Original Research

Cost-effectiveness of Low-dose Submicron Diclofenac Compared With Generic Diclofenac

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ABSTRACT

Purpose: NSAIDs are commonly prescribed for the treatment of pain and inflammation. Despite the effectiveness of NSAIDs, concerns exist regarding their tolerability. Worldwide health authorities, including the European Medicines Agency, Health Canada, and the US Food and Drug Administration, have advised that NSAIDs be prescribed at the lowest effective dosage and for the shortest duration. Effective lowering of NSAID dosage without compromising pain relief has been demonstrated in randomized, controlled trials of the recently approved NSAID lower-dose submicron diclofenac. Building on previously published work from an independently published systematic review and meta-analysis, a linear dose–toxicity relationship between diclofenac dose and serious gastrointestinal (GI) events was recently demonstrated, indicating that reductions in adverse events (AEs) may be seen even with modest dose reductions in many patients. The objective of the present study was to estimate the potential reduction in risk for NSAID dose–related AEs, corresponding savings in health care costs, and the incremental cost-effectiveness of submicron diclofenac compared with generic diclofenac in the United States.

Methods: Our decision-analytic cost-effectiveness model considered a subset of potential AEs that may be avoided by lowering NSAID dosage. To estimate the expected reductions in upper GI bleeding/perforation and major cardiovascular events with submicron diclofenac, our model used prediction equations estimated by meta-regressions using data from systematic literature reviews. Utilities, lifetime costs, and health outcomes associated with AEs were estimated using data from the literature. The face validity of the model structure and inputs was confirmed by clinical experts in the United States. Results were evaluated in 1-way and probabilistic sensitivity analyses.

Findings: The model predicted that submicron diclofenac versus generic diclofenac could reduce the occurrence of modeled GI events (by 18.0%), cardiovascular events (by 6.9%), and acute renal failure (by 18.8%), leading to a 9.8% reduction in costs of treating AEs. Submicron diclofenac was predicted to be cost-saving, with results relatively insensitive to parameter uncertainty.

Implications: Submicron diclofenac has the potential to provide clinical and economic value to patients using NSAIDs in the United States. Further investigation regarding the potential effects of submicron diclofenac on the risks for additional NSAID dose-related toxicities should be explored. (*Clin Ther*. 2016;38:2418–2429)

Key words: cardiovascular risk, cost-effectiveness, diclofenac, gastrointestinal risk, nonsteroidal anti-inflammatory drugs, NSAIDs.

INTRODUCTION

NSAIDs are a diverse group of medications used for treating pain and reducing inflammation.[1] Although NSAIDs are commonly prescribed and effective for acute and chronic pain, they often present tolerability

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concerns, including serious concerns related to gastrointestinal (GI), cardiovascular (CV), and renal toxicities. Several studies have demonstrated relationships between serious GI, CV, and renal adverse events (AEs) and NSAID dose.[2–4]

Patients who use NSAIDs have been reported to have a persistently increased risk for recurring CV events—63% greater than that in patients not treated with NSAIDs.[5] Conventional or nonselective NSAIDs have been associated with upper and lower GI AEs. Despite the known risks for NSAID-associated toxicities, an estimated 3.7% of US adults reported the use of an NSAID daily or nearly daily for 30 days or longer.[6] Efforts to mediate NSAID toxicity have included the development of NSAID/proton pump inhibitor fixed-dose combinations, cyclooxygenase (COX)-2 inhibitors, and topical NSAIDs.

Newer, selective NSAIDs have been developed in part to reduce the occurrence of GI events. However, an increased risk for CV events subsequently has been demonstrated with the use of at least some of these agents (eg, rofecoxib, a selective COX-2 inhibitor[7]). Rofecoxib in particular was taken off the market in late 2004 after a clinical study demonstrated that it was associated with increased rates of CV events in patients with colorectal polyps.[8] Afterward, efforts focused on understanding whether the risks observed with rofecoxib were present also with other selective COX-2 inhibitors and with nonselective NSAIDs.

Large-scale pharmacoepidemiologic studies[9–11] have corroborated findings from clinical studies of toxicity risks with NSAID use. Additional studies have examined the tolerability risks with the use of low versus high doses of NSAIDs and found increased risks in patients receiving high-dose NSAIDs compared with those in patients receiving low doses of these agents.[2–4,12–14] Based on pooled evidence, regulatory agencies around the world, including the US Food and Drug Administration,[15] the European Medicines Agency,[16] and Health Canada,[17] have recommended the use of NSAIDs at the lowest effective dosage and for the shortest duration.

To help physicians and patients to better comply with the recommendation of the use of the lowest effective doses of NSAIDs, a novel, nonselective NSAID was recently approved by the US Food and Drug Administration for use as a treatment for acute and chronic pain. This NSAID, a lower-dose submicron version of diclofenac, was created using SoluMatrix Fine Particle Technology (Iroko Pharmaceuticals, Philadelphia, PA), which generates diclofenac-containing submicron drug particles of 200 to 800 nm, ~20-fold smaller than the starting material. This particle-size reduction increased the total drug particle surface area, which resulted in a more rapid dissolution compared with that of the standard micronized drug product.[18]

Due to the low prevalence of serious GI and CV AEs, a randomized clinical trial to determine the difference in serious GI and CV AE rates between submicron diclofenac and generic diclofenac would likely require a patient sample size in the hundreds of thousands and a trial duration of many years. A comparison of AE rates between submicron and generic diclofenac using a Fisher exact test suggested that the following clinical trial sample sizes would be required for 80% power: 29,406 for perforation/bleed, 14,447 for ulcer, 168,074 for acute myocardial infarction (AMI), and 362,794 for stroke data on file, Iroko Pharmaceuticals, Philadelphia, Pennsylvania). Similarly, results from the comparison suggested that the following sample sizes would be required for 90% power: 39,061 for perforation/bleed, 19,255 for ulcer, 224,329 for AMI, and 484,330 for stroke. In the absence of data from randomized trials, Odom et al[19] conducted a meta-regression analysis using data obtained from observational studies included in recently published systematic literature reviews to quantify the relationship between diclofenac dosage and major GI and CV AEs, as recommended by the *Methods Guide for Comparative Effectiveness Studies* by the Agency for Health Care Research and Quality.[20] Other important AEs, such as hypertension and liver-related AEs, were not considered in the analysis primarily due to a lack of comparative data regarding the dose–toxicity relationship of these events.

Application of the published meta-regressions, which demonstrate the linear relationship between diclofenac dose and the risks for GI and CV AEs, provided a basis for the evaluation of various forthcoming reduced-dose pharmaceutical agents when the evidence from clinical studies of the tolerability advantages of a reduced-dosage product is limited. In our study, we used the diclofenac dose–toxicity relationship estimated by Odom et al[19] as key input for a decision-analytic model, which we developed to estimate the economic and health benefits of submicron diclofenac in reducing AEs, assuming pain relief similar to that with generic diclofenac, from a US payer's perspective.