COMMENTARIES

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Aciclovir

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing (biowaiver) for the approval of immediate release (IR) solid oral dosage forms containing aciclovir are reviewed. Aciclovir therapeutic use and therapeutic index, pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability (BA) studies were also taken into consideration in order to ascertain whether a biowaiver can be recommended. According to the Biopharmaceutics Classification System (BCS) and considering tablet strengths up to 400 mg, aciclovir would be BCS Class III. However, in some countries also 800 mg tablets are available which fall just within BCS Class IV. Aciclovir seems not to be critical with respect to a risk for bio*in*equivalence, as no examples of bio*in*equivalence have been identified. It has a wide therapeutic index and is not used for critical indications. Hence, if: (a) the test product contains only excipients present in aciclovir solid oral IR drug products approved in ICH or associated countries, for instance as presented in this article; and (b) the comparator and the test product both are *very rapidly dissolving*, a biowaiver for IR aciclovir solid oral drug products is considered justified for all tablet strengths. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:5061–5073, 2008

Keywords: absorption; aciclovir; bioequivalence; biopharmaceutics classification system (BCS); permeability; solubility; regulatory science

†This article reflects the scientific opinion of the authors and not the policies of regulating agencies.

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INTRODUCTION

A biowaiver monograph of aciclovir based on literature data is presented. The risks of basing a BE assessment on *in vitro* rather than *in vivo* study results for the approval of new IR solid oral dosage forms containing aciclovir ("biowaiving"), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing aciclovir as the only active pharmaceutical ingredient (API) and not to combination drug products.

The purpose and scope of this series of monographs have been previously discussed.[1] Summarized in few words, the aim is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver is advisable or not. This systematic approach to recommend or advise against a biowaiver decisions is referred to in the recently published World Health Organization (WHO) Guideline.[2] It is to be understood that these monographs do not simply apply the WHO,[2] FDA,[3] and EMEA Guidances,[4] but also aim to serve as a critical validation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),[5] acetazolamide,[6] amitriptyline,[7] atenolol,[1] chloroquine,[8] cimetidine,[9] ethambutol,[10] ibuprofen,[11] isoniazid,[12] prednisolone,[13] prednisone,[14] pyranisamide,[15] propranolol,[1] ranitidine,[16] and verapamil.[1] They are also available on-line at www.fip.org/bcs.

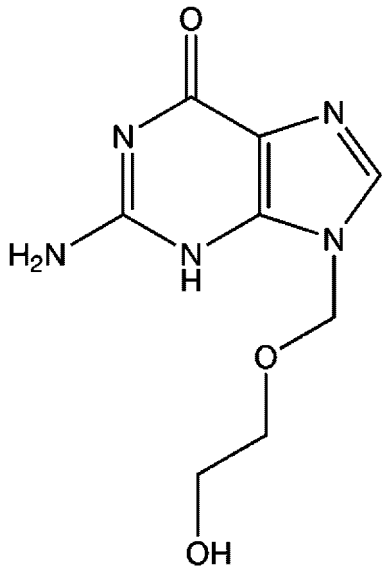
EXPERIMENTAL

Literature data was assessed from PubMed[17] and Micromedex[18] databases. Keywords used for searching, in various combinations were: aciclovir, acyclovir, solubility, permeability, dissolution. Information was also obtained from regulatory documents published by the EMEA,[4] the FDA,[3] and the WHO.[2,19] The USP[20]and the European Pharmacopoeia[21] were also consulted when necessary.

GENERAL CHARACTERISTICS

Name

The INN and WHO chemical name for aciclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one, or 9-[(2-hydroxyethoxy)methyl]-guanine.[20,22] Other names are: acyclovir, acycloguanosine and ACV.[23] Its molecular formula is $C_8H_{11}N_5O_3$, and its molecular weight is 225.21 g/mol. Its CAS number is 59277-89-3.[20,22]



Therapeutic Indications, Therapeutic Index and Toxicity

Aciclovir is used orally for the treatment and prophylaxis of initial and recurrent episodes of genital and labial herpes and for the acute treatment of herpes zoster for the treatment of varicella (chickenpox) in immunocompetent individuals.[24,25] Its defined daily dose, either orally or parenterally, is 4 g.[26] Oral administration up to doses of 4800 mg/day is usually well tolerated although high-dose treatment with oral aciclovir for herpes zoster results can cause more side effects than low-dose treatments.[27] Several patients have ingested up to 100 capsules, corresponding to 20 g of aciclovir, with no apparent adverse effects,[28] probably due to the limited solubility and absorption characteristics. Neurotoxicity may be seen with high doses in patients with compromised renal function.[28–30] Neurotoxicity can include coma, confusion,