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Adefovir Dipivoxil

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1. DESCRIPTION

Adefovir dipivoxil, 9-[2[[bis[(pivaloyloxy)-methoxy]phosphinyl]-methoxy]ethyl] adenine, also known as bis(POM)-PMEA, and PMEA-9-2-phosphonylmethoxyethyl-adenine, is the oral diester prodrug of adefovir, an acyclic nucleotide analog of deoxyadenosine monophosphate (Dando and Plosker, 2003). Adefovir dipivoxil is rapidly converted to adefovir in the gastrointestinal tract and then further sequentially phosphorylated intracellularly by cellular kinases to its active metabolite, adefovir diphosphate.

Adefovir diphosphate is a reverse transcriptase inhibitor which inhibits hepatitis B virus (HBV) DNA polymerase by competing with the natural substrate, deoxyadenosine triphosphate, and also causing DNA chain termination after its incorporation into viral DNA. The *in vitro* inhibition constant (K_i) for adefovir diphosphate for HBV DNA polymerase was 0.1 μM. This is ≈ 7- to 12-fold lower than the K_i for human DNA polymerase alpha, gamma, and epsilon and ≈ 4-fold and 704-fold lower than the K_i for delta and beta (Naesens and Andrei, 1997; Dando and Plosker, 2003; also see Table 255.1).

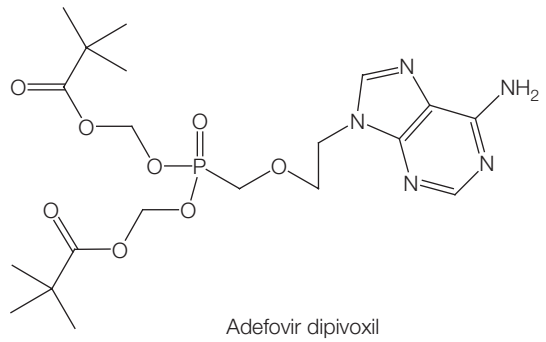
Table 255.1. Activity of adefovir against DNA viruses *in vitro*.

Virus	EC_{50} (μM)
Herpes simplex virus 1	26
Thymidine kinase–herpes simplex virus 1	26
Herpes simplex virus HSV-2	26
Varicella-zoster virus	27
human cytomegalovirus	136
Epstein–Barr virus	1.1
Human herpesvirus 6	30
Human adenovirus 5	> 400
Human adenovirus 8	> 400
Human hepatitis B virus	1.2
Duck hepatitis B virus	0.14
Vaccinia virus	> 500
Human polyomavirus	> 180
African swine fever virus	18

Abbreviation: EC_{50}: 50% effective concentration (concentration of drug at which 50% of its maximal effect is observed).
Source: Adapted with permission from Naesens and Andrei (1997).

Adefovir dipivoxil has the molecular formula $C_{20}H_{32}N_5O_8P$ and a molecular weight of 501.48. Its Chemical Abstracts Service number is 142340-99-6. Adefovir dipivoxil is a white to off-white crystalline powder with an intrinsic aqueous solubility in water of 19 mg/ml at pH 2 and 0.4 mg/ml at pH 7.2. It has an octanol/aqueous phosphate buffer (pH 7) partition coefficient (log p) of 1.91. The chemical structure of adefovir dipivoxil and adefovir is shown in Figure 255.1.

Adefovir dipivoxil is available for oral administration in a 10-mg tablet. In all developed countries it is sold by Gilead Sciences (2014) as Hepsera, where it is still under patent (it expires in 2018), but there are generic versions of the drug manufactured in India (Adesera, Adfovir, and Adheb).



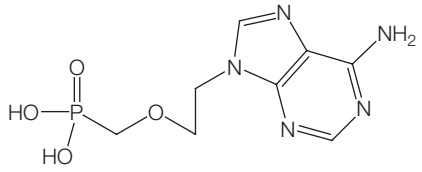


Figure 255.1. Chemical structure of the adefovir prodrug (adefovir dipivoxil) and adefovir.