Treating Mild to Moderate Acute Pain
With Oral Diclofenac Potassium
Liquid-Filled Capsules:
Rapid Absorption With
ProSorb Dispersion Technology

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Introduction

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the cyclo-oxygenase (COX) isoforms COX-1 and COX-2 and has anti-inflammatory, analgesic, and antipyretic activity. Today, diclofenac is available in various formulations (marketed under multiple trade names), and it is the most widely prescribed NSAID worldwide.

Results from previously published studies demonstrate the overall value of diclofenac as an anti-inflammatory in the treatment of mild to moderate pain. However, studies of the pharmacokinetic properties of the various formulations of diclofenac highlight inconsistencies in drug absorption across the various formulations. As a result, some formulations of diclofenac have been noted for reduced peak plasma concentrations ($C_{\text{max}}$) and/or delays in the time to achieve $C_{\text{max}}$ ($T_{\text{max}}$), as well as the presence of late and/or secondary plasma peaks. These characteristics of diclofenac may translate into delayed onset of analgesic effect and thus affect its efficacy as an analgesic for acute pain.1

The novel formulation of oral diclofenac potassium with a proprietary dispersion technology (Zipsor, Xanodyne; Newport, KY) has been developed to address these shortcomings. The product is designed to minimize the variability of diclofenac absorption and thus reduce delays in onset of action.2 This monograph reviews the history of diclofenac—its safety and efficacy as well as its mechanism of action—and summarizes the pharmacokinetic profile and efficacy of this novel formulation of diclofenac potassium.

Use of NSAIDs in Mild to Moderate Pain

The 3-step approach for the management of mild to moderate acute pain developed by the World Health Organization (WHO) recommends using an NSAID for first-line therapy; in fact, the WHO guideline supports NSAID use for second-line therapy (with a weak opioid such as codeine) and third-line therapy (with a strong opioid such as morphine or fentanyl) as well. According to the WHO, combination therapy that includes an NSAID can still minimize the need for adjuvant...
opioid therapy in patients with pain insufficiently controlled by NSAIDs.3

There are several reasons to consider NSAIDs as first-line therapy for mild to moderate pain. For example, unlike many analgesics functioning through activity in the central nervous system (CNS), particularly opioids, NSAIDs are not strongly associated with impairments in cognitive function or increased risk for accidents. NSAIDs also have low potential for addiction or other forms of abuse. As a class, NSAIDs also have proven effective in the management of acute pain. One study—a systematic review of the relative efficacy of I.V. NSAIDs and opioids in the acute treatment of renal colic—found that these agents were associated with a greater reduction in pain scores and lower likelihood of need for further analgesia than opioids.4

The importance of the specific choice of NSAID for pain management, however, remains complex. Although NSAIDs have the potential to vary in potency at specific doses as a result of variable metabolism and elimination, there are insufficient data to differentiate these agents by efficacy for specific indications. In multicenter trials comparing coxibs with nonselective NSAIDs, the primary end point in most cases was GI safety, although differences in control of pain were not observed.5,6 Large controlled trials for head-to-head comparisons of NSAIDs for the vast array of indications for acute pain control have never been performed. Several studies have suggested a numerical efficacy advantage of one NSAID over another, such as a controlled comparison of diclofenac and naproxen in osteoporosis of the hip,7 but statistical significance has been uncommon, possibly due to the small size of the trials.

It should be noted, however, that NSAIDs work differently in different patients. Patients who respond inadequately to one NSAID may respond to another, including agents with a similar molecular structure. This is an important rationale for routinely evaluating the adequacy of pain relief with every treatment and for including multiple NSAIDs in a formulary. Although more comparative studies would be useful for evaluating the relative efficacy of NSAIDs overall and for specific indications, the empirical experience of interindividual differences in response provides adequate evidence to suggest that these agents are not interchangeable.8,9

**Diclofenac: An Overview**

As a compound, the NSAID diclofenac is produced using 2 distinct salt bases: potassium and sodium; thus, its chemical formula is 2-[(2,6-dichlorophenyl)amino] benzene acetic acid monopotassium or monosodium salt, depending on the salt base being used. There are differences between the salt bases—for example, potassium-based diclofenac is soluble in water, whereas sodium-based diclofenac is sparingly soluble in water, and potassium salt is formulated to release diclofenac in the stomach, whereas sodium salt resists dissolution in the low pH of gastric fluid, allowing for a rapid release of diclofenac in the higher pH fluid of the duodenum.10 However, there is no evidence that diclofenac potassium differs from diclofenac sodium in its relative activities leading to an analgesic effect.

The first diclofenac formulations to receive FDA approval were sodium-based. Today, in the United States, sodium-based diclofenac formulations available include delayed-release (enteric-coated) and extended-release tablets as well as a topical gel (Voltaren, Novartis; Parsippany, NJ). The first diclofenac potassium formulation was approved by the FDA in 1993. Until recently, the only diclofenac potassium approved for use in the United States was 50-mg tablets. Diclofenac also is available in a transdermal patch system (Flector Patch, King Pharmaceuticals; Bridgewater, NJ), with an epolamine base. These formulations were approved in 2007 and 2008, respectively.

All NSAIDs inhibit both COX-1 and COX-2, which are upregulated by cytokines and growth factors to promote inflammation.11 Unlike most NSAIDs, however, diclofenac is a relatively equipotent inhibitor of both COX-1 and COX-2. It has a degree of COX-2 selectivity approaching that of the coxibs and far higher than that of other NSAIDs listed as nonselective. When measured in vitro with 50% inhibitory concentrations of comparator drugs, the ratio of COX-2 to COX-1 inhibition is 0.5 for ibuprofen, 0.7 for naproxen, 1.6 for acetaminophen, 1.9 for indomethacin, and 2.9 for diclofenac.12 Among other activities, COX is important for prostaglandin synthesis.13

**Mechanism of Action**

Diclofenac may have other important mechanisms of action. Experimental studies have demonstrated that diclofenac reduces the formation of products of the lipoxygenase pathway, which include 5-hydroxyeicosatetraenoic acid and leukotrienes.14 This activity may be an indirect effect on lipoxygenase inhibition through a reduction in the intracellular level of free arachidonic acid, which is not a uniform feature of COX inhibitors. Although the relative contribution of this activity to analgesic effect is unknown, a potential benefit is suggested by the fact that products of the lipoxygenase pathway, particularly leukotrienes, are upregulated in inflammatory conditions.15

**Selectivity and Safety**

The physiologic roles—such as maintaining mucosal integrity in the gastrointestinal (GI) tract—associated with each of these COX subtypes remain unclear. The most compelling example of the risks associated with an oversimplification of the functions of COX-1 and COX-2 has been the cardiovascular (CV) safety issues that resulted in the voluntary withdrawal of several coxibs, including rofecoxib and valdecoxib, from the clinical marketplace.16 Despite early signs of a potential for increased CV risk from coxibs,17 the appreciation of this risk was relatively slow because the activity of COX previously had not been linked to vascular or cardiac function. Although it is believed that some coxibs are associated with a greater CV
risk than other NSAIDs, all drugs in this class, including non-
coxibs, have carried a warning about the excess risk for CV
events since April 2005. The concern is considered most rele-
vant to patients with CV risk factors who are on chronic NSAID
therapy for inflammatory diseases.18

The relative CV risk associated with the remaining avail-
able coxibs and drugs described as nonselective NSAIDs
continues to be debated. Similarly, the risk for GI complica-
tions cannot be wholly attributed to nonselective NSAIDs.
Although several major multicenter studies have demonstrat-
ed that COX-2 inhibitors reduce GI risk relative to nonselective
NSAIDs, the advantage appears to be most relevant to individ-
uals who already are at risk for GI complications.19,20

In addition, cases of drug-induced hepatotoxicity (severe

| Table 1. Pharmacokinetic Parameters for Various Marketed Diclofenac Formulations
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>C_max, ng/mL</th>
<th>T_max, h</th>
<th>AUC, ng*h/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Potassium</td>
<td>25 mg tablet</td>
<td>588&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93&lt;sup&gt;b&lt;/sup&gt;</td>
<td>613&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>50 mg tablet</td>
<td>1,340&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.85&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,286&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diclofenac Sodium</td>
<td>50 mg enteric-coated tablet</td>
<td>1,383&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1,263&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>50 mg enteric-coated tablet</td>
<td>1,497&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.75&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>100 mg enteric-coated tablet</td>
<td>1,727&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4,179&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>100 mg sustained-release tablet (fasted state)</td>
<td>590&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2,710&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>100 mg sustained-release tablet (fed state)</td>
<td>1,060&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2,830&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Topical gel (4 x 4 g daily [160 mg diclofenac])</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>233&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Topical gel (4 x 12 g daily [480 mg diclofenac])</td>
<td>53.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>807&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diclofenac Epolamine</td>
<td>Topical patch 1.3%&lt;sup&gt;30&lt;/sup&gt;</td>
<td>1.73&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>Range: 10-20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15.24&lt;sup&gt;b,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Following administration in otherwise healthy volunteers.
<sup>b</sup> Mean value.
<sup>c</sup> Median value.
<sup>d</sup> Steady-state.

AUC, area under the plasma concentration-time curve to infinite time; C_max, maximum plasma concentration; SD, standard deviation; T_max, time to peak concentration (C_max).
Adapted from references 23-30.
hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure) have been associated with use of diclofenac in clinical trials. Typically, these incidents have occurred within the first month of use; however, they can occur at any time during treatment. Some of these reported cases resulted in fatalities or liver transplantation. Physicians should monitor transaminase levels periodically in patients receiving long-term therapy with diclofenac, particularly within 4 to 8 weeks of initiating treatment.21

**Pharmacokinetics and Delayed Onset of Action**

Diclofenac is an acidic molecule that is highly protein-bound. It has a low volume of distribution and a short plasma half-life. The physical and pharmacokinetic properties of diclofenac promote targeting of the NSAID to a site of inflammation. Coupled with a short plasma half-life (1-2 hours), a low volume of distribution helps to establish a high plasma/tissue gradient that favors movement of the drug to the site of inflammation.22 Absorption of diclofenac varies depending upon the formulation (Table 1).23,30 The time it takes diclofenac to achieve maximum plasma concentration ($T_{\text{max}}$) can affect the drug’s onset of action and thus its analgesic effect. Diclofenac sodium, delivered via enteric-coated tablet, for example, takes up to 2 hours to achieve $C_{\text{max}}$.10

Such variability is likely attributable to the dependence of absorption on mechanical agitation to disperse the drug in the stomach, where its entry into the small intestine is largely governed by the rate of gastric emptying. It is believed that a formulation of diclofenac potassium designed to improve the rate and consistency of absorption would lead to shorter and more consistent time to onset of analgesia, characteristics that are highly desirable when fast relief from pain is needed.31

**Diclofenac Potassium With ProSorb Dispersion Technology**

The introduction of a novel, liquid-filled, liquid-gelatin capsule with proprietary dispersion technology designed to improve the pharmacokinetics of diclofenac potassium shows promise in terms of clinical outcomes. The proprietary dispersion technology for these capsules is called ProSorb (Figure 1). The technology combines the active drug with dispersing agents so that the active drug is rapidly distributed in the gastric juice to maximize absorption and further reduce the time to maximum drug concentrations. The technology was based on the theory that rapid and consistent absorption would tend to accelerate pain relief.2 Several studies have looked at the safety and efficacy of diclofenac potassium with ProSorb dispersion technology. The initial studies demonstrated interindividual consistency of absorption.

An open-label, single-dose, 3-way crossover trial conducted in 24 healthy volunteers measured pharmacokinetics in a series of plasma samples obtained for 6 hours after dosing with 2 formulations of liquid-gel capsules and one liquid gel formulation of diclofenac potassium, each with ProSorb dispersion technology. The $C_{\text{max}}$, $T_{\text{max}}$, area-under-the-curve (AUC) pharmacokinetics, and the plasma concentration-time course were similar for all 3 agents. All 3 products displayed $T_{\text{max}}$ times below 30 minutes; however, the liquid formulation had the shortest, reaching its end point in 15 minutes. Importantly, there was no significant intersubject variability in $T_{\text{max}}$, $C_{\text{max}}$, or AUC.31 The authors concluded that “the characteristics” of diclofenac potassium liquid-gel capsules with ProSorb dispersion technology “will be advantageous in the treatment of mild to moderate pain.”31

**Table 2. Pharmacokinetic Properties of Diclofenac Potassium With ProSorb Dispersion Technology (Zipsor, Xanodyne)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zipsor 25 mg Capsules (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>0.47±0.17</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>1,087±419</td>
</tr>
<tr>
<td>AUC, ng*h/mL</td>
<td>597±151</td>
</tr>
</tbody>
</table>

AUC: area under the plasma concentration-time curve to infinite time; $C_{\text{max}}$: maximum plasma concentration; $T_{\text{max}}$: time to peak concentration

Adapted from reference 21.
In a second analysis of 2 studies conducted in volunteers, diclofenac potassium liquid-gel capsules with ProSorb dispersion technology were compared with an immediate-release diclofenac potassium tablet. In one of the studies, the volunteers received either 50 mg diclofenac potassium liquid-gel capsules with ProSorb or 50 mg immediate-release diclofenac potassium before being crossed over to the opposite agent after washout. In the second study, also employing a crossover design, patients received 25 mg diclofenac potassium liquid-gel capsules with ProSorb dispersion technology, 50 mg diclofenac potassium liquid-gel capsules with ProSorb dispersion technology, or 50 mg immediate-release diclofenac potassium. In both studies, 50 mg diclofenac potassium liquid-gel capsules with ProSorb dispersion technology was associated with a shorter $T_{\text{max}}$ and higher $C_{\text{max}}$ than the 50 mg immediate-release tablet. Additionally, the 25 mg diclofenac potassium liquid-gel capsules with ProSorb dispersion technology produced a shorter $T_{\text{max}}$ and an equivalent $C_{\text{max}}$ to the 50 mg immediate-release tablet (Table 2). The authors concluded that diclofenac potassium liquid-gel capsules with ProSorb dispersion technology “were more rapidly and consistently absorbed” and that “such improvements may result in a shorter and more consistent time to onset of analgesia.”

In a third study, 3 doses of diclofenac potassium liquid-gel capsules with ProSorb dispersion technology were compared with placebo in a randomized double-blind, double-dummy, dose-ranging study. Conducted at 6 centers in the United States, the study randomized 265 adults with moderate to severe pain after removal of one or more impacted molars. The dosages of the diclofenac potassium liquid-gel capsules with ProSorb dispersion technology were 25, 50, or 100 mg. Pain intensity and time to total pain relief were measured over 6 hours after dosing. A dose–response relationship was observed for the 100 mg dose relative to the 25 and 50 mg doses, but the 2 lower doses provided comparable efficacy (Figure 2). When each dose was compared with placebo, the time to first perceptible pain relief and the time to meaningful pain relief were significant. Overall, 68% of the patients treated with diclofenac potassium liquid-gel capsules with ProSorb dispersion technology versus 21% of placebo patients characterized their treatment as good to excellent. The authors concluded that single doses of diclofenac potassium liquid-gel capsules with ProSorb dispersion technology of 25, 50, and 100 mg were “superior to placebo with respect to reduction of pain … with an overall incidence of [adverse events] no greater than with placebo.”

In a multicenter, randomized study of diclofenac potassium liquid-gel capsules with ProSorb dispersion technology versus placebo, 201 patients undergoing first metatarsal bunionectomy were given diclofenac potassium liquid-gel capsules with
ProSorb dispersion technology in 25 mg doses or placebo. In addition to their assigned treatment, patients were permitted a rescue medication (1-2 hydrocodone/acetaminophen tablets as needed every 4 to 6 hours, to a maximum of 8 tablets per day). Patients were allowed to use the rescue medication, but were encouraged to wait at least 1 hour after taking a treatment dose; however, treatment was not withheld if requested. Of the 201 randomized patients, 198 completed the study; no patients discontinued the study as the result of an adverse event.33

Adapted from reference 33.

Table 3. Data for Diclofenac Potassium With ProSorb Dispersion Technology (Zipsor, Xanodyne)

<table>
<thead>
<tr>
<th>Formulation, Dose</th>
<th>Mean NPRS Score After 48 Hours</th>
<th>Patients Requiring Rescue Medication Day 1, %</th>
<th>Patients Requiring Rescue Medication Day 2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Potassium with ProSorb Dispersion Technology, 25 mg</td>
<td>2.5</td>
<td>39.2</td>
<td>21.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.6</td>
<td>87.9</td>
<td>64.6</td>
</tr>
</tbody>
</table>

NPRS, numeric pain rating scale (0-10)

P<0.001

NSAIDs have long been recognized as the first-line therapy for the management of mild to moderate acute pain, but there have been substantial developments in a rational application of these agents. Although opioid augmentation of NSAID analgesia may be required in periods of acute pain, there are numerous potential advantages in limiting use of these agents. The major advantage of diclofenac potassium liquid-gel capsules with ProSorb dispersion technology as a first-line therapy is that peak effect is achieved rapidly with minimal variability between patients, potentially speeding the time to patient pain relief.

Many institutions have created restrictive formularies to reduce health care costs. However, it is important to consider costs in the context of treatment goals, including costs beyond the acquisition of a specific agent and the incremental value. Rapid pain relief is not just an issue for quality of life, but patients in pain may be more likely to consume other health services. Institutions that treat NSAIDs as interchangeable, limiting formularies to options with the lowest acquisition costs, risk inadequately managed pain and dissatisfied patients. Objective differences in the absorption and distribution of diclofenac among the various available formulations demonstrate that drugs are not interchangeable and provide a rationale for formularies to include an array of choices for routine pain care.

Conclusion

In addition, a greater proportion of patients receiving diclofenac potassium liquid-gel capsules with ProSorb dispersion technology vs 2.0% placebo). The overall incidence of adverse events occurring in ≥2% of patients was significantly lower in the diclofenac potassium liquid-gel capsules with ProSorb dispersion technology group than in the placebo group (20.6% vs 44.4%; P<0.05); the increased use of opioid rescue medication by patients in this group should be taken into account when evaluating the adverse event profile. No patient receiving diclofenac potassium liquid-gel capsules with ProSorb dispersion technology had a serious adverse event.33

All meaningful measures favored diclofenac potassium liquid-gel capsules with ProSorb dispersion technology (Table 3). Diclofenac potassium liquid-gel capsules with ProSorb dispersion technology were associated with significant improvements compared with placebo in mean numeric pain rating scale (NPRS) score over 48 hours (2.5 vs 5.6, respectively; P<0.001). Significant differences in NPRS scores between diclofenac potassium liquid-gel capsules with ProSorb dispersion technology 25 mg and placebo were noted at all time points from baseline through 48 hours (P<0.001). The proportion of patients requiring rescue medication was significantly lower in the diclofenac potassium liquid-gel capsules with ProSorb dispersion technology group compared with the placebo group (39.2% vs 87.9% on day 1; 21.6% vs 64.6% on day 2; P<0.001 for both). Patients receiving diclofenac potassium liquid-gel capsules with ProSorb dispersion technology had a significantly faster onset of meaningful pain relief (defined as ≥30% reduction in pain intensity) compared with those receiving placebo—70.2 minutes versus 106.3 minutes (P=0.008). In addition, a greater proportion of patients experienced meaningful pain relief with diclofenac potassium liquid-gel capsules with ProSorb dispersion technology (56.9%) than with placebo (35.4%). The most commonly reported adverse events were nausea (7.8% diclofenac potassium liquid-gel capsules with ProSorb dispersion technology vs 18.2% placebo), headache (5.9% diclofenac potassium liquid-gel capsules with ProSorb dispersion technology vs 9.1% placebo), vomiting (3.9% diclofenac potassium liquid-gel capsules with ProSorb dispersion technology vs 9.1% placebo), and constipation (3.9% diclofenac potassium liquid-gel capsules with ProSorb dispersion technology vs 2.0% placebo). The overall incidence of adverse events occurring in ≥2% of patients was significantly lower in the diclofenac potassium liquid-gel capsules with ProSorb dispersion technology group than in the placebo group (20.6% vs 44.4%; P<0.05); the increased use of opioid rescue medication by patients in this group should be taken into account when evaluating the adverse event profile. No patient receiving diclofenac potassium liquid-gel capsules with ProSorb dispersion technology had a serious adverse event.33

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Many institutions have created restrictive formularies to reduce health care costs. However, it is important to consider costs in the context of treatment goals, including costs beyond the acquisition of a specific agent and the incremental value. Rapid pain relief is not just an issue for quality of life, but patients in pain may be more likely to consume other health services. Institutions that treat NSAIDs as interchangeable, limiting formularies to options with the lowest acquisition costs, risk inadequately managed pain and dissatisfied patients. Objective differences in the absorption and distribution of diclofenac among the various available formulations demonstrate that drugs are not interchangeable and provide a rationale for formularies to include an array of choices for routine pain care.
References
