Pharmacokinetic Properties and Tolerability of Low-dose SoluMatrix Diclofenac

Paul J. Desjardins, DMD, PhD[1]; Kemi Olugemo, MD[2]; Daniel Solorio, MS[3]; and Clarence L. Young, MD[3]

[1]Desjardins Associates, LLC, Maplewood, New Jersey; [2]Parexel International Corporation, Baltimore, Maryland; and [3]Iroko Pharmaceuticals, LLC, Philadelphia, Pennsylvania

ABSTRACT

Purpose: This study compared the pharmacokinetic properties and safety profile of low-dose (18- and 35-mg) diclofenac capsules manufactured using SoluMatrix Fine Particle Technology (Trademark of iCeutica Inc. (Philadelphia, Pennsylvania), and the technology is licensed to Iroko Pharmaceuticals, LLC (Philadelphia, Pennsylvania) for exclusive use in NSAIDs), which produces submicron-sized drug particles with enhanced dissolution properties, to those of diclofenac potassium immediate-release (IR) 50-mg tablets.

Methods: This Phase 1, single-center, randomized, open-label, single-dose crossover study was conducted in 40 healthy volunteers. Subjects received, in randomized order, SoluMatrix diclofenac 18- or 35-mg capsules in the fasting condition, SoluMatrix diclofenac 35-mg capsules under fed conditions, and diclofenac potassium IR 50-mg tablets under fasting and fed conditions. Pharmacokinetic parameters (T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) were calculated from the concentrations of diclofenac in the plasma. Absorption, food effect, and dose proportionality were determined using a mixed-model ANOVA for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Tolerability was assessed by recording adverse events, physical examination findings, vital sign measurements: clinical laboratory test results.

Findings: Overall, 35 healthy volunteers aged 18 to 52 years completed the study. The mean age of the subjects was 33.4 years, and approximately half were men (47.5%). Median T_{max} values were similar between the low-dose SoluMatrix diclofenac 35-mg capsules and the diclofenac potassium IR 50-mg tablets (both, ~1.0 hour). The mean maximum plasma concentration (C_{max}) after the administration of low-dose SoluMatrix diclofenac 35-mg capsules was 26% lower than that with diclofenac potassium IR 50-mg tablets under fasting conditions (868.72 vs 1194.21 ng/mL). The administration of low-dose SoluMatrix diclofenac 35-mg capsules was associated with a 23% lower overall systemic exposure compared with that of diclofenac potassium IR 50-mg tablets under fasting conditions. Food decreased the rate but not the overall extent of absorption of SoluMatrix diclofenac. No serious AEs and no clinically significant abnormalities in physical examination findings, including vital sign measurements, or clinical laboratory test results, were noted during this study.

Implications: The pharmacokinetic properties of low-dose SoluMatrix diclofenac capsules in the healthy volunteers in this study suggest rapid diclofenac absorption as measured by T_{max}. Low-dose SoluMatrix diclofenac capsules represent a potential option for the management of acute and osteoarthritis-related pain. (*Clin Ther.* 2015;37:448–461)

Key words: diclofenac, pain, pharmacokinetics, SoluMatrix, submicron.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a well-established analgesic class indicated for the treatment of acute and chronic pain.[1] Systematic reviews have described dose-dependent adverse events (AEs) associated with NSAID use, most notably AEs involving the cardiovascular, renal, and gastrointestinal systems.[2–4] The US Food and Drug Administration (FDA) has required standard labeling that advises physicians to prescribe NSAIDs for their patients "at

Accepted for publication October 22, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.10.018
0149-2918/$ - see front matter

the lowest effective dose for the shortest duration, consistent with individual patient treatment goals."[5]

Although minimizing of NSAID dosage could potentially address tolerability concerns regarding this drug class, reducing active drug concentrations could limit the efficacy of these agents. A portfolio of oral NSAID drug products is being developed to provide low-dose treatment options for patients who require these agents. Low-dose SoluMatrix* diclofenac capsules† are a drug product containing submicron particles of diclofenac. This product was designed to provide effective analgesia with lower systemic exposure compared with that of other diclofenac-containing drug products.

Diclofenac is the most commonly prescribed NSAID worldwide and has been available in the United States since 1988.[6] Diclofenac inhibits the activity of cyclooxygenase (COX)-1, which has been associated with the gastrointestinal AEs associated with NSAIDs, and COX-2, the inhibition of which has been associated with NSAID therapeutic efficacy, but is associated with an increased risk of cardiovascular AEs.[7–9] Diclofenac has been reported to achieve analgesia at concentrations associated with clinically relevant inhibition of the COX-2 enzyme (IC_{80}; the drug concentration that produces 80% inhibition), with a lesser degree of COX-1 inhibition.[8] However, diclofenac products are often dosed supratherapeutically. For example, the commonly used diclofenac dosage of 50 mg three times daily (TID) achieves $>90\%$ inhibition of COX-2 over 8 hours after dosing, with only partial inhibition of COX-1 (49.5%).[10] Consequently, lowering the dose would continue to provide analgesia with the potential of a reduced risk for AEs. SoluMatrix diclofenac capsules (35 mg) are equivalent to a 20% lower diclofenac dose compared with diclofenac potassium immediate-release (IR) 50 mg[11] and have reported analgesia in clinical trials in patients experiencing acute pain after bunionectomy[12] and pain associated with osteoarthritis.[13] In addition, SoluMatrix diclofenac capsules were recently approved by the FDA for the management of mild to moderate acute pain and osteoarthritis-related pain.[14]

SoluMatrix diclofenac capsules consist of submicron drug particles that are 200 to 800 nm in diameter, which is ~20 times smaller than the starting active pharmaceutical ingredient, diclofenac free acid.[15] The reduced particle size leads to faster diclofenac dissolution in vitro, with the goal of improving absorption in vivo (data on file, Iroko Pharmaceuticals, LLC, [2013]). A possible advantage of the finely milled diclofenac acid drug product compared with conventional products containing the diclofenac potassium salt is that the salt form becomes protonated to form diclofenac acid when dissolved in an acidic aqueous medium such as the stomach.[16] This protonation results in an uncontrolled precipitated solid formation with a particle size distribution that may vary widely depending on stomach pH and stomach contents. By selecting the free acid form for the SoluMatrix formulation and milling it to a uniform particle size and distribution, the dissolution and absorption of the drug substance are better controlled, allowing for more consistent and robust product performance. Thus, SoluMatrix diclofenac capsules, which contain diclofenac free acid, are not interchangeable with other oral diclofenac drug products that contain diclofenac potassium or sodium salt, although there is some similarity in the chemical properties.[17,18]

A previous Phase 1 study evaluated the pharmacokinetic profile of low-dose SoluMatrix diclofenac capsules in healthy adults. The administration of SoluMatrix diclofenac 35-mg capsules was associated with a $>19\%$ lower overall systemic exposure compared with that of diclofenac potassium IR 50-mg tablets.[18] The mean (SD) T_{max} of SoluMatrix diclofenac 18 and 35 mg and diclofenac potassium IR 50-mg tablets was 0.62 [0.35], 0.59 [0.20], 0.80 [0.50] hours, respectively, suggesting rapid absorption.[11] The analgesic efficacy of this low-dose SoluMatrix diclofenac drug product was reported in a Phase 2 study in patients with acute pain after dental surgery.[19]

After the completion of the Phase 1 and 2 proof-of-concept studies, the manufacturing process for low-dose SoluMatrix diclofenac included a change from a wet to dry granulation process and additional minor formulation changes downstream of the milling process to enable large-scale production. Although the dissolution of the SoluMatrix diclofenac drug product, based on in vitro profiling, remained unchanged,

*SoluMatrix® is a registered trademark of iCeutica Pty Ltd (Philadelphia, Pennsylvania) and is licensed to Iroko Pharmaceuticals, LLC (Philadelphia, Pennsylvania).

†Trademark: Zorvolex®, Iroko Pharmaceuticals, LLC (Philadelphia, Pennsylvania).