

COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Prednisone

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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 prednisone are reviewed. Due to insufficient data prednisone cannot be definitively classified according to the current Biopharmaceutics Classification System (BCS) criteria as both the solubility and the permeability of prednisone are on the borderline of the present criteria of BCS Class I. Prednisone'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. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 96:1480–1489, 2007

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INTRODUCTION

A monograph based on literature data is presented on prednisone 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 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 Although prednisone is not on the present WHO List of Essential Medicines, it was considered appropriate to include this widely used and important API in this series.

EXPERIMENTAL

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

GENERAL CHARACTERISTICS

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

Therapeutic Indication, Dose, and Therapeutic Index

Prednisone 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, allograft rejection, systemic lupus erythematosus, and certain hematological, infectious, cardiac, dermal, neurological, metabolic, gastro-

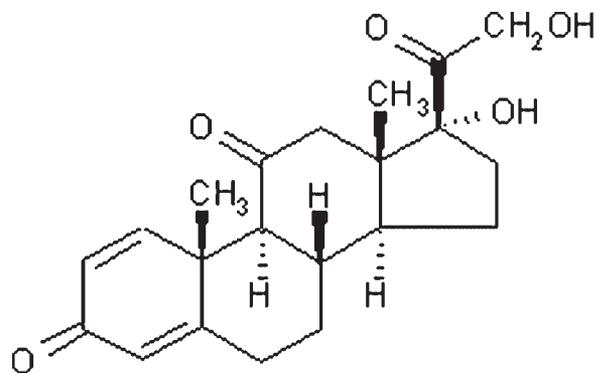


Figure 1. Structure of prednisone. C₂₁H₂₆O₅, molecular weight: 358.43.

intestinal (GI) as well as malignant diseases and many inflammatory states.^{10–14}

Prednisone is used over a wide dose range. Low-dose corticosteroid therapy is considered to include doses up to 10 mg prednisone 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. Prednisone 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 prednisone, a monitoring of blood levels may be advisable.¹⁴

A special consideration that should be given in prednisone 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 hypothalamic-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

Although commercially available as the acetate ester as well as prednisone itself, only prednisone is monographed in USP 29¹⁹ and EP 5th edition.²⁰

Polymorphism

Prednisone is known to form solvates; besides the anhydrous form, a monohydrate and a solvate with chloroform are described.^{19,21–23} Although EP 5th edition²⁰ indicates that prednisone exhibits polymorphism, no literature data describing this polymorphism could be found and a pseudo-polymorphism is thus assumed. USP 29 allows the anhydrous form and the monohydrate of prednisone.¹⁹ This monograph pertains both to prednisone anhydrous and the monohydrate, but not the ester form.

Solubility

Prednisone is practically insoluble in water (more than 10000 mL are needed to dissolve 1 g).²⁰ Aqueous solubility values of 0.12 mg/mL (without indicating the temperature),²⁴ and a value of 3.71×10^{-4} M at 25°C,²⁵ which corresponds to 0.133 mg/mL, have been reported. Table 1 summarizes solubility data available in the literature, together with the corresponding D/S ratio.

Partition Coefficient

Log *p* values of 1.46 and 1.47^{24,26} as well as 1.6²⁷ have been reported.

p*K*_a

Prednisone is a neutral substance as its chemical structure does not provide any acid or basic

elements. No reference to a p*K*_a value was found in the literature.

Dosage Form Strength

Strengths of IR solid oral dosage forms with a current marketing authorization (MA) in Germany (DE) are 1, 5, 20, and 50 mg, in Finland (FI) 5 and 40 mg, and in The Netherlands (NL) 5 mg only.

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability (BA)

Following oral intake prednisone is rapidly absorbed and metabolized to prednisolone, the biologically active form. Following the oral administration of prednisone, the systemic availability of prednisolone averages 80–100%.^{14,28–37} For very high oral doses of prednisone, that is, >50 mg, a slightly lower BA between 62% and 74% has been reported.^{38–41} Maximum serum concentrations occur within 1–3 h after administration of a single dose.^{10,11,14,35,42,43} Food intake prolongs the time to peak concentration, but does not affect the extent of absorption.^{11,37,44–46} No indications for the existence of an absorption window were found.

Permeability

Using artificial phospholipid membranes, a permeability coefficient of $0.3 \cdot 10^{-6}$ cm/s was reported.²⁷

Distribution

The volume of distribution was reported as 0.4–1 L/kg.⁴⁷ Prednisone binding to plasma proteins is rather low (<50%).³³ The concentration-dependent binding of the main metabolite prednisolone to the plasma proteins (i.e., transcortin and albumin) results in dose-dependent pharmacokinetics of prednisone. This nonlinear pharmacokinetics is due to saturable protein binding. Transcortin has high affinity and low capacity while albumin has low affinity and a high capacity. The fraction bound is not constant and decreases in a nonlinear fashion with increasing concentrations. The clearance and volume of distribution that are calculated from total drug concentrations increase with increasing dose, while systemic exposure shows a less than

Table 1. Solubility (mg/mL) of Prednisone at 25°C^{24,25} and Dose: Solubility Ratios (D/S) (mL) for Three Strengths Covering the Extremes of the Range

Medium Solubility	D/S (1 mg)	D/S (10 mg)	D/S (50 mg)
Water	0.133	7.5	376

D/S value not meeting the critical limit of <250 mL^{3,61–63} is shown in italic.

proportional increase with increasing dose. However, the unbound concentrations are not affected and systemic exposure for unbound concentrations is linearly related to the dose.^{42,48,49} Prednisone crosses the placenta^{14,50} but is generally considered safe with regard to breast-feeding.^{51,52}

Metabolism and Excretion

Prednisone is a prodrug and pharmacologically inactive. The 11-oxo group in prednisone is metabolically reduced, mainly in the liver, which results in the active moiety, prednisolone.^{10,31–33,35,42,53,54} Prednisone and prednisolone are metabolically interconvertible but equilibrium strongly favors the formation of prednisolone. This agent is considered to be by far the most biologically active form,^{11,31} and exhibits plasma concentrations four- to tenfold greater than those of the parent prednisone.^{36,42} The nonlinear interconversion varies with time and dose.^{11,29,42,48,49,55–57} The serum half-life of prednisone is known to be 2–4 h,^{10,11,35,43,58} and may be influenced by time of day, age, sex, physical exercise, pregnancy, drugs, and several diseases.¹⁴

Prednisone is almost completely metabolized. Only a small portion of the given dose is excreted unchanged in urine (2–5%). Further biotransformation results in the forming of several metabolites that are excreted free or as conjugates.

The mean oral plasma clearances of prednisone are reported to be dose-dependent and range from 572 mL/min/1.73 m² for a 5 mg dose to 2271 mL/min/1.73 m² for a 50 mg dose.⁴²

Pharmacokinetics of prednisone (and consequently prednisolone) are generally recognized as dose-dependent and nonlinear. Metabolism and elimination of prednisone and prednisolone, respectively, is not related to the route of administration, for example, intravenous prednisolone versus oral prednisone; both are dose-dependent and eventually result in similar profiles of both components. BA of prednisone is almost complete, with a concentration-time profile that is very similar to that when prednisolone is taken orally,^{31,32} suggesting that the extent of absorption of the two steroids are very similar and the interconversion of prednisone into prednisolone is not a limiting factor, even in patients with severely impaired liver function,^{32,33} although historically some clinicians prefer prednisolone over prednisone in patients with liver disease.

Prednisone and prednisolone are considered to be fully therapeutically equivalent. By administration of prednisone instead of prednisolone, high local concentrations of the biologically active species in the GI tract can be avoided. However, it has never been shown that this theoretical advantage of prednisone is relevant in clinical practice.

DOSAGE FORM PERFORMANCE

Excipients and/or Manufacturing Variations

A wide range of excipients have been used in several formulations of IR prednisone tablet products approved for marketing in DE, of which the market leader is Decortin[®]. Table 2 shows the excipients used in IR prednisone tablets with a MA in DE, FI, and NL. It is believed that none of these typically used excipients would be expected to exert a significant effect on the extent and rate of absorption of prednisone, thereby impacting its clinical use. Two published studies have confirmed BE among specific marketed prednisone products.^{10,14} In one study, the *in vivo* BE of five drug products (20 mg) was compared, as well as their *in vitro* dissolution, using the USP test, on the same lots. The data showed no statistical differences in any of the BE parameters and in *in vitro* dissolution. However, bioinequivalence among prednisone tablets has also been reported. Three commercial prednisone tablets (5 mg), of which one had a history of clinical failure, were compared in a three-way crossover *in vivo* BE study using a dose of 10 mg, and also compared using the *in vitro* dissolution test USP 18, utilizing the basket at 100 rpm and water as dissolution medium. In this study⁵⁹ carried out in 1974, plasma samples were assayed for prednisolone by a radioimmunoassay method. The results were not reported as bioequivalent/bioinequivalent, for which at that time no regulatory criteria existed, but rather indicated significant differences in the rate of appearance of prednisolone in plasma. The brand with the highest C_{max} also showed the fastest *in vitro* dissolution, whereas the two slower dissolving brands also showed lower C_{max} values. The same research group tested another eight commercial prednisone tablet brands.⁴³ *In vitro* testing was again carried out using USP 18 methodology; the eight brands (5 mg) were also compared for *in vivo* release profiles in two crossover *in vivo* studies using a dose of 10 mg. The results of both *in vivo*

Table 2. Excipients Present in Prednisone 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 Those Excipients Present Pro Dosage Unit in Solid Oral Drug Products with a MA in 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 USA (mg)
Carmellose sodium	NL ^b	2.2–160
Cellulose	DE ^{c,d,e,f,g}	4.6–1385 ^a
Croscarmellose sodium	DE ^{d,f}	2–180
Gelatin	FI ^h , NL ^{i,j}	1–756 ^a
Hydroxypropylcellulose	NL ^k	1–132
Hypromellose	DE ^l	0.8–80
Lactose	DE ^{c,d,e,f,g,l} , FI ^h , NL ^{b,i,j,k}	35–1020 ^a
Magnesium stearate	DE ^{c,d,e,f,g,l} , FI ^h , NL ^{b,i,j,k}	0.9–401 ^a
Maize starch	DE ^{f,l} , FI ^h , NL ^{i,j,k}	9.9–1135 ^a
Potato starch	FI ^h , NL ^b	2.1–80
Silica	DE ^{c,d,e,f,g,l} , NL ^{j,k}	0.65–99
Sodium starch glycolate	DE ^{c,e,g,l}	2–876 ^a
Starch, pregelatinized	NL ^b	6.6–600
Talc	DE ^l , FI ^h , NL ^{i,j}	0.1–220 ^a

Sources of data: DE: www.rote-liste.de (assessed 22/06/2005); FI: www.nam.fi (assessed 22/06/2005); NL: www.cbg-meb.nl (assessed 22/06/2005). USA: <http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose> (version date 06/05/2005).

*Colorants are not included.

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

^bPrednison 5 PCH, tabletten 5 mg.

^cPrednison 5 mg/20 mg/50 mg GALEN[®] tabletten.

^dPrednison acis[®] 5 mg/20 mg/50 mg tabletten.

^ePrednison HEXAL[®] 5 mg/20 mg/50 mg tabletten.

^fPrednison-ratiopharm[®] 5 mg tabletten.

^gPredni Tablinen[®] 5 mg tabletten.

^hPrednison[®] 5 mg/40 mg tabletti Orion-yhtymä Oyj.

ⁱPrednison 5 mg, tabletten Katwijk Farma.

^jPrednison CF 5 mg, tabletten.

^kPrednison Gf 5 mg, tabletten.

^lDecortin[®] 1 mg/5 mg/5 mg Rheuma/20 mg/50 mg tabletten.

and *in vitro* studies indicated that differences existed among the products in their rate, but not in their extent of absorption. The results of the two studies were combined and used to show that there was level C IVIVC, for instance between the percentage dissolved and the plasma concentration at the early time points 0.5 h and 1 h.⁶⁰

Dissolution and IVIVC

The USP 29 specification for dissolution of prednisone tablets is not less than 80% (Q) dissolved in 30 min in 500 mL water for tablets containing up to 10 mg of prednisone, and in 900 mL water for higher strengths, using the paddle at 50 rpm.¹⁹ IVIVCs were reported between pharmacokinetic measures for rate of absorption and the *in vitro* dissolution using the

basket at 100 rpm and water as dissolution medium.⁶⁰

DISCUSSION

Solubility

Solubility criteria defined in present regulatory guidances^{3,61–63} for classifying an API as “highly soluble” require 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 Biopharmaceutics Classification System (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, prednisone fails to meet the dose: solubility ratio

criterion of below 250 mL^{3,61–63} but only at the highest strength (50 mg). It is reasonable to assume that prednisone has an endothermic heat of solution and its solubility at 37°C will be higher, expecting the 50 mg strength also to meet the criterion of “highly soluble.”

Permeability

Numerous studies report essentially complete systemic availability of the biologically active drug, prednisolone, following oral administration of prednisone. Very limited *in vitro* studies on the permeability of prednisone could be located. The result, reporting 0.3×10^{-6} cm/s, used artificial phospholipid membranes. Using the same system, for metoprolol a log permeability of about -5.2 was reported,²⁷ corresponding to 6.3×10^{-6} cm/s, suggesting the permeability of prednisone to be slightly lower than the permeability of metoprolol, a substance often taken as reference for the criterion “highly permeable drug substance”.⁶⁴ Also, the log *p* of prednisone seems to be slightly below the log *p* of metoprolol.⁶⁴ However, definitive data for the fraction of prednisone absorbed orally in humans are not available and hence its permeability cannot definitively be defined according to the current BCS criteria.^{3,61–63} However, it is questionable if that is very critical for a biowaiver decision, as the numerous clinical data strongly imply a permeability consistent with the high absorption and, furthermore, it has been recently recommended that APIs exhibiting a fraction dose absorbed between 40% and 90% could also be considered for biowaivers.⁶⁵ The FDA and also the EMEA Guidances^{61,62} 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.^{3,63}

A lower BA after oral administration of high doses is in line with the reported dose-dependent and nonlinear pharmacokinetics. Nonlinear pharmacokinetics sometimes are seen as a “caveat” to a positive biowaiver decision.⁶² However, generally speaking, nonlinear pharmacokinetics have little relevance to equivalence testing, either *in vivo* or *in vitro*, since the test product will have the same dose as the reference product. In addition, the high doses of prednisone for which a lower BA has been observed (>50 mg) exceed by far the maximum tablet strengths and hence have no relevance for the prednisone biowaiver decision.

Taking all available evidence into consideration, the dataset is not fully conclusive, but suggests strongly prednisone to be “highly permeable” or very close to “highly permeable,” depending on the criterion set.

Prednisone is a prodrug. The FDA Guidance⁶¹ states that when the prodrug-to-drug conversion is shown to occur predominantly after GI membrane permeation, the permeability of the prodrug should be measured. This is the case for prednisone, thus it is adequate to consider the permeability of prednisone for the biowaiver decision.

BCS Classification

The data on solubility, oral absorption, and permeability suggest prednisone to be BCS Class 1, but the reported level C IVIVC is not in line with the present theory of BCS, in which no IVIVC is expected to be found for BCS Class 1 APIs.⁶⁶ Taken all together, the data are not totally conclusive, but suggest prednisone to be BCS Class 1 or borderline BCS Class 1, also depending on the criteria set.

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

The BCS classification of an API is only one aspect to be considered in a biowaiver decision. To be assessed is also the risk that a bioequivalent drug product occurs and in particular if the surrogate techniques are sufficiently reliable.

There are some reports of bioequivalent drug products with respect to the rate of absorption, but not with respect to the extent of absorption. However, *in vitro* dissolution testing in water as a medium has been shown to be quite sensitive to formulation changes, as for products showing differences in rate of absorption an IVIVC level C was established. It is reasonable to expect that comparative dissolution testing in three media according to the Guidances^{3,61–63} could also identify formulations being bioequivalent with respect to rate of absorption.

In addition to the dissolution properties, absorption can also be affected by pharmaceutical excipients. However, it is highly unlikely that excipients would modulate the activation of prednisone as the conversion to prednisolone mainly takes place after the absorption from the GI tract. A wide variety of excipients (Tab. 2) has been used to formulate prednisone drug products and the

extensive and global experience with these drug products suggests that the fraction absorbed is not crucially influenced by these excipients.

Risk of Bioinequivalence to the Patient

Another aspect to be considered is the risks of an incorrect biowaiver decision in terms of the therapeutic index and the clinical indications of the drug.⁶³

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 prednisone products. The second situation in which a false biowaiver decision would be clinically relevant is when the drug formulation is super-bioavailable, that is, the test formulation has a higher AUC than the reference. In this situation, the broad therapeutic index of prednisone 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 prednisone IR tablets, being usually prescribed for patients with chronic diseases.

So, all considerations taken together, there is no reason to classify prednisone as a "Narrow Therapeutic Range Drug," which would exclude it from biowaiving according to the FDA and EMEA regulation.^{61,62} 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 the biowaiver procedure may be applied".⁶³

CONCLUSION

Data on solubility, oral absorption, and permeability are not totally conclusive, but prednisone tends to be BCS Class 1 or borderline BCS Class 1. Whatever the exact BCS classification may be, 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.^{3,61–63} 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 conditions mentioned above are all fulfilled, a biowaiver can be recommended.

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