# Diclofenac in the treatment of osteoarthritis

Diclofenac is a nonselective NSAID that, in its oral form, has been used for decades in the treatment of osteoarthritis. More recently, topical formulations have been developed to decrease the significant systemic exposure associated with oral diclofenac. Several formulations of both oral and topical diclofenac are now approved for the treatment of osteoarthritis in the USA and Europe. Although diclofenac has generally been shown to be relatively safe, some significant safety risks have been observed. For instance, oral diclofenac displays the classic gastrointestinal and cardiovascular effects of the NSAID class; however, topical formulations of the drug show a reduced incidence of these effects. Diclofenac is, thus, well established as an effective and relatively safe option for the treatment for osteoarthritis.

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The worldwide burden of osteoarthritis represents a large and growing health problem. Although the true prevalence of osteoarthritis is difficult to estimate accurately because of variable reporting and differing definitions [1], the disease is estimated to afflict approximately 151.4 million individuals worldwide, according to the most recent Global Burden of Disease report from the WHO (FIGURE 1) [2]. In the USA, the prevalence of symptomatic osteoarthritis is estimated to be nearly 27 million individuals, based on an analysis of data from national surveys, including the National Health and Nutrition Examination Survey and the National Health Interview Survey [3,4].

As no single pharmacologic treatment is consistently effective or well tolerated in every patient with osteoarthritis, physicians need an array of therapeutic options from which to choose. In particular, because of the gastrointestinal and cardiovascular tolerability issues with existing selective and nonselective NSAIDs, there is a need for alternatives to these therapies. This article describes the nonselective NSAID diclofenac, in both oral and topical formulations.

## Diclofenac
### ■ Formulations
Diclofenac exists as diclofenac sodium and diclofenac potassium, both of which are used to treat pain and inflammation. Although these salts have most of the same physicochemical properties, diclofenac potassium is more soluble in water, and thus is more quickly absorbed and may have a more rapid onset of action than diclofenac sodium [5]. The availability of these products differs among countries.

### Oral diclofenac
Oral diclofenac is perhaps the most widely prescribed traditional NSAID in the world [6]. Available in both extended- and immediate-release tablets and capsules, this drug is often formulated with an enteric coating to mitigate the risks of gastrointestinal events that are common with NSAID use and to disguise its intensely bitter taste [7,8]. Diclofenac has been extensively studied, and its clinical profile is well established. Over more than 30 years, these formulations have demonstrated efficacy in the treatment of osteoarthritis of the hip, knee and spine that is generally comparable with that of other oral NSAIDs, including ibuprofen [9–11], naproxen [12,13], piroxicam [14–16], meloxicam [17] and indomethacin [18]. However, these studies were not generally designed to be equivalency trials, so they were not powered adequately enough to allow for further exploration of any differences between diclofenac and the other NSAID formulations that were assessed.

Microencapsulation is a novel drug delivery technology designed to sustain drug release, mask bitter taste, reduce the frequency of dosing and minimize or eliminate gastrointestinal irritation [19]. *In vitro* studies have shown that a novel formulation of sustained-release diclofenac sodium microcapsules has uniform drug content and a decreased rate of drug release [20]. An investigational formulation of oral diclofenac potassium is a liquid-filled soft gelatin capsule that uses
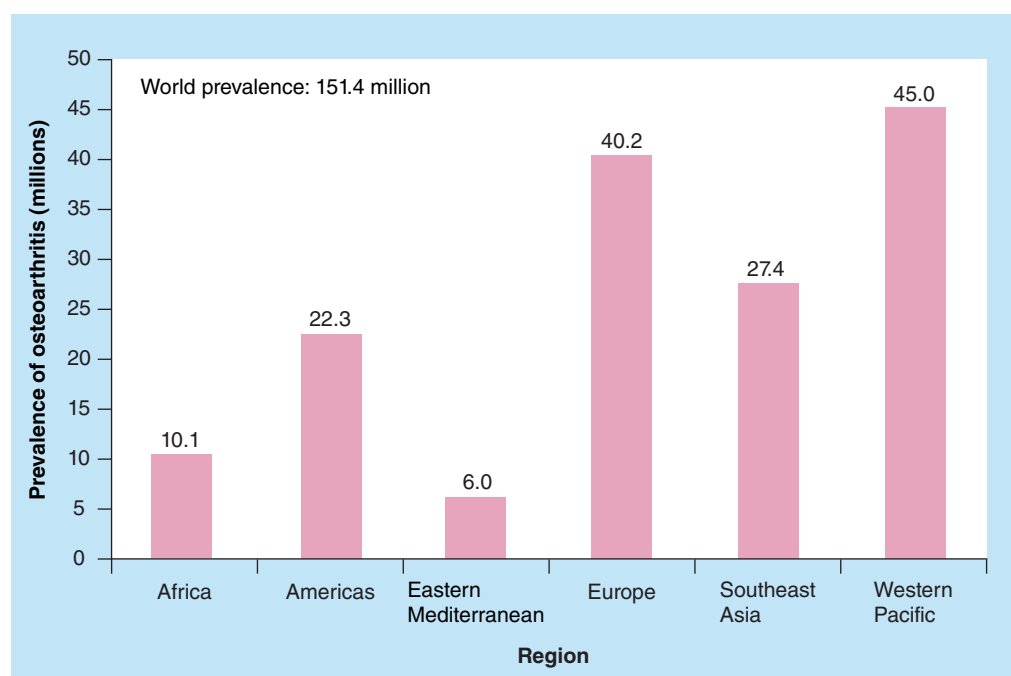
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**Figure 1. Global prevalence of osteoarthritis (selected WHO regions, 2004).**
Data taken from [2].

dispersing agents to facilitate rapid and consistent absorption of the drug [21]. Pharmacokinetic studies in healthy volunteers have established that this formulation is rapidly and consistently absorbed [22] and unaffected by food intake [21]. A Phase III placebo-controlled study showed it to be effective and well tolerated in the treatment of mild-to-moderate acute postbunionectomy pain [23]. Diclofenac potassium liquid-filled soft gelatin capsules 25 mg were associated with significant improvements compared with placebo in mean pain intensity (measured by a numeric pain rating scale) over the 48-h study period (p < 0.001) [23]. Nanotechnology is an approach to drug delivery that focuses on reducing particle size and increasing the surface area of the drug, thereby enhancing dissolution and absorption. Application of nanotechnology to the development of NSAIDs has been attempted to accelerate the onset of analgesia while allowing lower drug doses to be administered, and thus may ameliorate some of the gastrointestinal toxicities associated with NSAID use [24]. Compared with standard oral diclofenac 50 mg, an investigational, proprietary, nanoformulated, low-dose formulation of diclofenac 35 mg has demonstrated 19% lower systemic exposure under fasting conditions, comparable plasma concentrations ($C_{max}$: 1316 ± 577 vs 1347 ± 764 ng/ml, respectively) and more rapid absorption ($T_{max}$: 0.80 ± 0.50 vs 0.59 ± 0.20 h, respectively) [24]. It must be noted that further independent studies are needed to fully establish the pharmacokinetic, efficacy and safety profiles of formulations that utilize these, and other, experimental technologies.

## Topical diclofenac

In the USA, the three available formulations are diclofenac sodium topical gel 1% [25], diclofenac sodium topical solution 1.5% [26], and the diclofenac epolamine topical patch (DETP) 1.3% [27,28]. A formulation of diclofenac sodium gel 3% is also available in the USA but is indicated only for short-term treatment of actinic keratosis [29]. In Europe, in addition to diclofenac sodium 1.5% topical solution and DETP 1.3%, diclofenac sodium topical 1.16% gel and diclofenac 4% cutaneous spray solution are approved for use [30].

Several topical agents are currently in development. A novel topical diclofenac formulation uses a diclofenac acid–based delivery system, which has an intrinsically higher permeability than diclofenac salts. This formulation, at concentrations of 1 and 2.5% (with doses approximately three- to five-fold lower than those of the reference formulation), has shown up to 500% greater bioavailability, as determined from plasma diclofenac concentrations, than diclofenac 1% gel. Results suggest that these newer formulations produce higher local tissue concentrations, and subsequently higher elimination rates from the potential target sites [31]. In addition, an experimental formulation of diclofenac sodium gel has

been developed with a water-soluble polyacrylamide polymer delivery system. Stability studies under accelerated conditions showed that the polyacrylamide gel containing diclofenac sodium showed good physiochemical properties (i.e., consistency, homogeneity, spread ability and stability), thus showing promise for further development [32]. Other research is aimed at developing a topical diclofenac solution with components such as an enhancer and a bioadhesive polymer. Such formulations may have the potential to increase residence time, sustain drug delivery and retain physical stability characteristics [33]. A new formulation of diclofenac diethylamine emulgel 1.16% weight/weight (w/w) has been formulated without isopropyl alcohol to reduce associated skin and eye irritation. *In vitro* and *ex vivo* diffusion studies have demonstrated that its physiochemical properties and permeability are comparable with those of the marketed version of diclofenac emulgel [34]. In addition, a novel diclofenac spray gel 4% has shown favorable penetration characteristics and low systemic availability in Phase I studies [35]. Finally, a Phase I clinical trial has investigated the clinical utility of a 2% formulation of diclofenac sodium w/w topical gel compared with 1.5% w/w diclofenac sodium topical solution and diclofenac sodium 75 mg delayed-release tablet; the results are yet to be posted or published [201].

### ■ Place in guidelines
Current guidelines for the management of osteoarthritis include strategies that minimize the risks associated with oral NSAID use. In the USA, the 2012 ACR guidelines, which were developed using a case-based methodology involving an older patient with osteoarthritis and no other medical comorbidities, conditionally recommend oral NSAIDs (including cyclooxygenase [COX]-2 selective inhibitors, or coxibs) or topical NSAIDs for the initial management of patients with hand osteoarthritis, and oral or topical NSAIDs for patients with knee osteoarthritis. According to these guidelines, a conditional recommendation is defined as a weak recommendation to use or not to use a treatment based on lack of consistent, high-quality evidence or evidence demonstrating small differences between desirable and undesirable effects of treatment. A conditional recommendation is included for treatments that lack consistent, high-quality evidence or only demonstrate small differences between desirable and undesirable effects.

The ACR also conditionally recommends topical rather than oral NSAIDs for individuals 75 years of age or older with hand osteoarthritis. For the initial management of patients with knee osteoarthritis, the ACR conditionally recommends the use of oral or topical NSAIDs, and strongly recommends the use of topical NSAIDs for patients 75 years of age or older and those who do not have a satisfactory clinical response to full-dose acetaminophen. The ACR recommendations note that oral NSAIDs should not be used in patients with stage IV or V chronic kidney disease (estimated glomerular filtration rate below 300 cc/min), and that the decision to use an oral NSAID in patients with stage III chronic kidney disease (estimated glomerular filtration rate between 30 and 59 cc/min) should be made by the practitioner on an individual basis after consideration of the benefits and risks. Oral NSAIDs, but not topical NSAIDs, are included in the treatment options for the initial management of hip osteoarthritis [36].

In addition, in the USA, the 2008 American Academy of Orthopaedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend acetaminophen or NSAIDs in general, and acetaminophen, topical NSAIDs, nonselective oral NSAIDs plus gastroprotective agents, or COX-2 inhibitors for patients at increased gastrointestinal risk [37]. In 2009, the American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons included oral diclofenac as one of several recommended nonopioid analgesics [38].

In the UK, the 2008 NICE guidelines advise that topical NSAIDs or acetaminophen/paracetamol should be considered before oral NSAIDs, COX-2 inhibitors, or opioids in addition to core treatment in adult patients with knee or hand osteoarthritis. If topical NSAIDs or acetaminophen/paracetamol do not provide sufficient pain relief, the addition of, or substitution with, an oral NSAID or COX-2 inhibitor may be considered. In this case, the healthcare professional's first choice should be a standard agent (other than etoricoxib 60 mg). In either case, NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time, and should be coprescribed with the proton-pump inhibitor (PPI) with the lowest possible acquisition cost. In addition, healthcare professionals should consider individual patient risk factors, including age, when choosing the agent and dose, to avoid potential gastrointestinal, liver and cardio–renal toxicities. Finally, the NICE guidelines advise healthcare professionals to consider other analgesics before substituting or adding an oral NSAID or COX-2 inhibitor

(even with a PPI) in patients who need to take concomitant low-dose aspirin [39].

The 2003 European League Against Rheumatism (EULAR) recommendations for the management of knee osteoarthritis state that topical NSAIDs are safe and clinically effective and that oral NSAIDs should be considered in patients unresponsive to acetaminophen/paracetamol. EULAR suggests that for patients with an increased gastrointestinal risk, nonselective NSAIDs and effective gastroprotective agents, or selective COX-2 inhibitors, should be used [40]. The EULAR evidence-based recommendations for the management of hand osteoarthritis explicitly state that local treatments, including NSAIDs, are preferred over systemic treatments, especially for mild-to-moderate pain or when only a few joints are affected. EULAR also recommends that oral NSAIDs should be used at the lowest effective dose and for the shortest duration in patients who respond inadequately to acetaminophen and recommends that nonselective NSAIDs plus a gastroprotective agent or a selective COX-2 inhibitor should be used in patients with increased gastrointestinal risk. For patients with increased cardiovascular risk, EULAR states that COX-2 inhibitors are contraindicated and that nonselective NSAIDs should be used with caution [41].

Like the EULAR guidelines, evidence-based, expert consensus guidelines issued by the Osteoarthritis Research Society International (OARSI) in 2008 for the management of hip and knee osteoarthritis advise that oral NSAIDs should be used at the lowest effective dosage, that long-term treatment with NSAIDs should be avoided, that either a COX-2 inhibitor or a nonselective NSAID plus a gastroprotective agent should be used in patients with increased gastrointestinal risk, and that both nonselective NSAIDs and COX-2 inhibitors should be used with caution in patients with cardiovascular risk factors. The OARSI recommendations also state that topical NSAIDs can be effective adjunctively with or as an alternative to oral analgesic or anti-inflammatory agents in knee osteoarthritis [42].

■ Chemistry

A derivative of phenyl acetic acid, diclofenac contains a carboxylic acid group (Figure 2) [43]. As such, diclofenac is a weak acid with a pKa value of approximately four. This relatively lipophilic molecule is small [44], allowing for rapid diffusion through the skin [45] and access to all tissues [46] when applied topically.

The pure, free acid form of diclofenac has a high rate of intrinsic transdermal permeability – higher than any other NSAID tested in one *in vitro* study [47]. Nevertheless, topical diclofenac requires the addition of a penetration enhancer to facilitate transport of the molecule across the stratum corneum, past the epidermal layer, into the dermis and beyond [48].

Propylene glycol is part of the gel technology that helps facilitate the transport of diclofenac in diclofenac sodium topical gel and DETP through the skin [49]. Like ethanol, this form of alcohol may alter the thermodynamics of the drug or disturb the lipid packing in the bilayers, thereby modifying its diffusion [48]. The use of water is another longstanding approach to facilitating drug penetration that is employed to enhance the penetration of diclofenac in both the diclofenac sodium topical gel and DETP [48]. By achieving an equilibrium between the stratum corneum and the epidermal layer, water can increase the transdermal permeation of both hydrophilic and lipophilic molecules [48,49]. In the case of DETP, penetration is also enhanced by occlusion.

The penetration of diclofenac in diclofenac sodium topical solution is enhanced by dimethyl sulfoxide (DMSO). One of the most widely studied penetration enhancers, DMSO promotes the permeation of both the hydrophilic and lipophilic molecules through the skin in a concentration-dependent manner [48]. When applied to the skin, DMSO works through two distinct mechanisms: it changes the intercellular keratin conformation, allowing for easier diffusion across skin layers, and it interacts with the polar head groups of the lipid bilayer to actively change its structure, increasing penetration through the stratum corneum [48]. Penetration of DMSO into the cell membrane results in loss of lateral interactions between the lipid head groups and a progressive decrease in the thickness of the bilayer [50]. As this occurs, fluctuations in temperature can cause structural defects in the lipid/water interface, leading to accumulation of DMSO in the interface and the hydrophobic core [49]. DMSO induces the formation of transient water pores in the phospholipid membrane, allowing for a temporary increase in the flow of water molecules and salt ions and localized delivery of diclofenac through the membrane [49,50]. DMSO, thus, streamlines the pathway that the drug takes and facilitates its diffusion through the membrane [49]. In addition, it has been suggested that DMSO produces pharmacodynamic effects that mirror those of NSAIDs, such as COX inhibition and platelet aggregation, which will require further analysis to fully elucidate [51].

## Pharmacology

As a nonselective NSAID, diclofenac inhibits the activity of both COX isoenzymes, COX-1 and COX-2 [52]. As shown in FIGURE 3, diclofenac exerts its anti-inflammatory and analgesic effects primarily through the inhibition of COX-2, thus preventing the conversion of arachidonic acid into prostaglandins, thromboxanes and prostacyclins [52]. As with other nonselective NSAIDs, diclofenac also inhibits COX-1, which reduces the protective effects of this enzyme and the prostaglandins it produces on gastric mucosa and renal function [53,54]. Consequently, oral diclofenac can cause gastrointestinal ulceration and, rarely, renal toxicity. Estimates of the COX selectivity ratio of diclofenac vary widely based on the methodology that is employed, but the most consistent results suggest that the degree of COX-2 inhibition is one-to two-times greater than the inhibition of COX-1 [53,55]. It is important to note that systemically administered NSAIDs may theoretically produce analgesia because the COX enzymes, in particular COX-2, have expression in the spinal cord. Therefore, when orally administered, NSAIDs may also inhibit COX activity at the level of the CNS [56].

## Pharmacokinetics

### Oral diclofenac

Absorption of oral diclofenac is rapid and complete, with peak plasma concentrations achieved 10–30 min after administration [43,57,58]. Peak plasma concentration and area under the plasma concentration–time curve (AUC) are linearly dose-related over the range of 25–150-mg oral doses [59]. Like other lipophilic NSAIDs, oral diclofenac achieves its highest concentrations in blood [60]. Within its therapeutic concentration range, diclofenac sodium is highly protein bound (≥99.5%), chiefly to serum albumin [60,61]. The apparent volume of distribution of oral diclofenac sodium is 1.4 l/kg [62], which suggests that tissue binding is appreciably less extensive than plasma protein binding [58]. Whether administered orally or topically, diclofenac has been shown to penetrate synovial fluid and enter systemic circulation in patients with osteoarthritis; however, the elimination half-life from synovial fluid is three-times longer than from plasma, which may provide a more sustained therapeutic effect [58].

Diclofenac undergoes first-pass metabolism, with approximately 60% of the unchanged drug reaching the systemic circulation [59]. Elimination is mediated principally by metabolism and subsequent urinary excretion of glucuronide and sulphate conjugates of the metabolite [63].
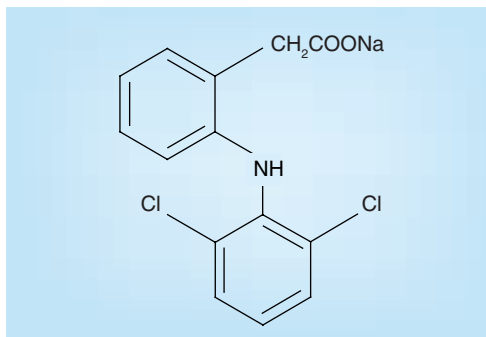


**Figure 2. Diclofenac.**

Significant drug interactions have been shown between oral diclofenac and aspirin, lithium, digoxin, methotrexate, cyclosporine, cholestyramine and colestipol [58].

### Topical diclofenac

In a form corresponding to 1% diclofenac sodium, topical diclofenac gel is absorbed from the application site throughout the dosage period [64]; the patch formulation has the advantage of occlusion, which allows progressive and continuous release of the drug [65]. Animal studies have shown that diclofenac in an aqueous solution reaches a depth of at least 3 mm through the dermis and subcutaneous tissue [66]. Approximately 6% of the applied dose is absorbed percutaneously, but systemic exposure, and hence the potential for systemic adverse events, is low [52,66,67]. As with oral diclofenac, topical diclofenac is extensively protein bound [52]. The strong protein binding is facilitated by the carboxylic acid group on the molecule, resulting in a low volume of distribution. These characteristics, along with a short plasma half-life of 1–2 h, establish a high plasma/tissue gradient that favors passage of the drug into the inflamed tissue [52]. As discussed earlier, diclofenac preferentially distributes to synovial fluid rather than plasma, resulting in therapeutic concentrations in the target tissues and rapid decline of concentrations systemically, such as would affect the cardiovascular and renal systems [46]. However, the concentration of diclofenac in the synovial membrane is significantly lower (p = 0.0181) with topical application (4.99 ng/ml$^{-1}$) than with oral administration (15.07 ng/ml$^{-1}$) [68]. It is currently hypothesized that topically administered diclofenac forms a depot either in subcutaneous fascia or periarticular tissues, from which the drug is released into the bloodstream over time [49]. However, as is common with the topical application of pharmaceuticals, significant interindividual variability in dosing with
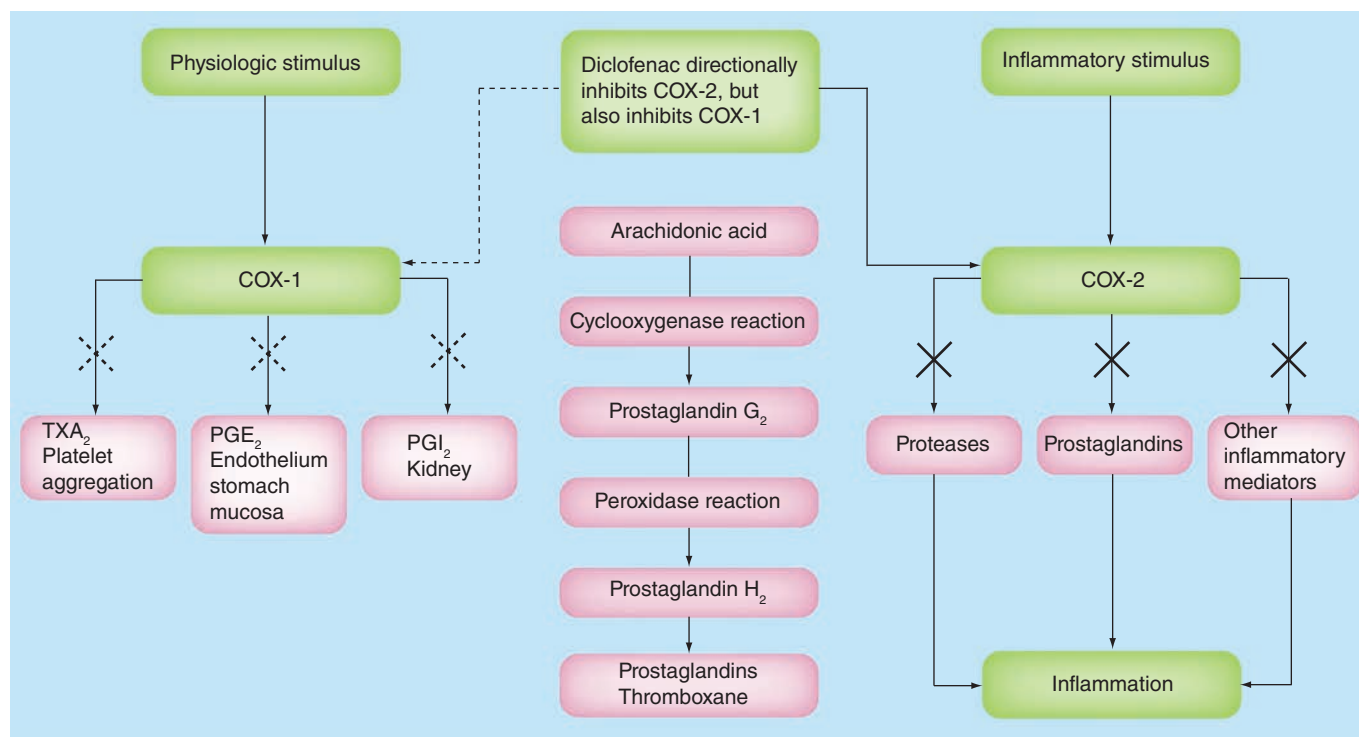
**Figure 3. Mechanism of action of diclofenac.** The dotted lines and crosses signify the moderate degree of COX-1 inhibition in relation to COX-2, shown by solid lines. The crosses signify the inhibitory downstream effects that stem from COX-1 inhibition.
$PGE_2$: Prostaglandin $E_2$; $PGI_2$: Prostaglandin $I_2$; $TXA_2$: Thromboxane $A_2$.
Adapted with permission from [52].

topically applied diclofenac has been reported, which could impact drug exposure at the site of action [69].

Topical diclofenac is metabolized in the same way as oral diclofenac – that is, the drug is metabolized mainly in the liver to mostly inactive metabolites and excreted mainly in the urine (60%), but also in the bile. Little or no unchanged drug is excreted [52].

The systemic exposure from diclofenac sodium gel 1% applied topically to the knee has been shown to be 151-fold lower than exposure from oral diclofenac 150 mg, measured by maximum plasma concentrations [69].

Although formal assessment is lacking, topical diclofenac has not been associated with clinically meaningful drug–drug interactions [70].

### ■ Clinical efficacy
#### Oral diclofenac
Oral diclofenac has been studied extensively in patients with osteoarthritis of the hip, knee and spine. In early, active-controlled studies that included a placebo control group, diclofenac 100–150 mg/day was shown to be statistically and clinically superior to placebo with respect to analgesic efficacy and functional improvement [15,16,71].

At doses of 75–150 mg/day, diclofenac has been compared with numerous other NSAIDs in randomized, usually double-blind clinical trials primarily involving patients with osteoarthritis of the hip and knee. These trials were conducted from the late 1970s through the 1990s and contained small numbers of patients (12–84 patients in ten trials and 335 patients in one trial). These studies were, therefore, generally underpowered to accurately establish the equivalence of diclofenac and the comparators that were assessed. Comparators included ibuprofen [9–11], naproxen [12,13,72], piroxicam [14–16], meloxicam [17] and indomethacin [18]. Although none of these trials specifically recruited older patients, the mean age of patients in studies that reported these data was approximately 60 years of age, as would be expected in a population of patients with osteoarthritis or other rheumatic disorders [12–18,72]. In these studies, which ranged from 2 weeks to 6 months in duration, the efficacy of oral diclofenac in relieving pain and improving functional capacity was shown to be generally similar to that of other oral NSAIDs (TABLE 1) [9–18,72]. In one study, naproxen produced a statistically greater treatment effect compared with diclofenac; however, in addition to the limitations associated with the population size discussed earlier, the doses

that were compared (diclofenac 150 mg/day vs naproxen 1000 mg/day) have been judged to be inappropriate [43,72].

Similar efficacy has been demonstrated in studies comparing diclofenac enteric-coated tablets versus either controlled-release diclofenac tablets or diclofenac resinate capsules [8,73]. Over 12 weeks, patients with osteoarthritis of the hip or knee treated with diclofenac resinate versus diclofenac sodium daily showed similar and clinically significant reductions from baseline in mean intensity scores of pain at rest (22.5 vs 25.4, respectively), pain on activity (34.2 vs 32.8) and stiffness after inactivity (34.2 vs 33.2); rates of drug-related adverse events also were similar (40 vs 38%) [8]. Finally, two more-recent studies showed that oral diclofenac was equal in efficacy to oral enzyme therapy and similarly well tolerated in the treatment of osteoarthritis

of the knee [74,75]. The longer of these studies showed comparable decreases in Lequesne's algo-functional index (23.6 vs 26.3%, respectively) and in a complaint index including pain at rest, pain on motion and restricted function (26.6 vs 30.2%) over 6 weeks of therapy. Safety profiles were similar, with no noteworthy differences between groups [75].

### Topical diclofenac

Topical diclofenac has been studied in several randomized controlled trials in patients with osteoarthritis of the knee (TABLE 2) [65,76–84].

DETP 1.3% was compared with placebo in two 2-week studies. In one study, patients treated with the patch showed improvements in Lequesne's algo-functional index and in spontaneous pain versus placebo (p < 0.01 vs placebo for both end points), and the patch was

**Table 1. Summary of efficacy results from selected randomized controlled trials of oral diclofenac versus other NSAIDs in patients with osteoarthritis and other rheumatic disorders.**

| Study (year) | Comparator/ site | Study duration and design | Dosage, n analyzed for efficacy (mg/day) | Results | | Ref. |
|---|---|---|---|---|---|---|
| | | | | Analgesic efficacy | Functional improvement | |
| Crook et al. (1981) | Ibuprofen/hip | 8-week, randomized, double-blind, parallel-group | Diclofenac 100–150 (n = 17) Ibuprofen 1600–2400 (n = 20) | No significant differences | No significant differences | [9] |
| Siegmeth and Sieberer (1978) | Ibuprofen/ spondylosis† | 2-week, randomized, single-blind, parallel-group | Diclofenac 75 (n = 15) Ibuprofen 1200 (n = 14) | No significant differences | No significant differences | [10] |
| Brooks et al. (1980) | Ibuprofen/NS | 5-week (per period), randomized, double-blind, crossover | Diclofenac (EC) 75–100 Ibuprofen 1200–1600 (n = 12) | Diclofenac significantly better | NA | [11] |
| Car et al. (1978) | Naproxen/hip | 2-week, randomized, double-blind, parallel-group | Diclofenac 100 (n = 39) Naproxen 500 (n = 40) | No significant differences | No significant differences | [12] |
| Scharf et al. (1982) | Naproxen/ knee | 12-week (per period), randomized, double-blind, crossover | Diclofenac 150 Naproxen 750 (n = 50) | No significant differences | No significant differences | [13] |
| Vetter (1985) | Naproxen/hip or knee | 12-week, randomized, double-blind, parallel-group | Diclofenac 150 (n = 30) Naproxen 1000 (n = 30) | Naproxen significantly better | Naproxen significantly better | [72] |
| Gerecz-Simon et al. (1990) | Piroxicam/hip or knee | 12-week, randomized, double-blind, parallel-group | Diclofenac 75–150 (n = 40) Piroxicam 20 (n = 40) | No significant differences | No significant differences | [14] |
| Marcolongo et al. (1985) | Piroxicam/hip, knee or spine | 2-week, randomized, double-blind, parallel-group | Diclofenac (SR) 100 (n = 61) Piroxicam 20 (n = 60) | No significant differences | No significant differences | [15] |
| Berry et al. (1982) | Piroxicam/hip or knee | 2-week (per period), randomized, double-blind, crossover | Diclofenac 150 Piroxicam 20 (n = 26) | No significant differences | NA | [16] |
| Hosie et al. (1996) | Meloxicam/hip or knee | 6-month, randomized, double-blind, parallel-group | Diclofenac (SR) 100 (n = 166) Meloxicam 7.5 (n = 169) | No significant differences | No significant differences | [17] |
| Gostick et al. (1990) | Indomethacin/ hip or knee | 4-week (per period), randomized, double-blind, crossover | Diclofenac (SR) 100 Indomethacin 75 (n = 84) | No significant differences | NA | [18] |

†Osteoarthrosis of the spine.
EC: Enteric coated; NA: Not assessed; NS: Not specified; SR: Sustained release.

significantly better than placebo in global assessments of efficacy by both patients (p < 0.05) and physicians (p < 0.01) [76]. In the other study, DETP showed superior analgesic effects versus placebo as assessed by both Huskisson's visual analog scale and Lesquesne's algo-functional index (p < 0.001 for both comparisons) and was judged to be either excellent or good by significantly more patients and physicians (p < 0.0001 for both comparisons) [65].

Diclofenac sodium gel has been assessed in three studies. In a 3-week study, diclofenac gel was shown to be superior to placebo gel in relieving pain (p = 0.006), reducing Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (p = 0.0002), improving physical function (p = 0.001) and reducing stiffness (p = 0.0004) [77]. In a 12-week study, diclofenac gel showed significant reductions versus placebo in mean WOMAC pain scores (p = 0.01), WOMAC physical function scores (p = 0.001) and global ratings of disease (p = 0.01) [78]. Pooled data from this trial and two other 12-week trials showed that among patients aged 25–64 years, the improvement from baseline to week 12 was greater for diclofenac versus vehicle for WOMAC pain (p = 0.007), WOMAC physical function (p = 0.002), global ratings of disease (p = 0.01) and pain on movement (p < 0.001). Among patients aged ≥65 years, improvements from baseline scores for most efficacy outcomes were significantly greater with diclofenac versus vehicle: WOMAC pain (p = 0.02); WOMAC physical function (p = 0.004); and pain on movement (p = 0.02) [79].

Diclofenac sodium topical solution was compared with vehicle-control solutions in three randomized, double-blind trials in osteoarthritis of the knee. In all of these studies, topical diclofenac solution was significantly more effective than the vehicle-control solution for all outcome measures: pain (p = 0.003, p = 0.001 and p < 0.05); physical function (p = 0.001, p = 0.002 and p < 0.01); and stiffness (p = 0.002, p = 0.005 and p < 0.05) [80–82]. A pooled analysis of safety data from seven multicenter, randomized, blinded Phase III clinical trials of diclofenac sodium topical solution in the treatment of osteoarthritis in patients 75 years of age or older was conducted [85]. This analysis showed that diclofenac topical solution was well tolerated during up to 12 weeks of treatment; although the incidence of dry skin was higher in the active treatment group than in the placebo group (36.2 vs 2.6%, respectively), there were

no other significant differences between groups in adverse events regarding the skin, cutaneous tissue or the gastrointestinal, cardiovascular or renal systems [85].

## Oral diclofenac versus topical diclofenac

Currently, there are only three trials that directly compare a topical diclofenac formulation with an oral NSAID. Zacher et al., conducted in Germany, was a noninferiority study comparing the efficacy and tolerability of topical diclofenac gel with oral ibuprofen in patients with activated osteoarthritis of the finger joints. Through this analysis, diclofenac gel applied four-times daily was observed to be at least as effective as ibuprofen 400 mg taken three-times daily after 21 days of treatment (5% equivalency limit; p = 0.007). In addition, of the 296 patients included as a part of the analysis, 66 patients (22%) taking diclofenac gel were considered responders compared with 50 patients (18%) taking ibuprofen [86].

The other two trials studying a diclofenac sodium topical solution and an oral NSAID were conducted in the USA and Canada. Simon et al. demonstrated similar efficacy of diclofenac sodium topical solution compared with oral diclofenac, with no significant differences in mean (standard deviation) change from baseline in the WOMAC pain (-6.0 [4.5] vs -6.4 [4.1], respectively; p = 0.429), WOMAC physical function (-15.8 [15.1] vs -17.5 [14.3]; p = 0.319), and patient overall health assessment (-0.95 [1.30] vs -0.88 [1.31]; p = 0.956). While this was not an equivalency study, the investigators concluded that diclofenac sodium topical solution showed efficacy comparable with oral diclofenac in relieving the signs and symptoms of osteoarthritis of the knee [84].

Tugwell et al. also demonstrated that there were no significant differences in efficacy between diclofenac sodium topical solution and oral diclofenac in the treatment of osteoarthritis of the knee. In this equivalence study, patients who received diclofenac sodium topical solution and those receiving oral diclofenac demonstrated improvement in all end points including WOMAC pain (-127 [120] vs -140 mm [127], respectively; p = 0.23), WOMAC physical function (-380 mm [396] vs -451 [431]; p = 0.06) and patient global assessment (-30 [31] vs -34 mm [31]; p = 0.13). An analysis of equivalence showed that the observed difference in confidence intervals between diclofenac sodium topical solution and oral diclofenac fell within the predetermined, acceptable range for all end points [83].

**Table 2. Summary of efficacy results from selected randomized controlled trials of topical diclofenac in patients with osteoarthritis.**

| Study (year) | Comparator(s) | Study duration and design | Dosage (n analyzed for efficacy) | Results | | Ref. |
|---|---|---|---|---|---|---|
| | | | | *Analgesic efficacy* | *Functional improvement* | |
| **DETP 1.3% patch** | | | | | | |
| Brühlmann and Michel (2003) | Placebo | 2-week, randomized, double-blind, parallel-group | Diclofenac two-times daily (n = 51) Placebo two-times daily (n = 52) | Diclofenac superior | Diclofenac superior | [76] |
| Dreiser and Tisne-Camus (1993) | Placebo | 2-week, randomized, double-blind, parallel-group | Diclofenac two-times daily (n = 78) Placebo two-times daily (n = 77) | Diclofenac superior | Diclofenac superior | [65] |
| **Topical diclofenac gel** | | | | | | |
| Niethard *et al.* (2005) | Vehicle | 3-week, randomized, double-blind, parallel-group | Diclofenac 4 g, four-times daily (n = 117) Vehicle 4 g four-times daily (n = 121) | Diclofenac superior | Diclofenac superior | [77] |
| Barthel *et al.* (2009) | Vehicle | 12-week, randomized, double-blind, parallel-group | Diclofenac 4 g, four-times daily (n = 253) Vehicle 4 g, four-times daily (n = 238) | Diclofenac superior | Diclofenac superior | [78] |
| Baraf *et al.* (2011) | Vehicle | Pooled data from three 12-week, randomized, double-blind, parallel-group trials† | Diclofenac 4 g, four-times daily (n = 719) Vehicle 4 g, four-times daily (n = 705) | Diclofenac superior | Diclofenac superior | [79] |
| **TDiclo** | | | | | | |
| Baer *et al.* (2005) | Vehicle | 6-week, randomized, double-blind, parallel-group | Diclofenac 40 drops, four-times daily (n = 107) Vehicle 40 drops, four-times daily (n = 109) | Diclofenac superior | Diclofenac superior | [80] |
| Roth and Shainhouse (2004) | Vehicle | 12-week, randomized, double-blind, parallel-group | Diclofenac 40 drops, four-times daily (n = 163) Vehicle 40 drops, four-times daily (n = 159) | Diclofenac superior | Diclofenac superior | [81] |
| Bookman *et al.* (2004) | Vehicle Placebo solution | 4-week, randomized, double-blind, parallel-group | Diclofenac 40 drops, four-times daily (n = 84) Vehicle 40 drops, four-times daily (n = 79) Placebo 40 drops, four-times daily (n = 84) | Diclofenac superior to vehicle and placebo | Diclofenac superior to vehicle and placebo | [82] |
| Tugwell *et al.* (2004) | ODiclo | 12-week, randomized, double-blind, parallel-group | TDiclo 50 drops, three-times daily (n = 311) ODiclo 150 mg (n = 311) | TDiclo equivalent to ODiclo | TDiclo equivalent to ODiclo | [83] |
| Simon *et al.* (2009) | Placebo tablet Vehicle Oral diclofenac SR TDiclo + ODiclo‡ | 12-week, randomized, double-blind, parallel-group | TDiclo 40 drops, four-times daily (n = 154) Placebo (n = 155) Vehicle (n = 161) ODiclo 100 mg/day (n = 151) | TDiclo superior to vehicle and placebo TDiclo equivalent to ODiclo | TDiclo superior to vehicle and placebo TDiclo equivalent to ODiclo | [84] |

†Including the Barthel 2009 trial above [78].
‡No comparison was made with TDiclo alone.
DETP: Diclofenac epolamine topical patch; ODiclo: Oral diclofenac; SR: Sustained-release; TDiclo: Topical diclofenac solution.

### Safety & tolerability

NSAID gastropathy, an array of adverse events ranging from mild dyspepsia or abdominal discomfort to potentially life-threatening complications such as ulcers, perforation and hemorrhage, has been recognized for more than two decades as a potential complication of long-term therapy with nonselective NSAIDs [87,88]. This condition is distinct from other gastrointestinal disorders, such as peptic ulcer disease, differing in pathophysiology, anatomic location and clinical pattern [85]. Such adverse events are linked to inhibition of COX-1, which mediates the production of prostaglandins involved in gastric acid secretion and, therefore, protection of the stomach lining [85,89]. The potential for NSAID gastropathy is increased greatly by certain risk factors, including advanced age, diabetes mellitus, a history of peptic ulcer (particularly bleeding ulcer), concurrent use of aspirin, oral corticosteroids or anticoagulants, and tobacco or alcohol use [88]. Although the addition of a PPI can mitigate both short- and long-term NSAID-related gastrointestinal effects [39], PPIs are associated with several risks, including a dose-related increase in the risk of hip fractures in individuals 50 years of age and older [90] and low serum magnesium concentrations, which can increase cardiovascular risk [85]. In addition, the well-known potential consequences associated with polypharmacy must be considered, such as drug interactions, adverse events and nonadherence, as well as the additional costs [85,91]. As a rule, high-risk patients simply should not use systemic NSAIDs, because complications of NSAID gastropathy are best avoided rather than treated [85,92].

Oral NSAIDs, particularly COX-2 inhibitors, also confer significant cardiovascular risks [88], both in healthy individuals and in patients with established cardiovascular disease [93–101]. Some data suggest that in the general population, only long-term NSAID treatment is associated with increased cardiovascular risk [102]. However, even short-term treatment with most NSAIDs is associated with an increased risk of cardiovascular outcomes in patients with a history of cardiovascular disease; there is apparently no safe therapeutic window for NSAIDs in patients with prior myocardial infarction [93]. Many studies have shown that naproxen carries the lowest cardiovascular risk of all NSAIDs [93]. It has been proposed that the lower cardiovascular risk associated with traditional NSAIDs compared with COX-2 inhibitors is related to the former agents' relative selectivity for COX-1 versus COX-2 enzyme inhibition [103]. Selective inhibition of COX-2 could produce a relative reduction in endothelial production of prostacyclin, while leaving the vasoconstrictive eicosanoid thromboxane $A_2$ intact [103–105]. This imbalance of hemostatic prostanoids may increase the risk of thrombotic cardiovascular events [103].

Finally, nonselective NSAIDs are among the most frequent causes of drug-induced liver injury, which in turn is the leading cause of acute liver failure [106,107], accounting for approximately 10% of all drug-induced hepatotoxicity [108].

### Oral diclofenac

A report published in 1985, describing worldwide clinical safety experience in more than 100,000 patients treated in clinical trials, showed that adverse experiences were infrequent and generally mild or transient over both short- and long-term use of oral diclofenac (TABLE 3) [109]. More recent studies have examined the gastrointestinal, cardiovascular and hepatic safety of oral diclofenac relative to that of other NSAIDs.

NSAID gastropathy has been attributed in a large part to their suppression of COX-1, which in turn inhibits the prostaglandins that protect the gastric mucosa. The loss of prostaglandins can cause the epithelium of the stomach to become more sensitive to corrosion and, thus, vulnerable to perforations, ulcerations, bleeding and enteropathy [52]. Unlike most nonselective NSAIDs, diclofenac has some coxib-related activity – that is, it shows some selectivity for the COX-2 isoenzyme – although inhibition of COX-1 still occurs [52]. Diclofenac's selectivity toward COX-2 has contributed to decreased potential gastropathy relative to that of other nonselective NSAIDs [110,111], as demonstrated by a systematic review of observational studies that recorded the incidence of upper gastrointestinal bleeding/perforation with several selective and nonselective NSAIDs [110,111]. Specifically, the relative risk (RR) of upper gastrointestinal bleeding or perforation with diclofenac was 3.95 (95% CI: 3.50–4.44), compared with ketorolac (RR: 14.02, 95% CI: 6.89–28.53), piroxicam (RR: 9.25, 95% CI: 7.51–11.38), ketoprofen (RR: 5.68, 95% CI: 4.41–7.31), indomethacin (RR: 5.30, 95% CI: 4.18–6.72) and naproxen (RR: 5.16, 95% CI: 4.33–6.15) [111]. In this review, the one exception to this pattern was ibuprofen, which demonstrated a RR of 2.69 (95% CI: 2.38–3.03); the authors attributed this aberration to the fact that ibuprofen is usually administered at low doses. Consistent with

**Table 3. Frequency of severe adverse reactions with oral diclofenac versus other NSAIDs in short-term trials in the USA.**

| Drug | Dosage (mg/day) | Total patients (n) | Severe adverse reaction, n (%) |
|------|-----------------|--------------------|--------------------------------|
| Diclofenac | 75–200 | 1227 | 57 (4.6) |
| Aspirin | 2400–4800 | 721 | 66 (9.2) |
| Ibuprofen | 2400 | 74 | 4 (5.4) |
| Naproxen | 500 | 92 | 3 (3.3) |
| Indomethacin | 75–125 | 130 | 13 (10.0) |
| Placebo | | 359 | 16 (4.5) |
| *Adapted with permission from* [109]. | | | |

the findings of this review, an endoscopic study involving more than 200 patients showed that ulcers and mucosal lesional disease were less likely to occur with diclofenac sodium than with naproxen. The incidence of ulcers 5 mm or larger was 8% in the diclofenac sodium group and 18% in the naproxen group, the endoscopy score increased from baseline in 29% of patients receiving diclofenac versus 65% of patients receiving naproxen (p < 0.001 between groups), and the endoscopy grades (adjusted for baseline score and ulcer history status) increased from baseline by a mean of 0.41 in the diclofenac group and 1.76 in the naproxen group (p < 0.001 between groups) [110]. In the systematic review described above, the gastropathy potential of diclofenac was similar to that of the selective COX-2 inhibitor meloxicam (RR of upper gastrointestinal bleeding or perforation: 3.95 [95% CI: 3.50–4.44] vs 4.01 [95% CI: 2.68–5.99], respectively) [111].

The cardiovascular safety of diclofenac has been examined in large-scale controlled, population-based and cohort studies, with varying results. Similar rates of thrombotic cardiovascular adverse events were observed in Phase II and III trials with rofecoxib, placebo and comparator nonselective NSAIDs (diclofenac, ibuprofen or nabumetone) [112]. In the CLASS study, which compared standard doses of diclofenac or ibuprofen with celecoxib 800 mg/day in patients with osteoarthritis and rheumatoid arthritis, no increased risk of serious cardiovascular thromboembolic events was observed in the diclofenac group versus the two other groups [113]. However, in a systematic review of population-based controlled observational studies (30 case–control and 21 cohort), oral diclofenac was found to have an elevated risk of cardiovascular events that was consistent with other agents that preferentially inhibit COX-2, but also inhibit COX-1 (e.g., meloxicam RR [95% CI]: 1.20 [1.07–1.33]; etodolac RR [95% CI]: 1.55

[1.28–1.87]) and higher than what was observed with the nonselective NSAIDs that were assessed (e.g., piroxicam RR [95% CI]: 1.08 [0.91–1.30]; naproxen RR [95% CI]: 1.09, [1.02–1.16]; ibuprofen RR [95% CI]: 1.18 [1.11–1.25]) (TABLE 4) [114]. Moreover, diclofenac was associated with earlier and higher cardiovascular risk than rofecoxib in a nationwide cohort study conducted in Denmark [93].

Diclofenac has been troubled by the potential for hepatotoxicity since its introduction [115–117]. A pooled analysis of 41 randomized controlled clinical trials showed that the incidence of hepatotoxicity in patients treated with diclofenac 100–150 mg/day (4.24%) was substantially higher than that in patients treated with celecoxib <200–800 mg/day (1.1%; p < 0.0001), ibuprofen 2400 mg/day (1.53%) and naproxen 1000 mg/day (0.68%) (TABLE 5) [118].

## Topical diclofenac

The safety and tolerability of topical diclofenac have been examined in several clinical trials. A systematic review and meta-analysis of 37 randomized, blinded, controlled trials with various formulations of topical diclofenac showed that although the risk of systemic and local skin reactions experienced with topical diclofenac was slightly higher than with placebo or vehicle, the risk was more than 50% lower than that observed with active topical comparators; as expected, the incidence of local skin reactions was significantly higher with topical diclofenac than with an active oral comparator (p < 0.0001; TABLES 6–8). The rate of local skin reactions was higher with diclofenac solution than with diclofenac patch or gel; nevertheless, these reactions were usually mild-to-moderate and self-resolving [119].

## Oral diclofenac versus topical diclofenac

In general, topical NSAIDs have been shown to be well tolerated compared with oral NSAIDs, with more common local (cutaneous) adverse

**Table 4. Relative risk of cardiovascular events with oral diclofenac versus other NSAIDs, including COX-2 inhibitors, in case–controlled and cohort studies: pooled results.**

| Drug | Pooled relative risk (95% CI) |
|---|---|
| Diclofenac | 1.40 (1.27–1.55) |
| Valdecoxib | 1.05 (0.81–1.36) |
| Piroxicam | 1.08 (0.91–1.30) |
| Naproxen | 1.09 (1.02–1.16) |
| Celecoxib | 1.17 (1.08–1.27) |
| Ibuprofen | 1.18 (1.11–1.25) |
| Meloxicam | 1.20 (1.07–1.33) |
| Indomethacin | 1.30 (1.19–1.41) |
| Rofecoxib | 1.45 (1.33–1.59) |
| Etodolac | 1.55 (1.28–1.87) |
| Etoricoxib | 2.05 (1.45–2.88) |
| Adapted with permission from [114]. | |

signs and laboratory assessments of hepatic and renal function, as well as changes in blood pressure were similar between groups. Topical diclofenac was not associated with hypertension. Rates of serious adverse events were lower with diclofenac (0.9%) than with placebo (1.5%), as were rates of severe adverse events (4.4 vs 7.6%, respectively; p = 0.023). The most common reason for study discontinuation was dry skin (2.5 vs 0.3%, respectively; p = 0.009) [121].

A pooled safety analysis of two 12-week, double-blind, randomized studies that enrolled a total of 927 patients showed that topical diclofenac had a more favorable safety profile than oral diclofenac. Adverse events occurred in a similar proportion of patients receiving diclofenac topical solution (67.1%) and oral diclofenac (64.5%). The most common adverse event with topical diclofenac was dry skin at the application site (24.1 vs 1.9% with oral diclofenac; p < 0.0001). Rates of gastrointestinal adverse events were lower with topical diclofenac compared with oral diclofenac (25.4 vs 39.0%, respectively; p < 0.0001), as were rates of cardiovascular adverse events (1.5 vs 3.5%, respectively; p = 0.055). Oral diclofenac was associated with significantly greater increases in liver enzymes (p < 0.001 for all end points) [122].

events, but fewer systemic (gastrointestinal, renal and hepatic) adverse events [120]. In the clinical study comparing diclofenac topical gel with oral ibuprofen, diclofenac gel was associated with fewer gastrointestinal adverse events and fewer adverse events resulting in discontinuation of therapy [86].

The safety of diclofenac topical solution (1.5% with DMSO) has been compared with placebo and oral diclofenac in pooled analyses of studies in patients with osteoarthritis of the knee. In the pooled analysis of data from 1252 patients enrolled in seven randomized controlled trials of topical diclofenac versus placebo, topical diclofenac was shown to be well tolerated. The most frequently reported adverse event was dry skin, occurring in 33.0% of patients receiving topical diclofenac and 5.0% of patients receiving placebo (p < 0.001). Dyspepsia was the most common gastrointestinal reaction, reported by 7.7% of patients receiving diclofenac and 2.9% of patients receiving placebo (p = 0.002). Changes in vital

## Conclusion

Both oral and topical formulations of diclofenac have been shown to be effective in the treatment of osteoarthritis compared with placebo and other NSAIDs. The chief difference between oral and topical formulations of diclofenac lies in their safety and tolerability profiles. Specifically, although topical diclofenac has demonstrated a higher incidence of cutaneous adverse events than oral diclofenac, oral diclofenac has demonstrated a higher incidence of systemic (gastrointestinal, renal and hepatic) adverse events. In addition, oral diclofenac has demonstrated cardiovascular risk potential similar to or higher

**Table 5. Incidence of hepatotoxicity with oral diclofenac versus celecoxib, ibuprofen and placebo: pooled results from 41 randomized controlled trials.**

| Drug | Dosage (mg/day) | Total patients (n) | Hepatobiliary adverse events, n (%) |
|---|---|---|---|
| Diclofenac | 100–150 | 7639 | 324 (4.24) |
| Celecoxib | <200–800 | 24,933 | 276 (1.11) |
| Ibuprofen | 2400 | 2484 | 38 (1.53) |
| Naproxen | 1000 | 2953 | 20 (0.68) |
| Placebo | | 4057 | 36 (0.89) |
| Adapted with permission from [118]. | | | |

than COX-2 inhibitors in some studies and a higher risk of hepatotoxicity than celecoxib and naproxen. Hence, for patients with osteoarthritis of the knee, topical diclofenac offers an effective and safer therapeutic alternative to oral diclofenac or other NSAIDs. However, because of the chronic nature of osteoarthritis, lengthier studies are necessary to determine any adverse events or effects on efficacy associated with long-term use of oral and topical diclofenac formulations. In addition, *in vivo* and *ex vivo* data exploring whether topical NSAID administration substantially inhibits COX enzyme activity away from the application site are lacking; therefore, a clear determination of whether topical administration produces COX inhibitory effects in other areas of the body (e.g., in cardiovascular or gastrointestinal tissue) cannot be made.

## Future perspective

Since ancient times, people have looked for relief from pain. Early homeopathic treatments led to the widespread use of NSAIDs and specifically, diclofenac. As we look ahead to the next 5 or 10 years, we expect that delivery systems for NSAIDs will continue to evolve, affecting these drugs' pharmacokinetic and pharmacodynamic profiles. In particular, the ability to use NSAIDs to relieve pain and reduce inflammation that targets the joint directly will be extremely important, as the global population continues to age and life spans continue to increase. Since organ systems tend to decline progressively in this population, the avoidance of systemic adverse effects of medications becomes an even higher priority. This need will continue to drive efforts to develop delivery systems that circumvent the

**Table 6. Summary of safety outcomes with topical diclofenac versus nonactive comparator (placebo or vehicle) in blinded, randomized clinical trials: pooled results.**

| Outcome | Trials, N[†] | Pooled results | | | | |
|---|---|---|---|---|---|---|
| | | *Topical diclofenac, n/N[‡] (absolute risk, %)* | *Nonactive comparator (placebo or vehicle), n/N[‡] (absolute risk, %)* | *RR* | *95% CI* | *p-value* |
| All AEs | 20 | 597/1599 (37.3) | 537/1576 (34.1) | 1.11[§] | 1.02–1.20 | 0.012 |
| • Gel | 12 | 281/865 (32.5) | | | | |
| • Patch | 5 | 42/309 (13.6) | | | | |
| • Solution | 3 | 274/425 (64.5) | | | | |
| Withdrawals due to all AEs | 19 | 55/1425 (3.9) | 33/1421 (2.3) | 1.65[§] | 1.10–2.48 | 0.015 |
| • Gel | 11 | 13/611 (2.1) | | | | |
| • Patch | 5 | 5/325 (1.5) | | | | |
| • Solution | 4 | 38/509 (7.5) | | | | |
| Local AEs | 19 | 186/1492 (12.5) | 134/1469 (9.1) | 1.40[§] | 1.15–1.70 | 0.001 |
| • Gel | 12 | 36/865 (4.2) | | | | |
| • Patch | 3 | 5/203 (2.5) | | | | |
| • Solution | 4 | 145/424 (34.2) | | | | |
| Withdrawals due to local AEs | 18 | 26/1344 (1.9) | 9/1313 (0.7) | 2.37[§] | 1.22–4.63 | 0.011 |
| • Gel | 11 | 13/748 (1.7) | | | | |
| • Patch | 5 | 3/325 (0.9) | | | | |
| • Solution | 2 | 10/271 (3.7) | | | | |
| Patient-rated tolerability (average) | 3 | 177/189 (93.7) | 169/189 (89.4) | 1.05[¶] | 0.98–1.11 | 0.14 |
| • Gel | 0 | | | | | |
| • Patch | 3 | 177/189 (93.7) | | | | |
| • Solution | 0 | | | | | |
| Physician-rated tolerability (average) | 4 | 222/229 (96.9) | 212/229 (92.6) | 1.04[¶] | 1.00–1.09 | 0.04 |
| • Gel | 1 | 38/40 (95.0) | | | | |
| • Patch | 3 | 184/189 (97.4) | | | | |
| • Solution | 0 | | | | | |

*†Includes trials with zero events.*
*‡n: Number of patient events; N: number of patients.*
*§RR >1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is greater than with the nonactive comparator. RR <1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is lower than with the nonactive comparator.*
*¶RR >1.00 indicates that patients/physicians believe that topical diclofenac is better tolerated than the nonactive comparator. RR <1.00 indicates that patients/physicians believe that the nonactive comparator is better tolerated than topical diclofenac.*
*AE: Adverse event; RR: Relative risk.*
*Adapted with permission from* [119].

**Table 7. Summary of safety outcomes with topical diclofenac versus active comparator in blinded, randomized clinical trials: pooled results; all studies used diclofenac gel.**

| Outcome | Trials, N[†] | Pooled results | | | | |
|---|---|---|---|---|---|---|
| | | Topical diclofenac, n/N[‡] (absolute risk, %) | Active topical comparator[§], n/N[‡] (absolute risk, %) | RR | 95% CI | p-value |
| All AEs | 11 | 22/995 (2.2) | 45/1007 (4.4) | 0.53[¶] | 0.32–0.89 | 0.018 |
| Withdrawals due to all AEs | 8 | 2/773 (0.3) | 4/780 (0.5) | 0.60[¶] | 0.15–2.46 | 0.44 |
| Local AEs | 9 | 12/621 (1.9) | 14/633 (2.2) | 0.98[¶] | 0.46–2.06 | 0.95 |
| Withdrawals due to local AEs | 6 | 1/575 (0.2) | 1/582 (0.2) | 1.02[¶] | 0.15–7.14 | 0.98 |
| Patient-rated tolerability (average) | 5 | 319/344 (92.7) | 324/347 (93.4) | 0.99[#] | 0.93–1.05 | 0.69 |
| Physician-rated tolerability (average) | 3 | 136/145 (93.8) | 145/152 (95.4) | 0.90[#] | 0.69–1.18 | 0.45 |

[†]Includes trials with zero events.
[‡]n: Number of patient events; N: Number of patients.
[§]Including NSAID gels, a ketoprofen patch, dimethyl sulfoxide gel, biophenyl acetic acid gel and comfrey extract.
[¶]RR >1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is greater than with the nonactive comparator. RR <1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is lower than with the active comparator.
[#]RR >1.00 indicates that patients/physicians believe that topical diclofenac is better tolerated than the nonactive comparator. RR <1.00 indicates that patients/physicians believe that the active comparator is better tolerated than topical diclofenac.
AE: Adverse event; RR: Relative risk.
Adapted with permission from [119].

systemic circulation. In addition to the topical formulations of NSAIDs that have already been introduced, future developments may include further improvements on the direct delivery of NSAIDs where they are needed. In the case of osteoarthritis, this may include sustained-release formulations that can be administered directly into affected joints to provide long-lasting, site-specific anti-inflammatory and analgesic effects. Such innovations would build on the success of this proven class of drugs to improve safety in all patients, especially the elderly.

**Financial & competing interests disclosure**

**Table 8. Summary of safety outcomes with topical diclofenac versus an active oral comparator in blinded, randomized clinical trials: pooled results.**

| Outcome | Trials, N[†] | Pooled results | | | | |
|---|---|---|---|---|---|---|
| | | Topical diclofenac, n/N[‡] (absolute risk, %) | Active oral comparator[§], n/N (absolute risk, %) | RR[¶] | 95% CI | p-value |
| All AEs<br>• Gel<br>• Solution | 4<br>2<br>2 | 350/655 (53.4)<br>37/190 (19.5)<br>313/465 (67.3) | 344/643 (53.5) | 1.01 | 0.92–1.01 | 0.96 |
| Withdrawals due to all AEs<br>• Gel<br>• Solution | 4<br>2<br>2 | 85/655 (12.9)<br>5/190 (2.63)<br>80/465 (17.2) | 107/652 (16.4) | 0.76 | 0.40–1.45[#] | 0.84 |
| Local AEs<br>• Gel<br>• Solution | 3<br>1<br>2 | 135/655 (20.6)<br>0/190 (0)<br>135/655 (29.0) | 16/487 (3.3) | 8.38 | 5.08–13.85 | <0.001 |
| Withdrawals due to local AEs | 2 | 31/311 (10.0) | 1/311 (0.3) | 31.0 | 4.25–225.80 | 0.001 |
| Patient-rated tolerability (average) | 0 | – | – | – | – | – |
| Physician-rated tolerability (average) | 0 | – | – | – | – | – |

[†]Includes trials with zero events.
[‡]n: number of patient events; N: number of patients.
[§]Includes the oral NSAIDs ibuprofen, naproxen and diclofenac.
[¶]RR >1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is greater than with the active comparator; RR <1.00 indicates that the risk of AEs or withdrawals due to AEs with topical diclofenac is lower than with the active comparator.
[#]Random effects, due to statistically significant heterogeneity ($\chi^2$ test for heterogeneity p = 0.05).
AE: Adverse event; RR: Relative risk.
Adapted with permission from [119].

## Executive summary

### Mechanism of action
- Diclofenac exerts its anti-inflammatory and analgesic effects primarily through inhibition of COX-2, thus preventing the conversion of arachidonic acid into prostaglandins, thromboxanes and prostacyclins.
- Diclofenac also inhibits COX-1, which reduces the protective effects of this enzyme and the prostaglandins it produces on gastric mucosa and renal function.

### Pharmacokinetic properties
- Oral diclofenac:
  - Complete and rapid absorption, achieving peak plasma concentrations 10–30 min after administration;
  - Peak plasma concentration and area under the plasma concentration–time curve that are linearly dose-related over the range of 25–150 mg oral doses;
  - Lipophilic NSAID that achieves its highest concentrations in blood;
  - Highly protein bound (≥99.5%), chiefly to serum albumin;
  - Apparent volume of distribution of 0.14;
  - Penetration of synovial fluid in patients with osteoarthritis and less-rapid elimination from this site than from plasma;
  - First-pass metabolism, with approximately 60% of unchanged drug reaching the systemic circulation.
- Topical diclofenac:
  - High rate of transdermal penetration and is absorbed from the application site throughout the dosage period;
  - Approximately 6% of the applied dose is absorbed percutaneously, with low systemic exposure;
  - Extensively protein bound, resulting in a low volume of distribution;
  - Preferential distribution to synovial fluid rather than plasma, resulting in therapeutic concentrations in the target tissues and rapid decline of concentrations in side-effect compartments such as the cardiovascular and renal systems;
  - Concentration in the synovial membrane that is significantly lower than that of oral diclofenac;
  - Metabolism mainly in the liver to mostly inactive metabolites and excretion mainly in the urine, but also in the bile.

### Clinical efficacy in osteoarthritis
- Randomized clinical trials with oral diclofenac:
  - Oral formulations of diclofenac have been shown to be statistically and clinically superior to placebo with respect to analgesic efficacy and functional improvement;
  - Oral formulations of diclofenac were shown to have efficacy comparable or superior to that of other oral NSAIDs.
- Randomized clinical trials with topical diclofenac:
  - Topical formulations of diclofenac have been shown to be superior to placebo in the treatment of osteoarthritis of the knee;
  - Diclofenac topical solution was shown to be the only topical NSAID approved in the USA to show equal efficacy with oral diclofenac in osteoarthritis of the knee.

### Safety & tolerability
- Oral diclofenac has demonstrated:
  - A gastropathy potential somewhat lower than that of other nonselective NSAIDs (e.g., naproxen and ibuprofen) and similar to that of the selective COX-2 inhibitor meloxicam;
  - A cardiovascular risk potential similar to or higher than that of COX-2 inhibitors;
  - A higher risk of hepatotoxicity than celecoxib and naproxen.
- Topical diclofenac has demonstrated:
  - A lower risk of local and systemic reactions than with other topical analgesics;
  - A higher incidence of cutaneous adverse events, but fewer systemic (gastrointestinal, renal and hepatic) adverse events than oral diclofenac.

### Drug interactions
- Significant drug interactions have been shown between oral diclofenac and aspirin, lithium, digoxin, methotrexate, cyclosporine, cholestyramine and colestipol.
- Topical diclofenac is not associated with clinically meaningful drug–drug interactions.

### Dosage & administration
- Oral diclofenac has been studied in doses of 75–150 mg/day in the treatment of osteoarthritis.
- Topical diclofenac is administered as follows:
  - Diclofenac sodium topical 1% gel: 4 g four-times daily for lower extremities; 2 g four-times daily for upper extremities;
  - Diclofenac sodium 1.5% topical solution: 40 drops on each painful knee, four-times daily;
  - Diclofenac epolamine topical patch 1.3%: one patch applied to the painful area twice daily.

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