangioma (by pairwise comparison) in females*

## Other relevant data

- Genotoxicity as reviewed in FDA (2004, pp. 101-113) and FDA (2010, p. 22)
  - Chromosome aberration in cultured human lymphocyte in the absence and presence of metabolic activation (*positive*)
  - Mutagenicity assays in *Salmonella typhimurium* and *E. Coli* with or without metabolic activation (*negative*)
  - Micronucleus and DNA repair assays *in vivo* in rats (*negative*)
  - Gene mutation assays in mammalian cells (*negative*)
  - *In vitro* transformation assays in Syrian hamster embryo cells (*negative*)
  
- Structure activity considerations
  - Entecavir belongs to the group of nucleoside analogues. Several chemicals in this group are Proposition 65 carcinogens, such as Ganciclovir, Zalcitabine and Zidovudine.

## Reviews

- FDA (2004)

## References<sup>1</sup>

FDA (2004). NDA review (NDA number: 21-797). Pharmacologist's review. September 30, 2004.

FDA approved drug label for BARACLUDE (Entecavir) Tablets and Oral Solution (2010).

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<sup>1</sup> Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.