# COMMENTARY

# Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Ketoprofen

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**ABSTRACT:** Literature and experimental 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 ketoprofen are reviewed. Ketoprofen's solubility and permeability, its therapeutic use and therapeutic index, pharmacokinetic properties, data related to the possibility of excipient interactions, and reported BE/bioavailability (BA)/dissolution data were taken into consideration. The available data suggest that according to the current Biopharmaceutics Classification System (BCS) and all current guidances, ketoprofen is a weak acid that would be assigned to BCS Class II. The extent of ketoprofen absorption seems not to depend on formulation or excipients, so the risk of bioinequivalence in terms of area under the curve is very low, but the rate of absorption (i.e., BE in terms of peak plasma concentration, $C_{max}$) can be altered by formulation. Current *in vitro* dissolution methods may not always reflect differences in terms of $C_{max}$ for BCS Class II weak acids; however, such differences in absorption rate are acceptable for ketoprofen with respect to patient risks. As ketoprofen products may be taken before or after meals, the rate of absorption cannot be considered crucial to drug action. Therefore, a biowaiver for IR ketoprofen solid oral dosage form is considered feasible, provided that (a) the test product contains only excipients present also in IR solid oral drug products containing ketoprofen, which are approved in International Conference on Harmonisation or associated countries, for instance, as presented in this paper; (b) both the test drug product and the comparator dissolve 85% in 30 min or less in pH 6.8 buffer; and (c) test product and comparator show dissolution profile similarity in pH 1.2, 4.5, and 6.8. When one or more of these conditions are not fulfilled, BE should be established *in vivo*. 

**Keywords:** ketoprofen; absorption; Biopharmaceutics Classification System (BCS); permeability; solubility; dissolution; regulatory science

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## INTRODUCTION

Ketoprofen is an ibuprofen-type nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. A biowaiver monograph based on literature and some additional experimental data with respect to its Biopharmaceutics Classification System (BCS) classification, biopharmaceutical properties, and the risks associated with waiving *in vivo* bioequivalence (BE) testing in the approval of new immediate-release (IR) solid oral dosage forms containing ketoprofen ("biowaiving"), including both reformulated products and new multisource drug products, is presented. This evaluation refers to drug products containing ketoprofen as the only active pharmaceutical ingredient (API) and not to combination products. The purpose and scope of this series of monographs have been previously discussed.[1] As stated in previous article, "These monographs do not intend to simply apply the World Health Organization (WHO),[2] United States Food and Drug Administration (US FDA),[3] and/or European Medicine Agency (EMA) Guidance,[4] but aim also as a critical evaluation of these and other countries' regulatory documents." Biowaiver monographs have already been published for several APIs, and are also available online at www.fip.org/bcs.[5]

## METHODS

Literature data were obtained from Web of Science, PubMed, Drugs.Com, and DrugBank databases up to May 2011. The keywords used for searching were ketoprofen, absorption, bioavailability, bioequivalence, log *P*, solubility, permeability, and dissolution. Information was also obtained from regulatory documents published by WHO,[2] US FDA,[3] and EMA.[4]

## GENERAL CHARACTERISTICS

International nonproprietary name: Ketoprofen.[6] International Union of Pure and Applied Chemistry name: (RS)-2-[3-(benzoyl)phenyl]propanoic acid.[7] Its structure is shown in Figure 1.

### Stereoisomers, Salts, and Polymorphs

Ketoprofen has one asymmetric carbon atom, giving rise to two enantiomers, both of which possess biological activity.[8,9] The majority of ketoprofen drug products contain the racemate.[10,11] Preparations containing a salt of the (S)-(+)-enantiomer, known as dexketoprofen, are also available,[10,11] claiming to reduce inflammation and pain,[12] whereas the (R)-(−)-enantiomer is used as a toothpaste additive to prevent periodontal disease.[13] The lysine salt and the sodium salt of ketoprofen are also known. These salts are used in dosage forms other than IR solid oral dosage forms such as suppositories and nonsystemic solutions.[10,11]

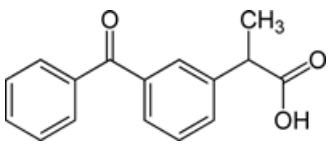


**Figure 1.** Ketoprofen structure formula.

Ketoprofen can exist as two polymorphs.[14] No data were found in the literature as to whether the polymorphic form of ketoprofen free acid affects dissolution performance or bioavailability (BA).

This monograph, which relates only to oral drug products, therefore considers only the free acid of ketoprofen in its racemate form.

### Therapeutic Indication, Dose, Therapeutic Index, and Toxicity

Ketoprofen is an ibuprofen-type NSAID with analgesic and antipyretic properties. It is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and to alleviate moderate pain. Ketoprofen has pharmacologic actions similar to those of other NSAIDs, and these are thought to be associated with the inhibition of prostaglandin synthesis. Its anti-inflammatory effects are believed to be due to the inhibition of both cyclooxygenase-1 and cyclooxygenase-2.[15]

The highest single dose recommended for ketoprofen in IR solid oral dosage forms is 100 mg and for extended-release dosage forms 200 mg. Depending on the indication, the dosage regimen varies from 12.5 mg every 4–6 h (usual adult dose for fever) to 100 mg orally as an initial dose, followed by 50 mg every 6 h (usual adult dose for acute gout).[16] The recommended maximum dose should not exceed 300 mg/day.[16] Ketoprofen is considered to be a wide therapeutic index drug according to the US FDA definition,[17] and there is no need to monitor blood levels. It is also not mentioned in the Health Canada Critical dose drugs list[18] or the Japanese list of narrow therapeutic index drugs.[19]

Ketoprofen's $LD_{50}$ is 62.4 mg/kg (rats, oral).[16] Overdose may cause adverse effects including breathing difficulty, coma, convulsions, drowsiness, high blood pressure, kidney failure, low blood pressure, nausea, sluggishness, stomach and intestinal bleeding, stomach pain, and vomiting.[15,16]

Generally, ketoprofen side effects are similar to other NSAIDs.[20] The most common side effects are rash, ringing in the ears, headache, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, heartburn, retention of fluid, and shortness of breath. Serious side effects are rare and mostly result from gastrointestinal (GI) damage. In fact, ketoprofen is one of the most ulcerogenic of the NSAIDs and its risk factor for serious GI complications against

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