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Bioequivalence of diclofenac sodium 2% and 1.5% topical solutions relative to oral diclofenac sodium in healthy volunteers

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Abstract

Background: Topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) are generally considered to be safer alternatives to oral NSAIDs due to lower systemic absorption. We conducted randomized, crossover studies that compared the pharmacokinetics (PK), bioequivalence and safety of topical diclofenac sodium 2% twice daily (BID), diclofenac sodium 1.5% four times daily (QID) and oral diclofenac sodium in healthy subjects.

Methods: The results of three bioequivalence studies are reviewed. Healthy adult subjects (n = 76) applied topical diclofenac sodium 2% solution (40.4 mg/2 mL) BID; or 1.5% solution (19.3 mg/40 drops) QID to each knee for 7.5 consecutive days separated by a washout period. Subjects (n = 22) in one study also received oral diclofenac sodium 75 mg BID for 7.5 days. Plasma diclofenac concentrations were determined from serial blood samples collected on Days 1 and 8 (steady state), and diclofenac PK parameters were estimated by noncompartmental methods.

Results: The studies demonstrated comparable bioequivalence between the 2% and 1.5% topical solutions as well as lower systemic exposure compared to oral dosing (approximately 93% less). Daily systemic exposure was comparable between the two formulations with only a 12% difference in the AUCss(0-24) (p = 0.140). Furthermore, both topical solutions demonstrated delayed elimination with a t(1/2) of 4- to 6-fold longer, as compared to oral diclofenac. The 2% solution provided more consistent dosing relative to the 1.5% solution when comparing AUCss(0-24) and Cmaxss across studies. Mild application site reactions were the most common treatment-emergent adverse event reported with topical diclofenac.

Conclusions: The steady-state PK profile of topical diclofenac 2% solution administered BID is similar to that of the 1.5% solution administered QID. Systemic exposure to diclofenac is substantially lower after topical application as compared to oral administration. (Study 2 was registered with ClinicalTrials.gov; NCT01202799; https://clinicaltrials.gov/ct2/results?term=01202799&Search=Search).

Keywords: Absorption; diclofenac; oral administration; pharmacokinetics; systemic exposure; topical application.

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