COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Prednisolone

M. VOGT,[1] H. DERENDORF,[2] J. KRÄMER,[3] H.E. JUNGINGER,[4] K.K. MIDHA,[5] V.P. SHAH,[6] S. STAVCHANSKY,[7] J.B. DRESSMAN,[1] D.M. BARENDS[8]

[1]Department of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

[2]College of Pharmacy, University of Florida, Gainesville, Florida

[3]Phast GmbH, Homburg/Saar, Germany

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

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

[6]International Pharmaceutical Federation FIP, Den Haag, The Netherlands

[7]Division of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, Texas

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

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing prednisolone are reviewed. Data on its solubility, oral absorption, and permeability are not totally conclusive, but strongly suggest a BCS Class 1 classification. Prednisolone's therapeutic indications and therapeutic index, pharmacokinetics, and the possibility of excipient interactions were also taken into consideration. Available evidence indicates that a biowaiver for IR solid oral dosage forms formulated with the excipients tabulated in this article would be unlikely to expose patients to undue risks.
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INTRODUCTION

A monograph based on literature data is presented on prednisolone with respect to its biopharmaceutical properties and the risk of waiving *in vivo* bioequivalence (BE) testing for the approval of new and/or reformulated immediate release (IR) solid oral dosage forms. The purpose and scope of these monographs has been discussed previously.[1] Briefly, the aim of these monographs is to evaluate all pertinent data available from literature sources for active pharmaceutical ingredients (APIs) on the WHO List of Essential Medicines,[2] to assess the appropriateness of such a biowaiver from the biopharmaceutical point of view and also from the perspective of public health. This systematic approach to

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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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recommend or advise against a biowaiver decision is referred to in the recently published WHO Guideline[3] stating that these monographs provide detailed information which should be taken into account whenever available in the biowaiver consideration. Monographs have already been published on acetaminophen (paracetamol),[4] amitriptyline,[5] atenolol,[1] chloroquine,[6] cimetidine,[7] ibuprofen,[8] propranolol,[1] ranitidine,[9] and verapamil.[1]

EXPERIMENTAL

Published information was obtained from PubMed, up to October 2005, and through the International Pharmaceutical Abstracts. Key words used were: prednisolone, prednisone, corticosteroids, indication, solubility, polymorphism, partition coefficient, permeability, absorption, distribution, metabolism, excretion, dissolution, and excipients.

GENERAL CHARACTERISTICS

Prednisolone (INN) is a synthetic steroid that is chemically defined as 11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione. Its structure is shown in Figure 1.

Therapeutic Indication, Dose, and Therapeutic Index

Prednisolone is a well-known corticosteroid that is used to treat a wide variety of acute and chronic disorders, including arthritis, asthma, allergic diseases, hepatitis, congenital adrenal hyperplasia, systemic lupus erythematosus and certain haematological, infectious, cardiac, dermal, neurological, metabolic, gastrointestinal (GI) diseases as well as malignant diseases and many inflammatory states.[10–14] Furthermore, prednisolone is used intravenously at very high doses for the treatment of severe shock.[14]

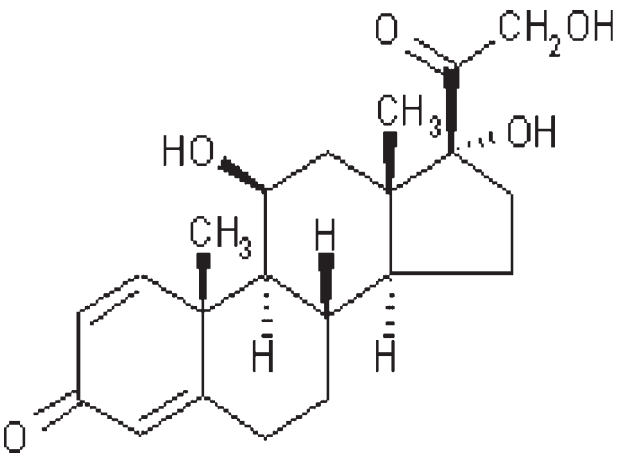

Figure 1. Structure of prednisolone $C_{21}H_{28}O_5$, Molecular weight: 360.4.

Prednisolone is used over a wide dose range. Low dose corticosteroid therapy is considered to include doses up to 10 mg prednisolone per day, being most commonly prescribed at approximately 5–7.5 mg/day. The dosage must be individualized and is highly variable depending on the nature and severity of the disease, and on patient response. There is no absolute maximum dosage, however, intensity and frequency of adverse events is observed to rise with increasing dose. Prednisolone is not considered to be a narrow therapeutic index drug and there is generally no need to monitor blood levels. However, for severe diseases that require very high doses of prednisolone, a monitoring of blood levels may be advisable.[14]

A special consideration that should be given in prednisolone therapy is to follow appropriate procedures for withdrawing chronically treated patients from high doses of the drug. The strategy to withdraw the patient from systemic corticosteroids depends on the period of treatment and the likelihood of the disease to relapse. In patients who have received systemic corticosteroids for more than 3 weeks at high doses, withdrawal should be gradual[14,15] in order to allow the hypothalamo-pituitary-adrenal (HPA) axis to recover. Abrupt withdrawal of systemic corticosteroid treatment which has continued for up to 3 weeks may be appropriate if the disease is unlikely to relapse[16,17] and is unlikely to lead to clinically relevant HPA-axis suppression.[18] In cases where a dose tapering schedule is appropriate, up to date recommendations can be found in the recent literature.[14] Low dose corticosteroid therapy can generally be terminated without dose tapering although a gradual withdrawal is often recommended.

PHYSICO-CHEMICAL PROPERTIES

Esters and Salts

Several esters of prednisolone are available. Apart from prednisolone itself, the USP 28 includes prednisolone acetate, prednisolone hemisuccinate, prednisolone sodium phosphate, prednisolone sodium succinate, and prednisolone

tebutate,[19] while the EP 5th edition monographs prednisolone acetate, prednisolone pivalate, and prednisolone sodium phosphate.[20] Ester compounds currently having a marketing authorization (MA) in Germany (DE) are prednisolone hydrogen succinate, prednisolone sodium phosphate, and prednisolone acetate.[12] This monograph pertains to prednisolone itself, but not to ester forms.

Polymorphism

Prednisolone exhibits polymorphism.[20] Two forms have been characterized.[21,22] Prednisolone also forms solvates with water and chloroform (pseudo-polymorphism).[19,22] USP 28 monographs both the anhydrous form and the sesquihydrate.[19] This monograph pertains both to prednisolone anhydrous and the sesquihydrate.

Solubility

Prednisolone is very slightly soluble in water (1 g dissolves in 1000–10000 mL).[20] An aqueous solubility ranging from 0.22 to 0.24 mg/mL has been reported (without indicating the temperature),[23,24] which is in accordance with a value of 243 μg/mL that was measured at 25°C.[25] Table 1 summarizes solubility data available in the literature, together with the corresponding dose:-solubility ratio. The WHO maximum dose strength is 5 mg.

Partition Coefficient

LogP values of 1.59 and 1.62 have been reported.[23,26,27] Calculated values obtained by different methods range from 1.38 to 1.49[27,28] and from 2.5 to 3.5.[29]

pKa

The chemical structure of prednisolone (see Fig. 1) does not provide any acid or basic elements, and hence is a neutral substance and no reference to a pK_a value was found in the literature.

Table 1. Solubility (mg/mL) of Prednisolone at 25°C[25] and Dose: Solubility Ratios (D/S) (mL) for Four Strengths Covering the Extremes of the Range

Medium	Solubility	D/S (1 mg)	D/S (5 mg)	D/S (10 mg)	D/S (50 mg)
Water	0.243 mg/mL	4.1 mL	21 mL	41 mL	206 mL

Five milligrams reflects the WHO maximum dose strength. The critical limit for D/S at 37°C is <250 mL.[3,72–74]

Dosage Form Strength

Strengths of IR solid oral dosage forms with a current MA in DE are 1, 2, 2.5, 5, 10, 20, and 50 mg, in Finland (FI) 5, 20, and 40 mg and in The Netherlands (NL) 5, 20, 30, and 50 mg, see Table 2.

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability (BA)

Following oral intake prednisolone is rapidly absorbed from the GI tract. The systemic availability is almost complete and reported to range from 75% to 98%,[11,14,30–39] with a concentration-time profile that is very similar to that when prednisone is taken orally.[40,41] Maximum serum concentrations occur within 1–2 h after administration of a single dose.[10,11,14,31,32,35,42–44] Food intake prolongs the time to peak concentration, but does not affect the extent of absorption.[45–47] No indication of existence of an absorption window was found in the literature.

Permeability

An apparent permeability coefficient of 2×10^{-5} cm/s was measured in Caco-2 cells.[28] Using artificial phospholipid membranes, a value of 0.2×10^{-6} cm/s was reported.[48]

Distribution

The volume of distribution of prednisolone was reported as 0.22–0.70 L/kg.[31,44,49] With increasing dose, the volume of distribution of prednisolone increases, due to a shift in a larger fraction of the body burden from the plasma compartment to other body tissues or to sites of greater metabolic activity.[44] The concentration-dependent binding of prednisolone to the plasma proteins (i.e., transcortin and albumin) results in the dose-dependent nonlinear pharmacokinetics observed for prednisolone.[11,50,51] Transcortin has high affinity and low capacity binding sites while albumin has low affinity and a high capacity for binding prednisolone. The fraction bound is not constant and decreases in a nonlinear fashion

Table 2. Excipients* Present in Prednisolon IR Solid Oral Drug Products with a Marketing Authorization (MA) in Germany (DE), Finland (FI), and The Netherlands (NL), 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)
Calcium stearate	FI(1)	0.7–43[a]
Castor oil hydrogenated	FI(1)	0.93–37.6[a]
Cellulose	DE(2–5) FI(1,6,7) NL(8)	4.6–1385[a]
Copovidone	FI(1)	86–500
Croscarmellose sodium	DE(3) FI(6,7)	2–180
Crospovidone	FI(1)	4.4–792[a]
Gelatin	DE(9)	1–756[a]
Hydroxypropylcellulose	DE(10)	1–132
Hypromellose	DE(2,3,11,12)	0.8–80
Lactose	DE(2–5,9–22) FI(1) NL(8,23–28)	23–1020[a]
Magnesium stearate	DE(2–5,9–22) FI(6,7) NL(8,23–28)	0.9–401[a]
Maize starch	DE(2–5,11,12) NL(28)	9.9–1135[a]
Mannitol	FI(6,7)	10–454
Potato starch	DE(9,13,14,16–18,20–22) NL(23–27)	2.1–80
Potato starch (pregelatinized)	NL(23–25,27)	
Povidone	FI(6,7) NL(8,26)	0.17–75
Silica	DE(2–5,10–14,16–18,20–22) FI(1,6,7) NL(23–27)	0.65–99
Sodium lauryl sulfate	DE(5)	0.65–50
Sodium starch glycolate	DE(2,9–22) NL(8,23–25,27,28)	2–876[a]
Starch, pregelatinized	NL(28)	6.6–600
Talc	DE(2,9,11,12) FI(1) NL(8,26)	0.1–220[a]

Sources of data: DE: www.rote-liste.de (April 4, 2006); FI: www.nam.fi (April 5,2006); NL: www.cbg-meb.nl. (April 3, 2006). USA: http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose (IIGQInte.txt version date 02-02-2006).

*Colorants, flavors, and ingredients present in printing ink only are not included.

[a]The upper range value reported is unusual high for IR solid oral dosage forms and the authors doubt its correctness.

1. PREDNISOLON 5 mg.
2. Decortin® H 1 mg.
3. Prednisolon 20 mg/–50 mg JENAPHARM®.
4. Prednisolon-ratiopharm® 5 mg Tabletten.
5. Prednisolon-ratiopharm® 50 mg Tabletten.
6. PREDNISOLON 40 mg.
7. PREDNISOLON 20 mg.
8. Prednisolon 30 mg, tabletten.
9. Prednisolon 1 mg/–5 mg JENAPHARM®.
10. Prednisolon 2 mg GALEN®.
11. Decortin® H 5 mg/–20 mg/–50 mg.
12. Duraprednisolon 5 mg.
13. Decortin® H 10 mg.
14. Dermosolon 5 mg/–10 mg/–20 mg/–50 mg.
15. Hefasolon®.
16. PrediHEXAL® 5 mg/–10 mg/–20 mg/–50 mg Tabletten.
17. Predni H Tablinen® 5 mg/–50 mg.
18. Predni H Tablinen® 20 mg.
19. Prednisolon 2,5/–5-Rotexmedica.
20. Prednisolon 5 mg/–20 mg/–50 mg GALEN®.
21. Prednisolon acis® 5 mg/–10 mg/–20 mg/–50 mg.
22. Prednisolon AL 5 mg/–10 mg/–20 mg/–50 mg Tabletten.
23. Prednisolon 20 PCH, tabletten 20 mg.
24. Prednisolon 30 mg PCH, tabletten.
25. Prednisolon 50 PCH, tabletten 50 mg.
26. Prednisolon CF 5 mg, tabletten.
27. Prednisolon 5 PCH, tabletten 5 mg.
28. Prednisolon ratiopharm 5 mg, tabletten.

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with increasing concentrations: at low concentrations protein binding appears to be quite high (80%–90%), but declines at higher prednisolone levels to 60%–70%.[33,44,49,50,52] For plasma concentrations of up to 400 ng/mL an approximate linear function of fraction bound can be assumed, which switches over to a constant (lower) relation above 600 ng/mL,[44] reflecting the saturable binding of prednisolone to transcortin. Binding of prednisolone to plasma protein is independent of the route of administration.[51]

Distribution and elimination of prednisolone have been described in terms of a two-compartment open model, with rapid distribution within the first half-hour followed by a slower terminal elimination phase.[11,36]

Prednisolone is able to penetrate the blood-brain barrier, reaching about 1/10 of the serum concentration in cerebrospinal fluid. Like all glucocorticosteroids, prednisolone crosses the placenta.[14,53] The use of prednisolone is usually compatible with breast feeding[54] since its concentrations in breast milk are minimal (<10% of serum level) and represents a negligible addition to the infants endogenous cortisol production.[55]

Metabolism and Excretion

Prednisolone is pharmacologically active and may be metabolized in a variety of tissues, including liver, lung, kidney, and skin.[14,56,57] Prednisolone is partially converted into prednisone, which is inactive. Both steroids undergo a reversible and dose-dependent metabolism. The interconversion equilibrium strongly favors the formation of prednisolone,[11,40] resulting in a ratio of prednisolone to prednisone plasma concentrations of 4:1 to 10:1.[44,58] The nonlinear interconversion varies with time and dose.[11,31,44,49,59–62] The serum half-life of prednisolone is known to be 2–4 h,[10,11,32,33,39,44,46] and may be influenced by time of day, age, gender, physical exercise, pregnancy, drugs, and several diseases.[14]

Prednisolone is cleared from the body primarily by hepatic metabolism by hydroxylation and reduction forming metabolites which conjugate with glucuronic acid and sulfate.[11,63] The most important unconjugated metabolite is 6β-hydroxyprednisolone. Eleven metabolites of prednisolone and prednisone have been identified.[51] Certain metabolites were found in both the unconjugated and the conjugated forms in the urine, the percentage in the unconjugated being about twice as large as that in the conjugated. An appreciable proportion, 11%–24% of a given dose of prednisolone, can be recovered in urine unchanged. Approximately 2%–5% is excreted in the urine as prednisone.[44]

The clearance of prednisolone is dose-dependent,[31–33,44,59,60,64] due to the concentration-dependent protein binding, that is, at high doses the increased free fraction of prednisolone is reflected in a greater plasma clearance and apparent volume of distribution. The total body clearance of prednisolone has been reported to be 111 mL/min/1.73 m^2 for a 5 mg dose and 194 mL/min/1.73 m^2 for a 40 mg dose of prednisolone.[35,44]

Renal elimination comprises 40% of total elimination.[65] The mean elimination half-life increases with the dose and ranges from 2.1 to 3.5 h.[11,33,66] The half-life in children is shorter than that recorded in most adult studies.[11] Children show no evidence of an abnormal prednisolone metabolism. Women appear to have a slightly higher clearance of prednisolone (around 18% higher)[67] and excrete significantly more 6β-hydroxyprednisolone than men[51]—in step with the finding that estrogens enhance the hydroxylation of cortisol.

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

A wide range of excipients has been used in several formulations of IR prednisolone tablet products approved for marketing in DE, where the market leader is Decortin® H. Table 2 shows the excipients used in IR prednisolone tablets with a MA in DE, FI, and NL. In view of these MAs, it is reasonable to expect that these formulations successfully passed an *in vivo* BE study. Indeed, a number of Summaries of Product Characteristics (SmPCs) with an MA in DE report results of successful *in vivo* BE studies.[68–70] Also, in view of the actual clinical use, it can be supposed that the excipients present in a large number of these drug products do not have a significant effect on the extent and rate of absorption of prednisolone, and hence no impact on its clinical use. One product from the German market contains sodium lauryl sulfate (Prednisolon-ratiopharm® 50). It is highly likely that the surfactant is included in order to ensure an appropriate dissolution rate of the drug. However, the SmPC of this 50 mg product containing sodium lauryl sulfate reports data showing *in vivo* BE to a reference product, at least with

respect to the AUC.[69] Numerous other 50 mg products do not contain any surfactant and are not inferior concerning the rate and extent of absorption. In an aqueous medium at 37.5°C, magnesium trisilicate seems to adsorb prednisolone and the presence of magnesium oxide leading to chemical degradation.[71] However, these excipients are not part of any formulation currently on the market in the above-mentioned countries and the clinical relevance of the adsorption has never been demonstrated. By contrast, aluminum hydroxide, calcium carbonate, and magnesium carbonate do not seem to adsorb prednisolone.

In Vivo Bioequivalence Studies

Several studies have demonstrated BE *in vivo* among specific marketed prednisolone products.[14] In a randomized crossover study in 13 healthy volunteers, prednisolone tablet formulations of 2, 5, and 20 mg were found to be bioequivalent *in vivo* to a reference if the same dosage was administered.[39] Two studies designed as four-treatment crossover evaluations in 12 adult male volunteers found seven different commercially available prednisolone tablets bioequivalent *in vivo*; these products demonstrated *in vitro* dissolution of at least 75 % in 30 min.[43]

Dissolution and *In Vitro*/*In Vivo* Correlation

The USP 28 specification for dissolution of prednisolone tablets is not less than 70% (Q) dissolved in 30 min in 900 mL water, using the paddle at 50 rpm.[19] Prednisolone became official in USP 15 (Second Supplement, April 1959), and the monograph was extended by the content uniformity requirement in USP 17. USP 18 included a dissolution test in which 60% of the labeled amount of prednisolone was required to dissolve in de-aerated water in not more than 20 min. *In vitro*/*in vivo* correlations were not found in the literature.

DISCUSSION

Solubility

Solubility criteria defined in present regulatory guidances[3,72–74] for classifying an API as "highly soluble" requires the highest dose strength to be soluble in 250 mL of water over the pH range of 1–7.5 at 37°C. The available data therefore do not provide all information necessary for BCS classification. Although solubility over this pH range can be assumed to be independent of pH (non-ionizable drug), literature results were determined at 25°C rather than 37°C. At 25°C, prednisolone meets already the dose:solubility ratio criterion of below 250 mL, that is, is "highly soluble."[3,72–74] It is reasonable to assume that prednisolone has an endothermic heat of solution and that the solubility at 37°C will be even higher.

Permeability

Numerous studies report averages of 80%–100% for the systemic availability of prednisolone following oral administration. Only very limited *in vitro* studies on the permeability of prednisolone could be located. One result, reporting a permeability of 0.2×10^{-6} cm/s, used artificial phospholipid membranes. Using the same system, for metoprolol a log permeability of about −5.2 was reported,[48] corresponding to 6.3×10^{-6} cm/s, suggesting the permeability of prednisolone to be slightly lower than the permeability of metoprolol, a substance often taken as reference for the criterion "highly permeable drug substance."[29] Also, the logP of prednisolone seems to be slightly below the logP of metoprolol.[29] On the other hand, in Caco-2 cells, a permeability of 2×10^{-5} cm/s was reported,[28] and using the same system, for verapamil an apparent permeability of 1.5×10^{-5} cm/s was reported. As verapamil is assumed to be highly permeable,[1] prednisolone can thus be assumed as "highly permeable" as well.

The FDA and also the EMEA Guidance[73] define "highly permeable" as having a fraction dose absorbed of not less than 90%. The recently adopted WHO Guidelines set a limit of not less than 85% of the fraction dose absorbed.[3,74]

Taking all available evidence into consideration, the data set is not fully conclusive, but suggests strongly prednisolone to be "highly permeable" or very close to "highly permeable," depending on the criterion set.

Prednisolone has nonlinear pharmacokinetics, which sometimes are seem as a caveat to a positive biowaiver decision.[73] Generally speaking, nonlinear pharmacokinetics has little relevance to equivalence testing, either *in vivo* or *in vitro*, since the test product will have the same dose as the reference product. Moreover, most reported *in vivo* studies include also higher doses, for example, 20 mg, indicating also that any nonlinear

pharmacokinetics is not relevant for the biowaiver decision over the full range of tablet strengths.

BCS Classification

Kasim et al.[29] classified prednisolone as BCS Class 1. However, their classification is based on correlations of partition coefficients with permeability and such correlations have only limited predictability. For instance, the correlation of logP with permeability resulted in 8 false negatives from 25 predictions and the correlation of ClogP® with permeability resulted in 8 false negatives and 1 false positive from 28 predictions. Moreover, their correlations are based on calculated partition coefficients, not on experimentally measured partition coefficients. Lindenberg et al.[75] also classified prednisolone as BCS Class 1. The recently adopted revised WHO Guideline classifies prednisolone as BCS Class 1.[3] Wu et al.,[76] using the disposition characteristics of the drug for BCS classification, assigned prednisolone to BCS Class 1 as well. Indeed, data on solubility, oral absorption, and permeability are not totally conclusive, but suggest strongly a BCS Class 1 classification. The lack of reported *in vitro*/*in vivo* correlations is consistent with that classification.[77]

Risks for Bioinequivalence and Surrogate Techniques for *In Vivo* BE Testing

What is the risk that bioinequivalent products could be approved if the biowaiver is applied? Prednisolone is "highly soluble" according to the present regulatory guidances.[3,72–74] So, the solubility is not critical and hence the risk of bioinequivalence caused by a difference in dissolution *in vivo* will be very small if the test formulation meets the criteria for *in vitro* dissolution profile similarity to the reference formulation, according to these guidances. In principal, bioinequivalence could also be caused by a difference in GI absorption, resulting from differences in composition between the test formulation and the reference formulation with respect to the excipients. However, prednisolone is on the borderline of "highly permeable" according to the present regulatory guidances[3,72–74] and so its GI absorption is not critical. Hence, the risk of bioinequivalence caused by a difference in permeability will be very small. Furthermore, a wide variety of excipients (Table 2) has been used to formulate prednisolone IR drug products, having a MA in a number of countries, suggesting that the fraction absorbed is not crucially influenced by these excipients.

Risk of Bioinequivalence to the Patient

Four possible situations could be envisaged resulting from a false biowaiver decision, that is, declaring a test formulation bioequivalent to the reference formulation, whereas this test formulation would be declared bioinequivalent when subjected to an *in vivo* BE study. The test formulation may give rise to a lower or to a higher AUC and/or to a lower or to a higher C_{max} than the reference product.

In the first instance, the test formulation has a lower AUC than that of the reference product and thus might be clinically less effective. This would have serious clinical consequence only in severe, life-threatening diseases that require acute treatment. But such situations require high doses, by parenteral administration, that is, such a therapeutic use is highly unlikely with oral prednisolone products, especially in the dose range listed by the WHO. A further safeguard is that, since prednisolone is a prescription-only drug, therapy will be under periodic review by the physician who can adjust the dose or substitute the product if necessary. The second situation in which a false biowaiver decision would be clinically relevant is when the drug formulation is superbioavailable, that is, the test formulation has a higher AUC than the reference. In this situation, the broad therapeutic index of prednisolone would protect the patient from very serious side effects, as no serious side effects have been observed with this API, even at exceptionally high (acute) doses and serum levels.

Lastly, bioinequivalence caused by a difference in C_{max} between the test formulation and the reference formulation would have few clinical implications in view of the therapeutic use of prednisolone IR tablets, being usually prescribed for patients with chronic diseases.

So, all considerations taken together, there is no reason to classify prednisolone as a "Narrow Therapeutic Range Drug," which would exclude it from biowaiving according to the FDA and EMEA regulation.[72,73] Also, the requirement of the recently adopted WHO Guideline is fulfilled, stating "only if the risk of an incorrect biowaiver decision and an evaluation of the consequences (of an incorrect, biowaiver-based equivalence

decision) in terms of public health and risks to individual patients is outweighed by the potential benefits accrued from the biowaiver approach may the biowaiver procedure be applied."[74]

CONCLUSION

Data on solubility, oral absorption, and permeability are not totally conclusive, but strongly suggest a BCS Class 1 classification for prednisolone. A false biowaiver decision is highly unlikely to be reached if the test product fulfills the criteria of dissolution profile similarity in three media according to the Guidances.[3,72–74] A false biowaiver decision is even more unlikely if the test product is formulated with the excipients shown in Table 2, in amounts usually present in IR solid oral dosage forms. Furthermore, even in the very unlikely situation that an incorrect biowaiver decision would be reached, this would not put the patient at undue risk. So, when the conditionsmentioned above are all fulfilled, a biowaiver can be recommended.

This conclusion is in line with the recommendation given by the WHO for biowaiving of prednisolone,[3] but is more explicit with respect to the excipients that are acceptable for a positive biowaiver decision.

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