Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Diclofenac Sodium and Diclofenac Potassium

B. CHUASUWAN,[1,2] V. BINJESOH,[1,3] J.E. POLLI,[1] H. ZHANG,[4] G.L. AMIDON,[5] H.E. JUNGINGER,[6] K.K. MIDHA,[7] V.P. SHAH,[9] S. STAVCHANSKY,[9] J.B. DRESSMAN,[10] D.M. BARENDS[11]

[1]Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, Maryland

[2]Research and Development Institute, The Government Pharmaceutical Organization, Bangkok, Thailand

[3]Faculty of Pharmacy, Rangsit University, Pathumtani, Thailand

[4]AstraZeneca Pharmaceuticals LP, Wilmington, Delaware

[5]College of Pharmacy, University of Michigan, Ann Arbor, Michigan

[6]Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand

[7]University of Saskatchewan, Saskatoon, Saskatchewan, Canada

[8]International Pharmaceutical Federation FIP, The Hague, The Netherlands

[9]Pharmaceutical Division, College of Pharmacy, University of Texas at Austin, Austin, Texas

[10]Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt, Germany

[11]RIVM—National Institute for Public Health and the Environment, Bilthoven, The Netherlands

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ABSTRACT: Literature data are reviewed regarding the scientific advisability of allowing a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing either diclofenac potassium and diclofenac sodium. Within the biopharmaceutics classification system (BCS), diclofenac potassium and diclofenac sodium are each BCS class II active pharmaceutical ingredients (APIs). However, a biowaiver can be recommended for IR drug products of each salt form, due to their therapeutic use, therapeutic index, pharmacokinetic properties, potential for excipient interactions, and performance in reported BE/bioavailability (BA) studies, provided: (a) test and comparator contain the same diclofenac salt; (b) the dosage form of the test and comparator is identical; (c) the test product contains only excipients present in diclofenac drug products approved in ICH or associated countries in the same dosage form, for instance as presented in this paper; (d) test drug product and comparator dissolve 85% in 30 min or less in 900 mL buffer pH 6.8, using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm; and (e) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1206–1219, 2009

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Correspondence to: D.M. Barends (Telephone: 31-30-2744209; Fax: 31-30-2744462; E-mail: dirk.barends@rivm.nl)

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INTRODUCTION

A biowaiver monograph of diclofenac is presented based on literature data and new experimental data. Risks are evaluated in basing a BE assessment on *in vitro* study results (i.e., "biowaiving"), rather than *in vivo* study results, for the approval of new IR solid oral dosage forms containing diclofenac sodium and diclofenac potassium, for example, plain IR tablets, dispersable tablets and powders for oral solutions. This risk evaluation considers diclofenac sodium and diclofenac potassium biopharmaceutical and clinical properties, as they pertain to reformulated products and new multisource products. This evaluation concerns drug products containing diclofenac as the only API and does not concern combination drug products. This evaluation does not concern delayed release products or any other modified release formulations of diclofenac.

The purpose and scope of this series of monographs have been previously discussed.[1] Briefly, 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 making an incorrect biowaiver decision, as well as the resulting consequences of such a 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 for or to advise against a biowaiver is described in the recently published World Health Organization (WHO) Guideline.[2] These monographs do not intend to simply apply the WHO, FDA[3] and/or EMEA Guidance,[4] but aim to apply these guidances and further serve as a critical validation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),[5] acetazolamide,[6] aciclovir,[7] amitriptyline,[8] atenolol,[1] chloroquine,[9] cimetidine,[10] ethambutol,[11] ibuprofen,[12] isoniazid,[13] metoclopramide, prednisolone,[14] prednisone,[15] pyrazinamide,[16] propranolol,[1] ranitidine,[17] and verapamil.[1] They are also available on-line at www.fip.org/bcs. Although diclofenac is not on the present WHO List of Essential Medicines,[18] it was considered appropriate to include this widely used and important API in this series.

Literature Review

Published information was obtained from PubMed up to November 2007. Key words used were: diclofenac potassium, diclofenac sodium, NSAID, indication, therapeutic index, solubility, polymorphism, partition coefficient, pK_a, absorption, permeability, distribution, metabolism, excretion, excipients, bioequivalence and dissolution.

GENERAL CHARACTERISTICS

Name and Structure

The chemical name of diclofenac is 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid. Its structure is shown in Figure 1.

Therapeutic Indication, Side Effect and Therapeutic Index

Diclofenac is a well-known nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties, comparable or superior to other NSAIDs.[19] Diclofenac shows preferential inhibition of the cyclooxygenase-2

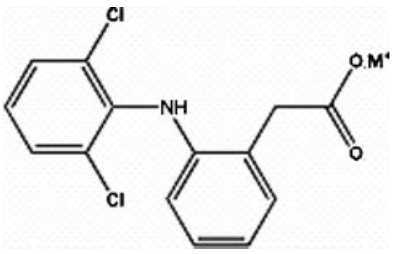

Figure 1. Structure of diclofenac, where M = K^+ or Na^+ for potassium or sodium salt, respectively.

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(COX-2) enzyme.[20] Diclofenac sodium is mainly indicated in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Diclofenac potassium is claimed to dissolve faster, and hence absorbed faster, than the sodium salt and is recommended for the treatments that need short onset of action, mainly for its analgesic properties. Diclofenac potassium is also indicated for the treatment of primary dysmenorrheal and mild to moderate pain.[21,22] As with other NSAIDs, diclofenac is known to increase the risk of gastrointestinal bleeding and cardiovascular side effects.[21,22] However, diclofenac has a relatively high therapeutic index in comparison to other NSAIDs.[23]

PHYSICOCHEMICAL PROPERTIES

Salts, Esters, Polymorphs, Hydrates

Diclofenac is usually formulated as the sodium or potassium salt, but other salts are also used, such as hydroxyethylpyrrolidine salt for oral preparations, and diethylammonium and diethylamine for topical preparation.[24] This monograph refers to drug products containing the sodium or potassium salt of diclofenac only. Most "plain" tablets contain the potassium salt, whereas most dispersable dosage forms contain diclofenac sodium, see Tables 1 and 2. In this monograph, the term diclofenac without indicating the salt form refers to the sodium and potassium salts. Trihydrates and tetrahydrates exist for both of diclofenac potassium and diclofenac sodium,[25,26] but in pharmacopoeial drug products only the anhydrate is used.[27,28]

Solubility

Solubility values for diclofenac sodium taken from the literature[29] are shown in Table 3 and experimentally determined solubilities of diclofenac potassium are show in Table 4, respectively, together with the dose to solubility ratios (D/S) for several tablet strengths.

Polymorphism

Reports of diclofenac potassium or diclofenac sodium polymorphs were not found in the literature.

Partition Coefficient

Partition coefficient in *n*-octanol/aqueous buffer ($\log D$) are reported to be 1.4 and 1.1 for pH 6.8 and 7.4, respectively.[30–32] The experimental $\log P$ (*n*-octanol/water) and $C\log P$ values of diclofenac are 4.40 and 4.71, respectively,[33,34] which are larger than the corresponding values of 1.72 and 1.35 for the highly permeable marker drug metoprolol.[35]

pK_a

The pK_a of diclofenac is about 3.80 at 25°C.[36,37]

Strengths of Marketed Drug Products

Dosage form strength is expressed in mg of salt present, not equivalent of the free acid. In the United States (US) and in the EU, Marketing Authorizations (MAs), that is, registrations, exist for IR solid oral dosage forms for 12.5, 25, and 50 mg diclofenac salt, see Tables 1 and 2. Higher strengths of these drugs have been marketed, but only as delayed release solid forms or combination oral products; however, such products are outside the scope of this monograph.

PHARMACOKINETIC PROPERTIES

The majority of pharmacokinetic data concerns diclofenac sodium. Literature reports indicate that diclofenac sodium and diclofenac potassium are similar in terms of extent of oral absorption, pattern of distribution, metabolism, and elimination.[38]

Absorption and Permeability

Diclofenac is 100% absorbed after oral administration, compared to intravenous administration, based on urine recovery studies.[21,22] Only about 60% of drug reaches the systemic circulation due to first pass metabolism.[39,40] In some fasting volunteers, measurable plasma levels are observed within 10 min of dosing with diclofenac potassium, although peak plasma levels are generally achieved after 0.33–2 h.[21] For enteric-coated diclofenac sodium tablets, drug is released once the tablet reaches the duodenum, with subsequent rapid absorption.[30,41,42] Absorption of diclofenac occurs throughout the intestinal tract.[43–46] Diclofenac shows linear pharmacokinetics. The absolute BA of diclofenac potassium after oral administration did not differ significantly when 1×12.5- and 2×12.5-mg were dose in a randomized, three-way, crossover study in

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Table 1. Excipients[a] Present in Diclofenac[b] IR Solid Oral Drug Products[c] With a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES), Sweden (SE), United Kingdom (UK) and the United States (US)[d], and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products With an MA in the USA[e]

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Benzoic acid	DK(1) NO(2) SE(3)	No data
Calcium hydrogen phosphate	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18) UK(19)	104–850
Calcium phosphate	DE(20) DK(21) FI(22) NL(23) NO(24) SE (25,26) US(27,28)	21–362
Carmellose sodium	DK(29) FI(30) NO(31) SE (32)	2.2–160
Cellulose	DE(20,33–36) DK(1,29,37) ES(38,39) FI(30,40) FR (41) NL(23,42,43) NO(2,31,44,45) SE (3,25,26,32,46,47) US(27,28,48,49)	4.6–1385[f]
Croscarmellose sodium	FI(40) US (48)	2–180
Crospovidone	DE(50,51)	4.4–792[f]
dimeticone	DE(33)	3.7
Glycerol	DK(29) FI(30,40) NO(31) SE (32)	0.14–198[f]
Glycerol dibehenate	DE(50,51)	5.7–14
Hypromellose	DE(34–36,50,51) DK(1,29,37) ES(38) FI(30,40) FR (41) NO(2,31) SE (3,32) US (28,48)	0.8–86
Lactose	DE(34–36) DK(1,29,37) ES(38,39) FI(30,40) FR (41) NL(42,43) NO(2,31,44,45) SE (3,32,46,47) US (28,48,49)	23–1020[f]
Lecithin	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18)	5–15
Macrogol	DE(20,33–36,50,51) DK(1,37) ES(38) FR (41) NL(23) NO(2) SE (3,25,26) US (27,28,48)	0.12–500[f]
Macrogol stearate	DK(1) NO(2) SE (3)	
Magnesium stearate	DE(4,20,33–36,50,51) DK(1,5–12,21,29,37) ES(38,39) FI(13,14,22,30,40) FR (41) NL(23,42,43) NO(2,15,16, 24,31,44,45) SE (3,17,18,25,26,32,46,47) UK(19) US (27,28,48,49)	0.15–401[f]
Maltodextrin	DE(35,36) DK(37) FR (41)	0.16–80
Mannitol	DE(50,51)	33–454
Octamethylcyclotetrasiloxane	DK(1) NO(2) SE (3)	No data
Polydextrose	US (48)	3.8–8.1
Polysorbate[g]	DK(37)	No data
Polysorbate 80	DE(35,36) FR (41)	2.2–418[f]
Poly(vinylalcohol)	DE(4) DK(5–8) FI(13,14) NO(15,16) SE (17,18)	0.7–20
Potassium hydrogen carbonate	DE(50,51)	12
Povidone	DE(4,20,33–36) DK(5–12,21,37) ES(38,39) FI(13,14,22) FR (41) NL(23,42,43) NO(15,16,24,44,45) SE(17,18,25,26,46,47) UK (19) US (27,28)	0.17–75
Silica	DE(4,20,34–36) DK(5–12,21,29,37) ES(38,39) FI(13, 14,22,30,40) FR (41) NL(23,42,43) NO(15,16,24,31,44,45) SE (17,18,25,26,32,46,47) UK (19) US (27,28,48)	0.65–99
Simethicone	DK(1) NO(2) SE (3)	0.0004–5.7
Sodium hydroxide	DE(33)	0.74–6.7
Sodium lauryl sulphate	DE(50,51) US (48)	0.65–50
Sodium starch glycolate	DE(4,20,33,35,36) DK(1,5–12,21,37) ES(38,39) FI(13,14,22) FR (41) NL(23,42,43) NO(2,15,16,24,44,45) SE (3,17,18,25,26,46,47) UK (19) US (27,28)	2–876[f]
Sorbic acid	DK(1) NO(2) SE (3)	0.94

(*Continued*)

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Table 1. (*Continued*)

Excipient	Drug Products Containing that Excipient With an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms With an MA in the USA (mg)
Starch	DE(4,20,33–36) DK(1,5–12,21,29,37) ES(38,39) FI(13,14,22,30,40) FR (41) NL(23,42,43) NO(2,15,16,24,31,44,45) SE (3,17,18,25,26,32,46,47) UK(19) US (27,28)	0.44–1135[f]
Starch, pregelatinized	US (49)	6.6–600
Sucrose	DE(20,33) NL(23) SE (25,26) US (27)	12–900
Talc	DE(4,20,33,34) DK(1,5–12) ES(38) FI(13,14) NL(23) NO(2,15,16) SE (3,17,18,25,26)	0.26–220[f]
Triacetin	US (48)	0.72–15
Xanthan gum	DE(4) DK(5–12) FI(13,14) NO(15,16) SE (17,18)	14

1. Eeze, filmovertrukne tabletter
2. Ezze 25 mg filmdrasjerte tabletter
3. Eeze 25/50 mg, filmdragerade tabletter
4. Diclac® Dolo 12.5 mg Filmtabletten (Mono)
5. Diclofenac Rapid "Actavis", filmovertrukne tabletter
6. Diclofenac Rapid "Copyfarm", filmovertrukne tabletter
7. Diclon Rapid, filmovertrukne tabletter
8. Diclopax, filmovertrukne tabletter
9. Fenaclo, filmovertrukne tabletter
10. Dictavis, filmovertrukne tabletter
11. Diclium, filmovertrukne tabletter
12. Fenacta, filmovertrukne tabletter
13. Diclofenac Rapid Actavis 25/50 mg tabletti, kalvopäällysteinen
14. Diclofenac Rapid Copyfarm 25/50 mg tabletti, kalvopäällysteinen
15. Diclofenackalium Actavis 25/50 mg tabletter, filmdrasjerte
16. Diclofenackalium Copyfarm 25/50 mg filmdrasjerte tabletter
17. Diklofenak T Actavis 25/50 mg filmdragerade tabletter
18. Diklofenak T Copyfarm 25 mg och 50 mg filmdragerade tabletter
19. Diclofenac potassium 12.5 mg tablets
20. Voltaren® K Migräne 50 mg überzogene Tabletten (Mono)
21. Voltaren Rapid, overtrukne tabletter
22. Voltaren Rapid 25/50 mg tabletti, päällystetty
23. Cataflam 25/50, omhulde tabletten 25/50 mg
24. CATAFLAM 50 mg drasjerte tabletter
25. Diklofenak T Sandoz 25/50 mg, tabletter
26. Voltaren T 25/50 mg, dragerade tabletter
27. Cataflam® tablet 50 mg, sugar-coated [Novartis Pharmaceuticals Corporation]
28. Diclofenac potassium tablets 50 mg, film-coated [TEVA Pharmaceuticals USA]
29. Diclofenac ratiopharm Rapid, filmovertrukne tabletter
30. Diclomex Rapid 25/50 mg tabletti, kalvopäällysteinen
31. DiclofenacKalium ratiopharm tabletter, filmdrasjert
32. Diclofenac T ratiopharm 25/50 mf filmdragerade tabletter
33. Diclofenac PB 50 mg Tabletten (Mono)[h]
34. Diclodoc® 50 Tabletten (Mono)[h]
35. Optalidon® Zahnschmerz mit Diclofenac Filmtabletten (Mono)
36. Voltaren® Dolo 12. mg Filmtabletten (Mono)
37. Voltaren Dolo, filmovertrukne tabletter
38. DICLOFENACO PENSA 50 mg comprimidos EFG[h]
39. Voltalgial 12.5 mg comprimidos

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