

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 bioinequivalence, as no examples of bioinequivalence 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

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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.

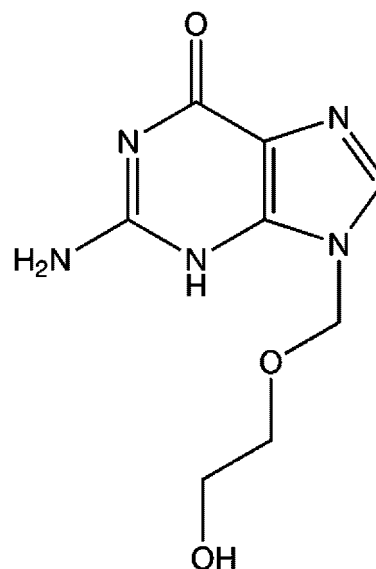
EXPERIMENTAL

Literature data was assessed from PubMed¹⁷ and Micromedex¹⁸ 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 USP²⁰ and the European Pharmacopoeia²¹ 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 C₈H₁₁N₅O₃, 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,

delirium, encephalopathy, hallucinations, paresthesias, psychosis, seizures, or tremor. Neurologic adverse reactions usually occur within 1–2 days of achieving the maximum aciclovir concentration and may not be directly correlated with the aciclovir serum concentrations at the time the toxic effects appear. The threshold for neurotoxicity was reported to be 4.5 $\mu\text{g/mL}$, whereas the normal peak range is 0.4–2 $\mu\text{g/mL}$.²⁸ Diarrhea, nausea and vomiting, and elevated serum creatinine levels may be observed in conjunction with plasma levels over 20 mcg/mL , but recede when the dose is reduced.²⁸

Serious neurological and/or psychiatric adverse effects been reported in a few patients administered bolus injections of high doses intravenous aciclovir.^{27,28,30} Aciclovir has low solubility in urine and aciclovir crystals may precipitate in the renal tubules if the solubility is exceeded in the intratubular fluid, resulting in renal dysfunction, renal failure or anuria,^{24,28} but this crystalluria is most likely to occur only during administration of large, parenteral doses. All these latter adverse drug reactions are not associated with the oral administration and hence are not relevant for this monograph.

PHYSICOCHEMICAL PROPERTIES

Salts, Esters, Polymorphs, Hydrates

Aciclovir is commonly used as the free acid form in solid oral dosage forms, whereas the sodium salt is used in parenteral dosage forms.^{22,23} Valaciclovir, the L-valyl ester of aciclovir, has been used orally to increase its BA.^{31–36} Several dipeptide ester prodrugs are being tested to assess their usefulness in therapeutics,^{37,38} as well as some bile acid conjugate prodrugs³⁹ and a phospholipid prodrug.⁴⁰ The scope of this monograph is restricted to drug products containing aciclovir as the free acid.

Aciclovir is normally present in a hydrated form consisting of three aciclovir molecules to two molecules of water,⁴¹ corresponding to a theoretical water content of about 5%, but dose and solubility are normally expressed in units of anhydrous aciclovir.^{20,42} A stable anhydrous form can be obtained by drying hydrated aciclovir at temperatures above 150°C.⁴¹ Although only slight and insignificant differences in solubility values exist between these two forms, the anhydrous form of aciclovir possesses poorer dissolution properties than the hydrated form.⁴¹

Solubility

Aciclovir is described as “slightly soluble in water” in different Pharmacopoeias.^{20,21} Most data found in literature are calculated at room temperature (22–25°C), reporting solubility values that range from 1.2 to 1.6 mg/mL .^{41,43–47} In water at 37°C, solubility has been reported to be 2.5 mg/mL .²⁴ A plot of the pH-solubility in de-ionized water at 37°C was published, showing the solubility to vary slightly with pH, with a lowest solubility of 2.3 mg/mL at pH 5.8 at 37°C.⁴⁸ The solubility data in Table 1 were obtained from this pH-solubility profile.

Partition Coefficient

The partition coefficient ($\log P$) in *n*-octanol at 22°C is -1.57 .^{45,49}

At 25°C, $\log P$ and $\log D$ were both reported to be -1.8 ^{44,50} at pH 6.8. Calculations by Kasim et al. using fragmentation methods based on atomic contributions to lipophilicity and by using the $C\log P^{\text{R}}$ program (version 3.0, Biobyte Corp., Claremont, CA, <http://www.biobyte.com>) gave values of -2.42 for $C\log P^{\text{R}}$, and -1.59 for $\log P$, respectively.⁵¹

pK_a

Aciclovir is an ampholyte with both weak acid and basic groups. Common literature pK_a values for aciclovir are 2.27 and 9.25, but it is not stated at which temperature they were measured.^{23,24} Balon et al.⁵⁰ reported pK_a values of 2.16 and 9.04 at 37°C.

Table 1. Solubility Data at 37°C and the Corresponding Dose/Solubility (D/S) Ratios for Different Tablet Strengths

pH	Solubility ^a (mg/mL)	D/S^b (mL)		
		200 mg^c	400 mg	800 mg^d
1.2	>3.5	<57	<114	<229
4.5	~2.6	~77	154	~308 ^e
5.8	~2.3	~87	174	~348 ^e
6.8	~2.4	~83	167	~333 ^e
7.4	~2.5	~80	160	~320 ^e

^aData read from the plot published by Shojaei et al.⁴⁸

^bCritical limit: <250 mL.^{2–4}

^cStrength of WHO Essential Medicines List.¹⁹

^dHighest strength on some EU markets and the USA market.

^eExceeds critical limit.

Dosage Form Strengths

The WHO Model List of Essential Medicines lists a dosage strength of 200 mg for aciclovir.¹⁹ Most European countries have Marketing Authorizations (MAs) for IR solid oral dosage forms of 200 and 400 mg, but some countries also have an MA for a 800 mg strength, see Table 2. The USA has MA's for IR solid oral dosage forms of 200, 400, and 800 mg.⁵²

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

Data found in the literature for Caco-2 permeability are summarized in Table 3.

A permeability study employing 3H-aciclovir indicated an apparent permeability coefficient of about 1.19×10^{-5} cm/s,⁵³ but other reports obtained considerably lower values, ranging from 0.12×10^{-6} to 2.0×10^{-6} cm/s,⁵⁴ see Table 3. As drugs with a permeability in the range 70–100% absorbed usually have a P_{app} value greater than 10×10^{-6} cm/s,⁵⁴ most of these data suggest that permeability of aciclovir is low. It has also been hypothesized that a $\log P$ value greater than that of metoprolol (1.72) indicates high permeability.⁵¹ As all $\log P$ values reported for aciclovir lie far below that value (see above), according to this paradigm aciclovir is expected to have low permeability.

Aciclovir's absolute BA following oral administration has been reported to be in a range of 10–30% in humans.^{18,22,23,25} This poor systemic BA is considered to be a result of the characteristics of the drug itself and not its delivery vehicle.^{18,25} Its absorption occurs mainly by passive diffusion mechanism and it is slow, variable and incomplete.^{23,55} Maximum plasma concentrations are reached within 1.5–2.5 h.^{18,22,23,55,56} Aciclovir shows a two compartment pharmacokinetic behavior, regardless of the dosage, duration of treatment or frequency of administration.³⁶ After multiple dose administration, steady-state concentrations are reached in 1–2 days.¹⁸ Some studies suggest that increasing doses result in decreasing BA^{23,25,35} or less than proportional increases in C_{max} ⁵⁷ and it has been suggested that this behavior may be due to a saturable carrier system or a limited area for absorption in the gastro-intestinal (GI) tract or to the low solubility of this API.^{18,46,55} Other studies found near-

proportional increases in AUC with increasing doses in the dose range used clinically of 100–800 mg.^{34,47} Food does not appear to affect the rate and extent of absorption.^{18,23,25,55}

Distribution

Aciclovir is widely distributed into most body tissues, including the brain, kidney, lung, liver, heart tissue, muscle, spleen, placenta, uterus, vaginal mucosa and secretions, semen, saliva, amniotic fluid, aqueous humor and cerebrospinal fluid.^{18,23} Aciclovir demonstrates minimal protein binding (9–33%) at therapeutic plasma concentrations.^{18,23,24}

Metabolism and Excretion

Most of a single aciclovir dose (62–91% of an intravenous dose) is excreted unchanged in urine via glomerular filtration and tubular secretion, in adults with normal renal function.^{23,24} Aciclovir is metabolized in the liver, partially to 9-(carboxymethoxy)methyl]guanine (CMMG) and minimally to 8-[(hydroxy-9-(2-hydroxyethoxy)methyl]guanine.^{18,23,24} The only known urinary metabolite is CMMG. Plasma concentrations of aciclovir appear to decline in a biphasic manner. In adults with normal renal function, $t_{1/2\alpha}$ averages 0.34 h and $t_{1/2\beta}$ averages 2.1–3.5 h.^{18,23,24,55}

DOSAGE FORM PERFORMANCE

Bioequivalence of Different Formulations

Six *in vivo* BE studies comparing drug products with the innovator drug product, Zovirax[®], were identified. Details of these studies are presented in Table 4. In all of them, the comparator and the generic formulations were bioequivalent.^{58–62}

Moreover, in some Summary of Products Characteristics (SmPCs) of drug products with a MA in DE, results of successful *in vivo* BE studies are reported. The SmPCs of Aciclovir-CT 200/400/800 mg Tabletten⁶³ reports *in vivo* BE studies of each of the three tablet strengths, while the SmPC of Virzin 200/400/800 mg⁶³ reports *in vivo* BE studies of the 400 and 800 mg strength. All these studies used 20 volunteers and BE was established according to AUC, C_{max} , and T_{max} . It is very

Table 2. Excipients* Present in Aciclovir IR Solid Oral Drug Products[†] with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES) and Sweden (SE),[‡] and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a MA in the USA[§]

Excipient	Drug Products Containing that Excipient with a MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with a MA in the USA (mg)
Aluminum magnesium silicate ^a	DE(1,2)	8–24
Cellulose	DE(1–16), DK(17–23), ES(24–37), FI(38–47), FR(48–64), NL(65–73), NO(74–79), SE(80–87)	4.6–1385 ^b
Crospovidone	DE(3,6–14,16), DK(18–20), ES(24), FI(39,41,43), NL(69), NO(76), SE(82,83)	86–500
Croscarmellose	ES(27)	
Gelatin	SE(85)	1–756 ^b
Hypromellose	DE(1,2), FI(44,45), NO(77), SE(80)	0.8–86
Lactose	DE(3,4,6,9,12,14), DK(18,19,21), ES(25,28,30,32,34,36), FI(39,41,46), FR(50,54,58,60,63), NL(69,71), NO(76,78), SE(82,85,86)	23–1020 ^b
Macrogol	DE(1,2)	0.12–500 ^b
Magnesium stearate	DE(1–16), DK(17–23), ES(24–37), FI(38–47), FR(48–64), NL(65–73), NO(74–79), SE(80–84,86,87)	0.15–401 ^b
Povidone	DE(1,2,4,5,15), DK(21–23), ES(25–37), FI(38,42,46,47), FR(48–64), NL(65–68,70–72), NO(75,78,79), SE(84,86,87)	0.17–75
Silica	DE(7,8,10,11,13,15,16), DK(17,20,23), ES(24,26,29,31,33,35,37), FI(38,40–43), FR(48,49,52,53,56,57,61,62), NL(66–68,70,73), NO(74,75), SE(81,83,84)	0.65–99
Sodium starch glycolate	DE(1–16), DK(17–23), ES(24–26,28–37), FI(38–47), FR(48–64), NL(65–73), NO(74–79), SE(80–87)	2–876 ^b
Sodium stearyl fumarate	SE(85)	1.2–24
Starch	DE(15), SE(85)	0.44–1135 ^b
Starch, pregelatinized	DK(17), FI(40), NL(73), NO(74), SE(81)	6.6–600

1. Zovirax[®] 200 mg/–400 mg/–800 mg Filmtabletten (Mono)
2. Acyclovir-ratiopharm[®] 200 mg/–400 mg/–800 mg Filmtabletten (Mono)
3. ACERPES[®] 800 mg Tabletten (Mono)
4. Acic[®] 200 Tabletten (Mono)
5. Acic[®] 400 mg/–800 mg Tabletten (Mono)
6. Aciclobeta[®] 200 Tabletten (Mono)
7. Aciclobeta[®] 400 mg/–800 mg Tabletten (Mono)
8. Aciclostad[®] 200 mg/–400 mg/–800 mg Tabletten (Mono)
9. Acyclovir 200 mg/–400 mg—1 A Pharma[®] Tabletten (Mono)
10. Acyclovir 800—1 A Pharma[®] Tabletten (Mono)
11. Acyclovir AL 200 mg/–400 mg/–800 mg Tabletten (Mono)
12. Acyclovir-CT 200 mg Tabletten (Mono)
13. Acyclovir-CT 400 mg/–800 mg Tabletten (Mono)
14. Herpetad[®] 200 mg Tabletten (Mono)
15. Virzin 200 mg/–400 mg Tabletten (Mono)
16. Virzin 800 Tabletten (Mono)
17. Acyclovir Ranbaxy, tableter 200 mg/–400 mg/–800 mg
18. Acyclovir 1A Farma, tableter 200 mg/–400 mg/–800 mg
19. Acyclovir HEXAL, tableter 200 mg/–400 mg/–800 mg
20. Aciclodan, tableter 200 mg/–400 mg/–800 mg

(Continued)

Table 2. (Continued)

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21. Zovir, tableter 200 mg
 22. Zovir, tableter 400 mg/–800 mg
 23. Acyclovir Actavis, tableter 200 mg/–400 mg/–800 mg
 24. Aciclostad[®] 200/–800, comprimidos de 200 mg/–800 mg
 25. ACICLOVIR BEXAL 200 mg Comprimidos EFG
 26. ACICLOVIR BEXAL 800 mg Comprimidos EFG
 27. ACICLOVIR COMBINO PHARM 800 mg EFG
 28. ACICLOVIR CUVEFARMA 200 mg comprimidos EFG
 29. ACICLOVIR CUVEFARMA 800 mg comprimidos EFG
 30. ACICLOVIR KORHISPANA 200 mg comprimidos EFG
 31. ACICLOVIR KORHISPANA 800 mg comprimidos EFG
 32. ACICLOVIR MERCK 200 mg comprimidos EFG
 33. ACICLOVIR MERCK 800 mg comprimidos EFG
 34. ACICLOVIR RANBAXY 200 mg COMPRIMIDOS EFG
 35. ACICLOVIR RANBAXY 800 mg COMPRIMIDOS EFG
 36. ACICLOVIR STADA 200 mg COMPRIMIDOS EFG
 37. ACICLOVIR STADA 800 mg COMPRIMIDOS EFG
 38. Acyclovir Alpharma 200 mg/–400 mg/–800 mg tabletti
 39. Acyclovir HEXAL 200 mg/–400 mg/–800 mg tabletti
 40. Acyclovir Ranbaxy 200 mg/–400 mg/–800 mg tabletti
 41. Aclovir 200 mg/–400 mg tabletti
 42. Aclovir 800 mg tabletti
 43. Acyclostad 200 mg/–400 mg/–800 mg tabletti
 44. ACYRAX 200 mg/–400 mg/–800 mg tabletti
 45. Asikloviiri Orion 200 mg/–400 mg/–800 mg tabletti
 46. Zovirax 200 mg tabletti
 47. Zovirax 400 mg/–800 mg tabletti
 48. ACYCLOVIR ALMUS 200 mg cp
 49. ACYCLOVIR ARROW 200 mg/–800 mg cp
 50. ACYCLOVIR BIOGARAN 200 mg cp
 51. ACYCLOVIR BIOGARAN 800 mg cp
 52. ACYCLOVIR EG 200 mg/–800 mg cp
 53. ACYCLOVIR G GAM 200 mg cp
 54. ACYCLOVIR MERCK 200 mg cp
 55. ACYCLOVIR MERCK 800 mg cp
 56. ACYCLOVIR QUALIMED 200 mg/–800 mg cp
 57. ACYCLOVIR RATIOPHARM 200 mg/–800 mg cp
 58. ACYCLOVIR RPG 200 mg cp
 59. ACYCLOVIR RPG 800 mg cp
 60. ACYCLOVIR SANDOZ 200 mg cp
 61. ACYCLOVIR SANDOZ 800 mg cp
 62. ACYCLOVIR TEVA 200 mg/–800 mg cp
 63. ZOVIRAX 200 mg cp
 64. ZOVIRAX 800 mg cp
 65. Acyclovir 200/–400/–800, tabletten 200/–400/–800 mg
 66. Acyclovir CF 200 mg/–400 mg/–800 mg, tabletten
 67. Acyclovir 200 mg/–400 mg/–800 mg, tabletten
 68. Acyclovir ratiopharm 200 mg/–400 mg/–800 mg, tabletten
 69. Acyclovir Sandoz tablet 200/–400/–800, tabletten 200/–400/–800 mg
 70. Acyclovir 200/–400/–800 PCH, tabletten 200/–400/–800 mg
 71. Acyclovir 200 mg, tabletten
 72. Acyclovir 400 mg, tabletten
 73. Acyclovir 200 mg/–400 mg/–800 mg, tabletten
 74. Acyclovir tableter Ranbaxy 200 mg/–400 mg/–800 mg
 75. Acyclovir Alpharma 200 mg/–400 mg/–800 mg tableter

(Continued)

Table 2. (Continued)

76.	Acyclovir HEXAL 200 mg/–400 mg/–800 mg tabletter
77.	Aciklovir Merck NM 200 mg/–400 mg/–800 mg tabletter
78.	Zovirax tabletter 200 mg
79.	Zovirax tabletter 400 mg/–800 mg
80.	Acyclovir Merck NM 200 mg/–400 mg/–800 mg tabletter
81.	Acyclovir Ranbaxy 200 mg/–400 mg/–800 mg
82.	Acyclovir Sandoz 200 mg/–400 mg/–800 mg, tabletter
83.	Aciklovir STADA 200 mg/–400 mg/–800 mg tabletter
84.	Acyclovir Alpharma 200 mg/–400 mg/–800 mg tabletter
85.	Geavir 200 mg/–400 mg/–800 mg tabletter
86.	Zovirax 200 mg tabletter
87.	Zovirax 400 mg/–800 mg tabletter

*Colourants and water are not included.

[†]Excluded are: dispersible tablets, oral suspension, and oral solutions.

[‡]DE: www.rote-liste.de (assessed February 28, 2007); DK: www.dkma.dk (assessed February 28, 2007); FI: www.nam.fi (assessed February 28, 2007); FR: www.vidal.fr (assessed February 28, 2007); NL: www.cbg-meb.nl. (assessed February 27, 2007); NO: www.legemiddelverket.no (assessed March 1, 2007); ES: www.agemed.es (assessed February 28, 2007); SE: www.lakemedelsverket.se (assessed March 1, 2007).

[§]USA: <http://www.fda.gov/cder/iig/iigfaqweb.htm#purpose> (version date January 9, 2007).

^aIncludes aluminum magnesium silicate and aluminum magnesium trisilicate.

^bThe upper range value reported is unusual high for solid oral dosage forms and the authors doubt on its correctness.

Excipients

In the above-mentioned BE studies, various excipients were used in the formulations. Aciclovir-CT tabletten contain cellulose, crospovidone, magnesium stearate, sodium starch glycolate, lactose (200 and 400 mg strengths only) and silica (800 mg strength only);⁶³ Virzin contains cellulose; magnesium stearate silica, sodium starch glycolate, starch (200 and 400 mg strengths only), crospovidone (800 mg strength only) and povidone (200 and 400 mg strengths only),⁶³ whereas Zovirax[®] contains aluminum magnesium silicate, cellulose, hypromellose, macrogol, magnesium stearate, povidone, and sodium starch glycolate;⁶³ see also Table 2.

A study carried out with Caco-2 showed that, of nine common excipients studied, only sodium lauryl sulfate slightly increased the permeability

of aciclovir, whereas lactose, hydroxypropyl methyl cellulose, Tween 80, propylene glycol, polyethylene glycol 400, dioctyl sodium sulfosuccinate, sodium EDTA and anhydrous cherry flavor, had no effect on the permeability.⁶⁴

Excipients present in aciclovir IR solid oral drug products with a MA in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES) and Sweden (SE), are shown in Table 2. Additionally, the minimum and maximum amount of the listed excipients present per dosage unit in solid oral drug products with a MA in the USA, taken from the FDA Inactive Ingredient Data Base,⁶⁵ is indicated.

It can be expected that the drug products having a MA in the reported countries successfully passed an *in vivo* BE study. In DE, the exemption from demonstration of BE *in vivo* that existed for some APIs in the 1980s and 1990s was not applied to

Table 3. Apparent Permeability of Aciclovir in Caco-2 Cell Monolayers

Permeability ($\times 10^{-6}$ cm/s)	pH	Initial Concentration	References
0.12	7.4	0.02–6 mM (not specified)	Bergstrom et al. ⁴⁴
0.25	7.4	0.01–0.1 mM (not specified)	Yazdanian et al. ⁷⁴
0.43	7.4	Not specified	Friedrichsen et al. ⁷⁵
1.08	—	Not specified	de Vruet et al. ⁷⁶
1.26	6.8	Below saturation	Rege et al. ⁶⁴
2.00	6.5(A), 7.4(B)	Not specified	Yee ⁵⁴
11.9	7	0.5 mCi/mL (radioactive ACV)	Salama et al. ⁵⁰

(A), apical compartment; (B), basolateral compartment.

Table 4. Aciclovir Bioequivalence Studies Found in Literature

Reference	Composition of Test Formulation	Study Design	Number of Subjects	Estimates for BE	Result
Al-Yamani et al. ⁶¹	400 mg tablet	2-way crossover	24	C_{max} AUC_{0-t} $AUC_{0-\infty}$ $C_{max}/AUC_{0-\infty}$	Test formulation bioequivalent
Bahrami et al. ⁶²	400 mg tablet	Non crossover	12	T_{max} C_{max} AUC_{0-72} $AUC_{0-\infty}$	Test formulation bioequivalent
Rojanasthien et al. ⁶⁰	200 mg tablet	Two-period crossover	Not reported	$T_{1/2}$ T_{max} $AUC_{0-\infty}$	Test formulation bioequivalent
Vergin et al. ⁵⁸ , 1st study	200 mg tablet + 250 mg IV infusion	Three-way	24	C_{max} T_{max} AUC_{0-t} Dose renally excreted	Test formulation bioequivalent
Vergin et al. ⁵⁸ , 2nd study	400 mg tablet	Two-way	24	C_{max} T_{max} AUC_{0-t} Dose renally excreted	Test formulation bioequivalent
Yuen et al. ⁵⁹	Not reported	Two-way crossover	12	$AUC_{0-\infty}$ C_{max} T_{max} K_{el} , $t_{1/2}$, V_d	Test formulation bioequivalent

aciclovir.⁶⁶ Similarly, aciclovir is not on the list of APIs exempted from demonstration of BE *in vivo* for IR solid oral drug products seeking a national MA only in The Netherlands.⁶⁷

Dissolution

The USP 29 dissolution specifications for Aciclovir Tablets are not less than 80% (Q) of the labeled amount dissolved within 45 min in 900 mL of 0.1 N hydrochloric acid, using the paddle at 50 rpm, and for Aciclovir Capsules the specification is not less than 75% (Q) within 45 min in 900 mL of 0.1 N hydrochloric acid, using the basket at 100 rpm, respectively.²⁰ The dissolution of the innovator and five generic drug products, each containing 800 mg aciclovir, was compared using USP apparatus 2 and USP apparatus 3. The dissolution of all drug products was complete within 15 min, in both apparatus.⁶⁸

One of the six *in vivo* BE studies mentioned above compared the dissolution of innovator and

generic drug products as stipulated by USP XXIII, finding them to be not statistically different.⁶¹

DISCUSSION

Solubility

D/S values for different pHs are shown in Table 1. The WHO recommended dosage strength and the 400 mg strength qualify as *highly soluble* according to all Guidelines.²⁻⁴ However, in some markets, the highest dosage strength is 800 mg, for which that criterion is not met.

Permeability

The BA for aciclovir ranges from 10% to 30%, indicating, given the small amount of metabolism, that this API is not *highly permeable* according to all Guidelines.²⁻⁴ Caco-2 permeability data and $\log P_{oct}$ values support that conclusion.

BCS Classification

Combining the data on solubility and permeability, according to all Guidelines,²⁻⁴ the 200 and 400 mg tablet strengths are BCS Class III. Kasim et al.⁵¹ also classified aciclovir as BCS Class III, but their classification was based on correlations of partition coefficients with permeability, a method not supported by HHS-FDA and other regulatory authorities due to its limited predictability. Lindenberg et al.⁶⁹ and the recently adopted revised WHO Guideline² also classify aciclovir as BCS Class III. Wu and Benet,⁷⁰ using the disposition characteristics of the API as estimate for its permeability, assigned aciclovir to Class III of their Biopharmaceutics Drug Disposition Classification System (BDDCS). For pH values 4.5 and above, the 800 mg tablet strength shows D/S ratio's outside the 250 mL limit. If 800 mg is taken as highest tablet strength, aciclovir would be classified in BCS Class IV.

Surrogate Techniques for *In Vivo* Bioequivalence Testing

The low permeability of aciclovir is the limiting step in its absorption process. Bioinequivalence caused by differences in GI permeability between test and comparator, caused by an excipient effect, can only be circumvented by formulating the test product only with excipients known not to affect GI permeability. Bioinequivalence caused by differences in *in vivo* disintegration and/or *in vivo* dissolution between test and comparator, being a potential cause of bioinequivalence in particular for 800 mg tablet strengths, can be excluded by requiring the comparator and the test product to be both *very rapidly dissolving*, that is, dissolve 85% in 15 min or less, using a basket apparatus at 100 rpm or paddle apparatus at 50 rpm, in a volume of 900 mL or less, in the three BCS-media.^{2,71-73}

Risks of Excipient and/or Manufacturing to Cause Bioinequivalence

One report was identified of an excipient interaction, being an *in vitro* study only, using Caco-2, with sodium laurylsulfate, and the effect was limited.⁶⁴ For the excipients shown in Table 2, it can be supposed that they show no influence on the absorption of aciclovir when present in usual amounts; note that Table 2 does not include

sodium laurylsulfate. From a more general perspective, aciclovir seems not to be a critical API with respect to a risk for bioinequivalence: not one single example of bioinequivalence was identified, whereas eight *in vivo* BE studies were identified demonstrating *in vivo* BE of different formulations. Furthermore, 87 drug products (with MAs) were identified, for which it can be assumed that an *in vivo* BE study was successfully passed, which contain a wide variety of compositions with respect to excipients.

Patient's Risks Associated with Bioinequivalence

Aciclovir has a broad therapeutic index. Oral administration of aciclovir is usually well tolerated, and oral overdosing does not provoke serious adverse effects. Oral aciclovir has no life-threatening indication, and its therapeutic range seems wide enough to open the possibility for a biowaiver.

CONCLUSION

Aciclovir cannot unequivocally be classified to the BCS because different countries have different highest tablet strengths on their markets, which would lead to different BCS classifications in different countries. But the BCS classification of an API is not a purpose in itself, the relevant question being: is a biowaiver scientifically justified and if justified, which restrictions have to be formulated?

Up to now, the FDA³ and the EMEA⁴ do not accept biowaivers for BCS Class III and BCS Class IV APIs, so acyclovir would obviously be excluded from consideration for a biowaiver in these jurisdictions at the present time. However, the recently revised WHO guidance² extended the possibility of a biowaiver approval to BCS Class III APIs under certain conditions.

The risk of an acyclovir drug product being bioinequivalent appears to be very low, provided it contains only excipients present in IR aciclovir solid oral drug products approved in ICH or associated countries, for instance those presented in Table 2 of this article, and meets the biowaiver dissolution criteria. Also, the patient risks associated with a bioinequivalence inadvertently not detected by application of *in vitro* BE test can be deemed acceptable.

The preponderance of evidence indicates that a biowaiver for IR aciclovir solid oral drug products with strengths up to 800 mg is justified, if: (a) the test product contains only excipients present in aciclovir solid oral drug products approved in ICH or associated countries, for instance as presented in Table 2 of this article, and (b) the comparator and the test product both are *very rapidly dissolving*, that is, dissolve 85% in 15 min or less, using a basket apparatus at 100 rpm or paddle apparatus at 50 rpm, in a volume of 900 mL or less, in pH 1.2, pH 4.5, and pH 6.8 buffers.

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