REVIEW ARTICLE

Clin Drug Invest 2007; 27 (3): 163-195
1173-2563/07/0003-0163/$44.95/0

Diclofenac Potassium 12.5mg Tablets for Mild to Moderate Pain and Fever

A Review of Its Pharmacology, Clinical Efficacy and Safety

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Contents

Abstract

Non-prescription (over-the-counter [OTC]) analgesics are used for the short-term treatment of acute painful conditions of mild to moderate intensity in everyday life. Well documented safety and efficacy, a rapid onset of action and a flexible daily dosing regimen are essential in this context. Film-coated, immediate-release, low-dose diclofenac potassium, developed for OTC use, offers a flexible daily dosing regimen with an initial dose of two tablets (2 × 12.5mg) followed by one or two tablets up to a maximum daily dose of six tablets (75 mg/day). The maximum plasma drug concentration is reached 30 minutes after administration, and the mean terminal half-life is 1–2 hours, allowing a 4- to 6-hour duration of activity, depending on the condition.

Thirteen randomised, double-blind trials with both placebo and active controls have demonstrated the efficacy of diclofenac potassium 12.5mg tablets in conditions suitable for treatment with OTC medication, for example, acute lower back pain, headache, acute pain after dental extraction, symptoms of cold and influenza (including fever), and dysmenorrhoea. A single dose of diclofenac potassium 12.5mg is the lowest recommended effective dose. A two-tablet single dose of 25mg is at least as effective as ibuprofen 400mg. A flexible dosing regimen of an initial two tablets followed by one or two tablets up to a total daily dose of 75mg is as effective as ibuprofen used in comparable fashion up to a total daily dose of 1200mg.

The incidence of adverse events in patients taking single or multiple doses of diclofenac potassium is similar to that of ibuprofen and placebo. In a safety study conducted to compare diclofenac potassium with ibuprofen for up to 3 months in patients with osteoarthritis of the knee, no differences in the pattern of adverse events were noted. There was no evidence of either hepatic injury or cardiovascular safety-related issues at any time during the study.

Patients are generally capable of taking diclofenac potassium appropriately. A maximum OTC treatment duration of 5 days for pain and 3 days for fever is recommended.

1. Introduction

Diclofenac is a potent NSAID with anti-inflammatory, analgesic and antipyretic properties. Chemically it is a phenylacetic acid derivative. Oral diclofenac is available in sodium- or potassium-salt formulations. Diclofenac sodium was first marketed in Japan in 1974 as Voltaren® [1] for anti-inflammatory use. Since its introduction, diclofenac sodium has been used by >1 billion patients. Diclofenac potassium was introduced in the early 1980s as Cataflam®/Voltaren Rapid®, primarily for analgesic indica-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tions. Currently, it is approved as an over-the-counter (OTC) medication in many countries around the world, for example Germany, Switzerland, Italy, Spain, The Netherlands, Norway, Sweden, Hungary, Poland, Iceland, Czech Republic, Slovakia, Latvia, Lithuania, Russia, Australia, New Zealand and several countries in South America.

This article gives an overview of the relevant pharmacological aspects, clinical efficacy and tolerability of low-dose diclofenac and underlines its suitability for non-prescription use.

2. Pharmacodynamics

Diclofenac is a typical, potent, non-selective inhibitor of cyclo-oxygenase (COX), which reduces the formation of the proinflammatory and nociceptive prostaglandins. In addition, diclofenac inhibits the synthesis of prostacyclin and thromboxane and downregulates the lipoxygenase pathway.[1] Furthermore, it has been reported to decrease levels of the proinflammatory cytokine interleukin-6 and substance P in the synovial fluid and plasma of patients with rheumatoid arthritis.[2]

The concentrations required to produce 50% inhibition of enzyme activity (IC_{50}) of diclofenac for COX-1 and COX-2 *in vitro* in a human whole blood assay are 0.075 µmol/L and 0.038 µmol/L, respectively, and the concentration of diclofenac that inhibits COX-2 activity by 80% (IC_{80}) produces approximately 70% inhibition of COX-1.[3] The concentrations reached *in vivo* during an ascending dose pharmacokinetic study (figure 1) were well within the range of the *in vitro* and *ex vivo* COX inhibitory concentrations.[4] Diclofenac belongs to the class of drugs presenting almost a similar level of inhibition for both COX-1 and COX-2 (<5-fold COX-2 selective).[3] The IC_{50} of diclofenac indicates that it is slightly more specific in inhibiting the activity of COX-2 than COX-1; however, no major difference is observed at the therapeutically relevant inhibition potency IC_{80}.

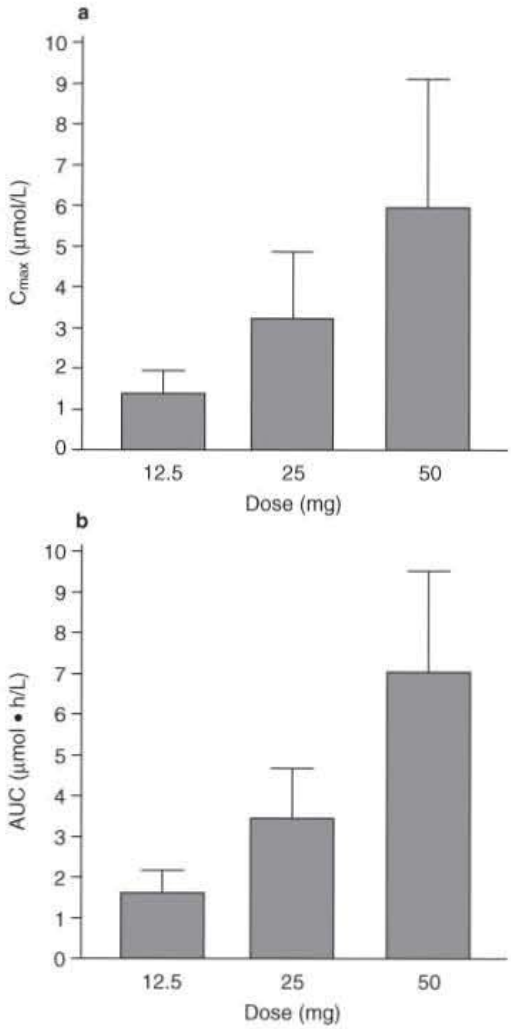

Fig. 1. Ascending dose pharmacokinetics of diclofenac in study P33[4]: (**a**) maximum concentration (C_{max}) and (**b**) area under the plasma concentration-time curve (AUC) at different doses.

Diclofenac is highly bound to serum protein (99.7 %), mainly albumin, and it is a weak acid (pKa = 4.0) and amphiphilic. Because of these characteristics, diclofenac distributes unequally. It reaches high concentrations and persists in inflamed tissue, as is demonstrated by its measured concentration in the synovial fluid in rheumatic diseases, while the elimination in the central body compartment such as blood, liver and kidney is fast with a half-life of 1–2 hours.[5,6] NSAIDs such as diclofenac associate and dissociate with albumin rapidly. The ongoing dissociation makes bound drug available for transvascu-

lar exchange towards the target compartment and thereby diminishes the pharmacokinetic significance of binding measured *in vitro*.[6]

It is now well established that COX-2 plays a major role in nociception if inflammatory processes are involved. However, there is also evidence that COX-1 may play an important role in the local transmission and central integration of pain, and that simultaneous inhibition of both COX-1 and COX-2 is generally superior to inhibition of either alone.[7] This is especially relevant because the anti-inflammatory effect of diclofenac is minimal at the doses used in OTC medications, and the objective in this setting is pain relief rather than an anti-inflammatory action.

3. Pharmacokinetic Properties

Immediate-release, sugar-coated diclofenac potassium tablets dissolve rapidly in the stomach and the time to maximum concentration (t_{max}) is approximately 30 minutes. In contrast, enteric-coated diclofenac sodium (Voltaren®, Voltarol®) dissolves in the more alkaline environment of the duodenum (t_{max} >2 hours). The two salts of diclofenac, diclofenac potassium and diclofenac sodium, have the same mechanism of action and identical pharmacodynamic effects, are absorbed to the same extent following oral administration,[8] and are distributed, biotransformed and eliminated in identical fashion.

3.1 Absorption

The bioequivalence of diclofenac potassium has not been tested in a pharmacokinetic study of standard crossover design. However, several trials have measured plasma concentrations after various doses of either diclofenac sodium or diclofenac potassium were administered to fasted individuals in either buffered solution (pH 7.5) or plain water. An analysis of the combined data from these studies (95 individuals given diclofenac sodium and 21 given diclofenac potassium) shows that the two diclofenac salts are equivalent with respect to the rate and extent of absorption, as measured by maximum concentration (C_{max}) and area under the plasma concentration-time curve (AUC), respectively, when normalised by dose.[8] Dose-normalised AUCs were 27.7 ± 8.6 nmol • h/L • µmol for diclofenac sodium and 24 ± 6.3 nmol • h/L • µmol for diclofenac potassium.

Diclofenac is completely absorbed. First-pass metabolism accounts for approximately 40% of an oral dose, which means that about 60% of the administered dose reaches the systemic circulation as unchanged diclofenac.[9] Absolute bioavailability of low-dose diclofenac potassium from tablet formulations was investigated by Hinz et al.[10] The mean absolute bioavailability of diclofenac potassium 12.5mg (administered as a single dose of a 12.5mg capsule-shaped tablet) and 25mg (administered as a single dose of two 12.5mg tablets) was 63.1% in the 12.5mg group and 65.1% in the 25mg group, results that were consistent with those of a previous investigation[11,12] showing 50–60% oral availability. The 90% CIs for the AUC_∞ and AUC_t (t = 4h) ratios for the two oral regimens were 82.6, 103.4 (point estimate 92.4) and 86.2, 112.9 (point estimate 98.6), respectively, which are within the acceptance criteria for bioequivalence (80, 125).[13] In conclusion, the study demonstrated that diclofenac potassium is rapidly and well absorbed at low doses of 12.5 and 25mg and shows linear pharmacokinetics.

After ingestion of one or two diclofenac potassium 12.5mg tablets the median t_{max} was approximately 30 minutes.[10,14,15] With increasing doses of diclofenac potassium the corresponding AUC as well as the C_{max} were proportionally increased and dose linearity has been confirmed for the low-dose range of 12.5–50mg (figure 1).[4] In volunteers given a high-fat breakfast, the C_{max} of a single dose of diclofenac potassium 12.5mg was decreased and the t_{max} increased.[15] The AUC and the elimination half-life ($t_{½\beta}$), on the other hand, were not affected.

Thus, the total amount of drug absorbed does not seem to be affected by the presence of food in the stomach.

The bioequivalence of several rapid-release formulations of low-dose diclofenac potassium (capsules, and sugar- or film-coated tablets in a variety of shapes) has been confirmed in several bioavailability studies taking into account intra-subject variability.[14-16] The film-coated tablets were used in the diclofenac potassium 12.5mg phase III development programme.

Since the quantities of diclofenac potassium administered are usually lower than those of diclofenac sodium, the potential for end-organ failure or metabolic interaction with diclofenac potential is accordingly lower. Thus, it is relevant to note that the pharmacokinetic data presented in the following sections are from studies of high-dose diclofenac sodium, not low-dose diclofenac potassium.

3.2 Distribution

Diclofenac is 99.7% protein bound with a volume of distribution of 0.12–0.17 L/kg.[17]

3.3 Biotransformation

After absorption, diclofenac is metabolised by both phase I and II enzymes.[18] The biotransformation of diclofenac includes glucuronidation of several phenolic metabolites, which are generated by single and multiple hydroxylation and methoxylation. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac. The aromatic hydroxylated metabolite and the conjugated metabolites have been reported to be pharmacologically inactive.[18] The metabolism of diclofenac *in vivo* and in liver microsomes has recently been demonstrated to be similar in six different cytochrome P450 (CYP) enzyme 2C9 genotypes,[19] with no evidence of polymorphism (figure 2).[18]

3.4 Elimination

Total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min.[12] The terminal $t_{½}\beta$ in plasma is 1–2 hours. Four of the metabolites, including the two active ones, also have a short plasma $t_{½}\beta$ of 1–3 hours. A fifth, virtually inactive, metabolite (3′-hydroxy-4′-methoxy-diclofenac) has a much longer plasma half-life. Approximately 60% of the administered dose of diclofenac potassium is excreted in the urine as the glucuronide of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates.[20] Less than 1% is excreted unchanged. The remainder of the dose is eliminated as metabolites through the bile in the faeces.[17]

3.5 Influence of Age and Renal or Hepatic Function

No relevant age-dependent differences in the absorption, metabolism or excretion of diclofenac have been observed. Renal impairment does not result in accumulation of diclofenac with the usual dosage schedule.[20] At a creatinine clearance <10 mL/min, the steady-state plasma concentrations of the hydroxy metabolites are about four times higher than in healthy individuals. However, these metabolites are ultimately cleared through the bile. Nevertheless, neither chronic hepatitis nor non-decompensated cirrhosis affect the pharmacokinetics or metabolism of diclofenac.[21] While active alcoholic cirrhosis may increase the AUC of diclofenac, chronic active hepatitis has also been shown to not affect the pharmacokinetics of diclofenac.[22]

3.6 Pregnancy and Lactation

During pregnancy, as with all NSAIDs, diclofenac should be used only for compelling reasons and only in the lowest effective dose, particularly in the last trimester because of the risk of

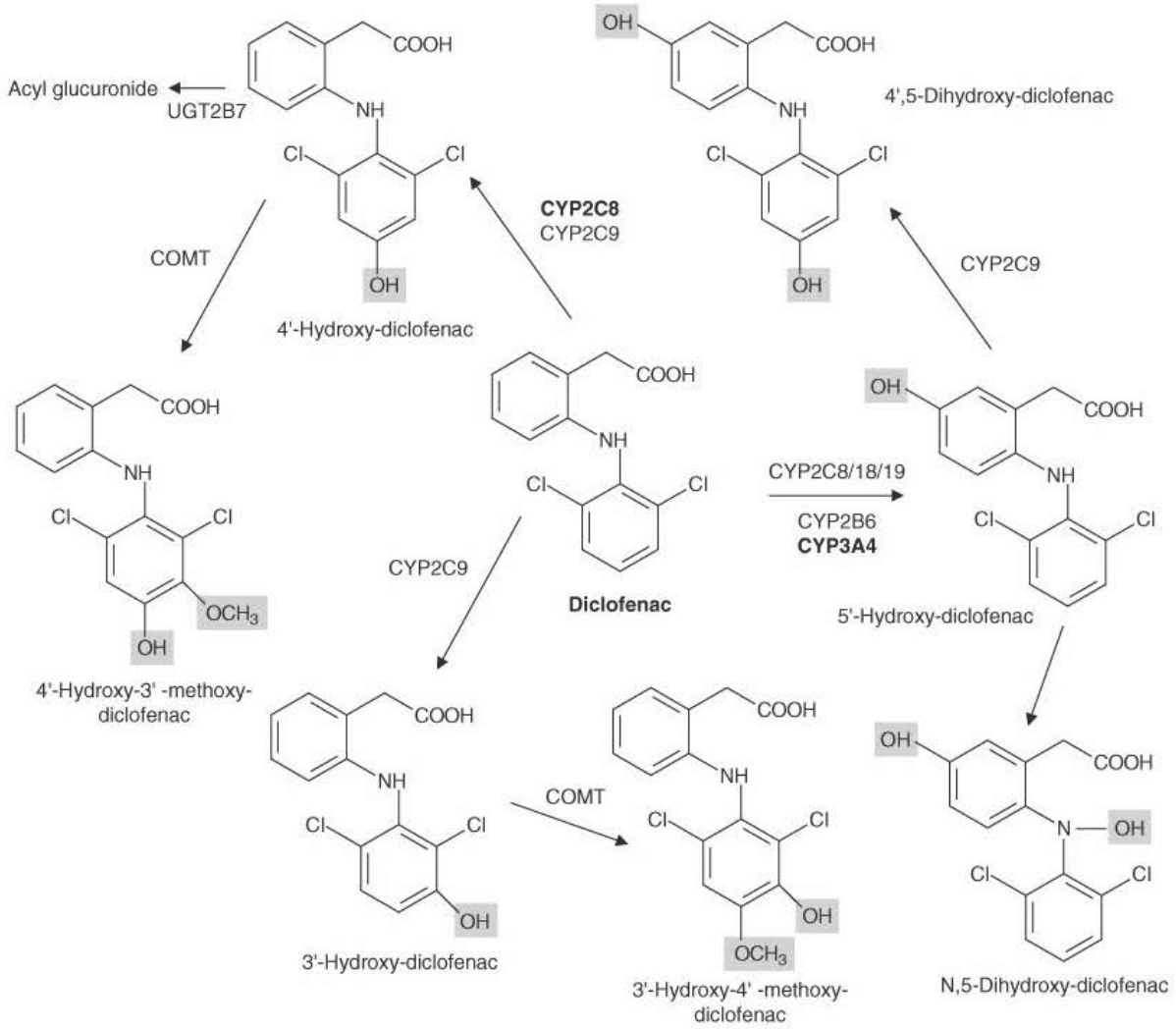

Fig. 2. Biotransformation of diclofenac. **COMT** = catechol-O-methyltransferase; **CYP** = cytochrome P450; **UGT** = uridine diphosphate glucuronosyltransferase.

uterine inertia and/or premature closure of the ductus arteriosus.[23]

Diclofenac passes into breast milk in very low quantities when oral doses of 50mg are taken every 8 hours.[24] The risk to the infant of diclofenac-related adverse effects should therefore be minimal, especially with the recommended OTC dosing regimen (≤75 mg/day). Although in two studies diclofenac could not be detected in breast milk, the presence of diclofenac metabolites in breast milk has not yet been excluded.[9]

3.7 Summary

The pharmacokinetics of diclofenac, including its potassium salt, are well known. Diclofenac potassium 12.5mg is provided in a rapid-release formulation, which means that it has a more rapid onset of pharmacodynamic activity. The elimination of diclofenac is complete. At low doses it is unlikely that other exogenous factors such as commonly used drugs or endogenous factors such as age or impaired clearing-organ functions cause any critical changes in the pharmacokinetics of diclofenac. Based on the wide therapeutic experience with diclofenac and

Table I. Comparison of some characteristic pharmacokinetic parameters of non-prescription analgesics and diclofenac

Compound	Half-life (h)	t_{max} (h)	Metabolism (e.g. site, metabolites and enzymes)	Excretion
Aspirin (acetylsalicylic acid)	0.25	1–2	Liver and other tissue	Renal
Salicylic acid	2–3[a] 15–30[b] 15–30[b]		Salicyluric acid, salicyl phenolic glucuronide	Renal
Ibuprofen (R/S)[25-28]	2–3	1–2	Hydroxylation, carboxylation (2-hydroxy-ibuprofen and carboxy-ibuprofen) followed by conjugation[29] formation of R(−)-thioesters	Renal
Naproxen	12–25	2–4[30,31]	6-O-desmethylnaproxen[32] (CYP2C9, CYP2C18)	Renal
Diclofenac potassium	1–3	0.4–0.8	Liver: CYP2C8, CYP2C9, CYP3A4	Renal

a For low doses of salicylates.

b Because of saturable kinetics, half-life increases to 15–30h.

CYP = cytochrome 450 enzyme; **R/S** = racemic (containing equal quantities of R(−)- and S(+)-ibuprofen); **t_{max}** = time to maximum concentration.

taking into account the known pharmacokinetics of the drug, low-dose diclofenac potassium pharmacokinetics seem appropriate for a non-prescription status.

3.8 Comparison of the Pharmacokinetics of Low-Dose Diclofenac Potassium with Established Non-Prescription Analgesics

There are relatively few non-prescription analgesics containing chemically defined compounds on the market. Aspirin (acetylsalicylic acid), paracetamol, ibuprofen and naproxen appear to be the most relevant compounds for comparison with diclofenac potassium.

Important comparative pharmacokinetic parameters of diclofenac and other OTC analgesics are summarised in table I.[25-32]

Diclofenac is a non-chiral compound. Naproxen is a stereochemically pure drug, of which the S-enantiomer is available on the market. Ibuprofen is chiral and the marketed product is racemic, containing equal quantities of R(−)- and S(+)-ibuprofen. The active S(+)-enantiomer (eutomer) is capable of inhibiting COX at clinically relevant concentrations. R(−)-ibuprofen is not a COX inhibitor. Even if the inactive enantiomer (distomer) undergoes metabolic inversion to the active eutomer, inactive R(−)-ibuprofen may represent an additional metabolic load for the organism. Additionally, metabolic inversion may be impaired in hepatic dysfunction, resulting in delayed elimination of ibuprofen.[33]

Rapid onset of analgesia is essential in the treatment of acute pain. The observed t_{max} for diclofenac is, in general, shorter than that of naproxen and similar to that of ibuprofen, indicating that the onset of the analgesic effect of diclofenac should occur rapidly, as confirmed by several clinical studies.[34-37]

The available OTC analgesics differ markedly in their metabolism. Diclofenac is metabolised by phase I hydroxylation and by phase II conjugation, with the CYP enzyme 2C subfamily (CYP2C9, CYP2C8) playing a key role. Naproxen is metabolised to a 6-O-desmethyl derivative and then conjugated with glucuronide. When racemic ibuprofen is administered to humans, a substantial fraction (50–90%) of the dose of R(−)-ibuprofen undergoes metabolic inversion to yield S(+)-ibuprofen.[29,38] However, the degree of this inversion varies from individual to individual. Moreover, the extent of inversion appears to be reduced when the racemate is given to patients experiencing acute pain.[39] The chiral inversion is unidirectional from the inactive R(−)- to the active S(+)-enantiomer.[40]

Both isomers are metabolised in the liver by hydroxylation and carboxylation to 2-hydroxyibuprofen and carboxyibuprofen followed by conjugation.[29]

The R(−)-enantiomer of ibuprofen becomes involved in pathways of lipid metabolism by forming coenzyme A thioesters.[41,42] The resulting interaction leads to the formation of hybrid triglycerides, which may impair membrane function or endogenous lipid synthesis.[43] Additionally, hybrid triglycerides result in depots of slowly eliminated ibuprofen ($t_{1/2}\beta$ >100 hours).

There are also marked differences in the $t_{1/2}\beta$. The apparent $t_{1/2}\beta$ of aspirin is approximately 18–40 minutes.[44,45] Aspirin is rapidly hydrolysed in the body to salicylic acid. Correspondingly, the decrease in plasma aspirin concentration is associated with a rapid increase in salicylic acid concentration.[46] The average plasma half-life of salicylic acid is about 3 hours.[45] Salicylate, but not aspirin itself, exhibits Michaelis-Menten (saturable) pharmacokinetics. At low doses, the elimination is first order and the half-life remains constant at 2–3 hours. However, at higher doses, the enzymes become saturated and the apparent half-life can increase to 15–30 hours. The effect of aspirin is therefore prolonged as a result of irreversible acetylation of COX and metabolism to salicylate. Similarly, the half-life for naproxen with values between 12 and 25 hours is also relatively long, resulting in prolonged inhibition of gastric COX-1. Scharf et al. have hypothesised that NSAIDs with longer half-lives are of particular concern as they may be more toxic in the gastrointestinal (GI) tract, particularly in the elderly, and that NSAIDs with short half-lives are associated with lower GI toxicity than NSAIDs with long half-lives.[47] This, combined with the low doses used and the common lack of risk factors, could be a factor contributing to the excellent GI tolerability of ibuprofen and diclofenac, which are among the NSAIDs with the shortest half-lives.

4. Therapeutic Efficacy

The therapeutic efficacy and safety of diclofenac potassium administered as a single dose (12.5mg, 25mg), or in multiple doses of 25mg up to 75 mg/day, has been demonstrated in randomised, double-blind, placebo-controlled trials with active comparators (ibuprofen, paracetamol, aspirin) in established pain and fever models. These include dental pain after extraction of impacted third molars, acute benign lower back pain (lumbago), episodic tension-type headache, fever and sore throat, cold and influenza-like symptoms, and menstrual pain arising from primary dysmenorrhoea. An overview of the clinical trials and a summary of the outcomes are presented in table II.

All the efficacy studies described in this article included timed evaluations of pain intensity and pain relief or fever reduction over the first 6 hours after the first dose. In those studies that emphasised pain relief, the primary outcome for first-dose efficacy was either the pain-relief assessment at a specific timepoint or an aggregated total pain relief (TOTPAR-t_a) outcome, defined as the area under the pain relief-versus-time curve from hour zero to a fixed post-dosing timepoint. The secondary outcome, sum of pain intensity difference (SPID-t_a), is defined as the area under the pain-intensity difference from the baseline-versus-time curve from hour zero to a fixed post-dosing timepoint.

4.1 Dental Pain

Dental pain is widely accepted as a validated model for documenting the efficacy of analgesics. The efficacy of low doses of diclofenac potassium against moderate-to-severe pain after the extraction of impacted third-molar teeth has been evaluated in several randomised, placebo-controlled studies involving 1259 patients aged 16–75 years (table II).[48,50-52] Single-dose, dose-ranging studies conducted with diclofenac potassium 6.25, 12.5 and

Table II. Efficacy studies of over-the-counter indications: summary of trial designs and results

Study	Study design[a]	Treatment dose (mg)	Total randomised	Primary efficacy parameters (secondary parameters)	Evaluation of efficacy
Dental pain (impacted third-molar extraction)					
P34[48]	mc, pg, md	Diclo-K FMD Par FMD Pbo	245	FD: PR 1h MD: ES-GE (FD: PR and PID; 0.5–6h: SPID-3, TOTPAR-3, FD-GE; MD: TTR, daily-GE)	After FD and after MD: Diclo-K and Par > Pbo Diclo-K = Par
P21[49]	sc, pg, sd	Diclo-K 12.5 Diclo-K 25 Diclo-K 50 ASA 650 Pbo	253	TOTPAR-8 (PR and PID over 8h, TOTPAR-3, -4, SPID-3, -4, -8, TTR, GE)	Diclo-K 50, 25, 12.5 > Pbo ASA 650 > Pbo Diclo-K 50 ≥ Diclo-K 25 Diclo-K 50 and 25 > ASA 650 and Diclo-K 12.5 Diclo-K 12.5 = ASA 650
P22[50]		Diclo-K 6.25 Diclo-K 12.5 Diclo-K 25 ASA 650 Pbo	253	TOTPAR-6 (PR and PID over 6h, TOTPAR-3, -4, SPID-3, -4, -6, TTR, GE)	Diclo-K 25, 12.5, 6.25 > Pbo ASA 650 > Pbo Diclo-K 25 = ASA 650 Diclo-K 12.5 = Diclo-K 6.25 Diclo-K 25 and ASA 650 > Diclo-K 12.5 and 6.25
P23[51]	2 centres, pg, sd	Diclo-K 6.25 Diclo-K 12.5 Diclo-K 25 Ibu 200 Pbo	252		Diclo-K 25 and Ibu 200 > Pbo Diclo-K 12.5 and 6.25 ≥ Pbo Diclo-K 25 = Ibu 200 Diclo-K 12.5 = Diclo-K 6.25 Diclo-K 25 and Ibu 200 > Diclo-K 12.5 and 6.25
P24[52]	mc, pg, sd	Diclo-K 6.25 Diclo-K 12.5 Diclo-K 25 Ibu 200 Pbo	255		Diclo-K 25, 12.5, 6.25 > Pbo Ibu 200 > Pbo Diclo-K 25 = Ibu 200 Diclo-K 12.5 = Diclo-K 6.25 Diclo-K 25 and Ibu 200 > Diclo-K 12.5 Diclo-K 25 and Ibu 200 ≥ Diclo-K 6.25
Episodic tension-type headache					
P35[53]	mc, pg, sd	Diclo-K 12.5 Diclo-K 25 Ibu 400 Pbo	489[b]	PID and PR for 4h (PID-6h, PR-6h, TOTPAR-3, TOTPAR-6, TTR, GE)	Diclo-K 25, 12.5 and Ibu 400 > Pbo Diclo-K 25 = Diclo-K 12.5 = Ibu 400
P39[54]		Diclo-K 12.5 Diclo-K 25 Ibu 400 Pbo	620[b]	TOTPAR-3 (PID and PR over 6h, TOTPAR-6, SPID-3, SPID-6, TTR, GE)	Diclo-K 25, 12.5 and Ibu 400 > Pbo Diclo-K 25 = Diclo-K 12.5 = Ibu-400

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Table II. Contd

Study	Study design[a]	Treatment dose (mg)	Total randomised	Primary efficacy parameters (secondary parameters)	Evaluation of efficacy
P32[55]		Diclo-K 12.5 Diclo-K 25 Par 1000 Pbo	516	PID and PR over 4h (PR-6h, PID-6h, TTR, GE)	Diclo-K 25 = Diclo-K 12.5 = Pbo Par-1000 ≥ Pbo Diclo-K 25 = Diclo-K 12.5 = Par-1000
Fever and sore throat					
P36[56]	mc, pg, md	Diclo-K FMD Ibu FMD Pbo	345	FD: Change in temperature over 6h MD: ES-GE of overall relief (FD and daily GE's of overall relief, of fever, headache and muscle/joint pain, TTR)	After FD and after MD: Diclo-K and Ibu > Pbo Diclo-K = Ibu
P37[57]		Diclo-K FMD Ibu FMD Pbo	356		After FD and after MD: Diclo-K and Ibu > Pbo Diclo-K = Ibu
P38[58]	mc, pg, sd	Diclo-K 6.25 Diclo-K 12.5 Diclo-K 25 Par 1000 Pbo	343	$AUTC_{0\text{-}4h}$ (Change in temperature and PR over 6h, TOTPAR-4, TTR, GE)	Diclo-K 25, 12.5, 6.25 > Pbo Par 1000 > Pbo Diclo-K 25 ≥ Diclo-K 6.25 Diclo-K 25 and 12.5 ≥ Par 1000 Diclo-K 6.25 = Par 1000
Acute benign lower back pain					
P40[59]	mc, pg, md	Diclo-K FMD Ibu FMD Pbo	372	FD: TOTPAR-3 MD: ES-GE (FD: PID and PR over 6h, FD-GE, TOTPAR-6, SPID-3, -6; MD: daily-GE, TTR, PID and R-M at site visits)	After FD: Diclo-K > Pbo, Ibu ≥ Pbo, Diclo-K ≥ Ibu After MD: Diclo-K and Ibu > Pbo, Diclo-K = Ibu
Mild to moderate primary dysmenorrhoea					
P26[60]	mc, co, md	Diclo-K FMD Ibu FMD Pbo	174	PID and PR over 4h (FD: SPID-3, TOTPAR-3, FD-GE; MD: daily-GE, TTR, ES-GE)	FD: Diclo-K and Ibu > Pbo, Ibu ≥ Diclo-K MD: Diclo-K and Ibu > Pbo, Diclo-K = Ibu

a All studies were randomised, double-blind, double-dummy and placebo-controlled.

b Treated patients only. Patients were administered treatment only if they experienced a headache within 30 days of randomisation.

ASA = aspirin (acetylsalicylic acid); **AUTC** = area under the temperature-time curve; **co** = crossover; **Diclo-K** = diclofenac potassium; **ES** = end of study; **FD** = first dose; **FMD** = flexible multiple dosing regimen; **GE** = global evaluation; **Ibu** = ibuprofen; **mc** = multicentre; **md/MD** = multiple dose; **Par** = paracetamol; **Pbo** = placebo; **pg** = parallel-group; **PID** = pain intensity difference; **PR** = pain relief rating; **R-M** = Roland-Morris disability questionnaire; **sc** = single-centre; **sd** = single dose; **SPID-x** = sum of pain intensity differences up to x hours; **TOTPAR-x** = sum of pain relief ratings up to x hours; **TTR** = time to rescue medication. > indicates greater efficacy; = indicates similar efficacy; ≥ indicates greater efficacy on specific outcomes.

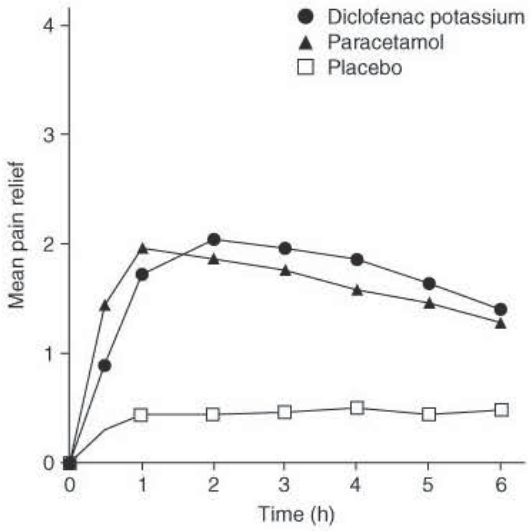

Fig. 3. Mean relief of pain with diclofenac potassium, paracetamol or placebo at different timepoints following dental extraction in study P34.[48] The pain relief scores in both active groups were significantly higher than placebo at all timepoints ($p < 0.01$). At 30 minutes only, pain relief was significantly greater for paracetamol than for diclofenac potassium ($p < 0.01$). Pain relief scale is: 0 = no relief; 1 = a little; 2 = some; 3 = a lot; 4 = complete.

25mg evidenced the logarithmic dose-response profile of diclofenac potassium.[48,50-52] Timepoint-by-timepoint comparisons of least square means for pain relief, and pain-intensity differences for each treatment group, show a classic dose-proportionality profile with regularly increasing efficacy and a flat placebo line.

Over 6 hours a single dose of diclofenac potassium 25mg tended to provide better relief than the two comparator drugs, aspirin 650mg and ibuprofen 200mg, and the two lower doses of diclofenac potassium 6.25 and 12.5mg, especially between 1 and 3 hours.[48,50-52]

Efficacy was confirmed in the multiple-dose study P34.[48] This randomised, double-blind, double-dummy, placebo-controlled, multicentre, parallel-group trial compared the efficacy of an initial dose of diclofenac potassium 25mg up to 75 mg/day with an initial dose of paracetamol 1000mg up to 3000 mg/day and placebo over 2 days. This study showed that an initial dose of diclofenac potassium 25mg effectively relieves pain from dental extraction for up to 6 hours (figure 3) and that the flexible multiple-dose regimen is suitable for managing pain over the normal course of 2 days. This study also demonstrated that after the initial dose and during re-medication, multiple doses of diclofenac potassium 12.5mg, given as one or two tablets as needed, provided a consistent profile of analgesia similar to that obtained with paracetamol 1000mg tablets and significantly better than placebo.

4.2 Acute Lower Back Pain

The efficacy of the flexible dosing regimen of diclofenac potassium 12.5mg in a daily dose of 25–75mg versus ibuprofen 2 × 200mg in a daily dose of 400–1200mg or placebo was investigated in study P40, a 7-day trial in 370 patients with at least moderately acute lower back pain, such as lumbago (table II).[59] This study showed that diclofenac potassium was at least as effective as ibuprofen, with a suggestion of superior efficacy based on statistically significant superiority in a subset of efficacy outcomes. The primary efficacy outcome for the first dose of two tablets was TOTPAR-3 – the time-weighted sum of the pain relief scores after 3 hours. Secondary first-dose outcomes included TOTPAR-6, SPID-3 and SPID-6, time to rescue or re-medication, and the end-of-first-dose global efficacy assessment. Diclofenac potassium 2 × 12.5mg was significantly superior to placebo on TOTPAR-3 ($p = 0.03$). Diclofenac potassium was also superior on all other first-dose outcomes, except for time to rescue or re-medication, for which the three treatments did not differ. Diclofenac potassium was also significantly superior to ibuprofen 2 × 200mg on SPID-3 ($p = 0.04$). Ibuprofen 2 × 200mg was superior to placebo only on the end-of-first-dose global efficacy assessment.

Flexible dosing outcomes in this study included daily and end-of-study global efficacy assessments, time to rescue or re-medication, and pain-intensity assessment on a visual analogue scale (VAS)

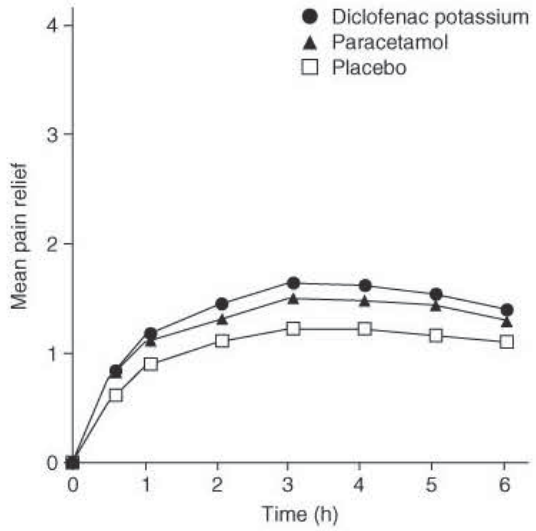

Fig. 4. Mean relief of acute lower back pain with diclofenac potassium, ibuprofen or placebo at different timepoints after initial dosage in study P40.[59] The pain relief scores for diclofenac potassium were significantly higher than for placebo over 2–5 hours ($p < 0.05$). The scores for ibuprofen did not differ significantly from placebo at any timepoint. Pain relief scale is: 0 = no relief; 1 = a little; 2 = some; 3 = a lot; 4 = complete.

[100mm] and the Eifel algofunctional questionnaire at study-site visits on day 3 (visit 2) and day 8 (visit 3).[59] The flexible dosing regimens of both diclofenac potassium and ibuprofen were significantly superior to placebo on the end-of-study global evaluation of treatment ($p < 0.02$). Both active treatments were superior to placebo in terms of time to rescue over the entire study period, reduction from baseline in pain intensity (VAS) at visit 3 and reduction from baseline in disability (Eifel index) at visits 2 and 3 for diclofenac potassium and at visit 3 only for ibuprofen.

End-of-day global assessments are particularly appropriate for evaluating the short-term use of NSAIDs. A rate ratio (RR) can be calculated for diclofenac relative to placebo. Dreiser et al. undertook such an extrapolation in their publication of the study using the end-of-study categories for relief of 'some', 'a lot' and 'complete' relief of acute lower back pain, which were then grouped into a success category; similarly, the minimal or absent relief categories of 'none' and 'a little' were grouped into a failure category.[59] Using such methodology, the RR for diclofenac potassium relative to placebo is 1.26 (i.e. 73.9% ÷ 58.5%). Furthermore, if the category 'some' relief is included in the failure category rather than in the success category, the RR increases to 1.64. Using the same methodology for the end of day 1 and the end of day 2, global efficacy assessments yield results supportive of the utility of diclofenac (figure 4). Therefore, whilst this study describes a 7-day flexible dosing programme for diclofenac potassium 12.5mg, it nonetheless supports the efficacy of a 4-day treatment regimen for the treatment of lower back pain.

4.3 Headache

Three single-dose, double-blind, placebo-controlled, parallel-group trials in patients with episodic tension-type headache (studies P32, P35, P39) compared diclofenac 12.5 or 25mg with ibuprofen 400mg or paracetamol 1000mg (table II).[53-55] These studies showed that a single dose of either one or two tablets of diclofenac potassium 12.5mg is effective within 30 minutes to 1 hour and is an appropriate medication for management of the pain of episodic tension-type headache. Summaries of the outcomes of TOTPAR-3 and TOTPAR-6 are presented in table III. In study P35 (n = 562), all active treatment groups were significantly superior to placebo with respect to pain relief, differences from baseline in pain intensity and time to rescue medication.[53] No significant differences were observed between the active treatment groups from 45 minutes post-dose onwards. The average pain relief over time is shown in figure 5.

In study P39 (n = 684), the mean pain relief in all active treatment groups was significantly superior to placebo at each timepoint from 30 minutes through to 6 hours.[54]

Table III. Efficacy of diclofenac potassium 12.5 or 25mg vs ibuprofen or paracetamol in tension-type headache (studies P32, P35, P39)[53-55]

Drug	TOTPAR-3 [mean (SD)]			TOTPAR-6 [mean (SD)]		
	P35	P39	P32[a]	P35	P39	P32[a]
Diclo-K 12.5mg	5.2 (3.6)[b]	5.2 (2.7)[b]	5.3 (3.3)	12.9 (8.6)[b]	14.0 (6.2)[b]	13.0 (8.3)
Diclo-K 25mg	5.6 (3.5)[b]	5.6 (3)[b]	5.1 (3.4)	14.1 (8.1)[b]	14.4 (6.7)[b]	12.8 (7.9)
Ibuprofen 400mg	5.6 (3.4)[b]	5.4 (3.1)[b]		14.1 (7.5)[b]	14 (7.1)[b]	
Paracetamol 1000mg			5.1 (3.3)			13.5 (7.8)
Placebo	4.1 (3.5)	3.5 (3)	4.3 (3.6)	9.8 (8.9)	9.3 (7.8)	10.9 (8.5)

a A preliminary, non-bioequivalent diclofenac potassium 12.5mg tablet formulation was used in this study.

b $p < 0.01$ vs placebo. Data presented as least square means (standard error).

Diclo-K = diclofenac potassium; **TOTPAR-3** = total pain relief during the first 3h; **TOTPAR-6** = total pain relief during the first 6h.

4.4 Fever, Sore Throat and Influenza-Like Symptoms

The febrile sore throat model has been used in clinical trials of various analgesics such as paracetamol 1000mg and ibuprofen 400mg.[61,62] Having antipyretic and analgesic activities, NSAIDs are an option for alleviating influenza-like symptoms, such as fever, headache and muscle/joint aches and pains. Three trials (studies P36, P37, P38) evaluated the efficacy of diclofenac potassium 12.5mg in patients with influenza-like symptoms or a benign sore throat (table II).[56-58] Study P38 was an ascending single-dose comparison with paracetamol and placebo in patients with a benign febrile sore throat.[58] Studies P36 and P37 were multiple-dose trials in patients with influenza-like symptoms and fever lasting 3 days.[56,57] These studies found that the smallest effective antipyretic and analgesic single dose of diclofenac potassium in the sore-throat model is 12.5mg and that a single dose of diclofenac potassium 25mg effectively relieves influenza-like symptoms of fever/feverishness, headache and muscle/joint aches and pains for up to 6 hours. In addition, these studies showed that a flexible, multiple-dose regimen with diclofenac potassium provides overall relief over the normal 3-day course of treatment.

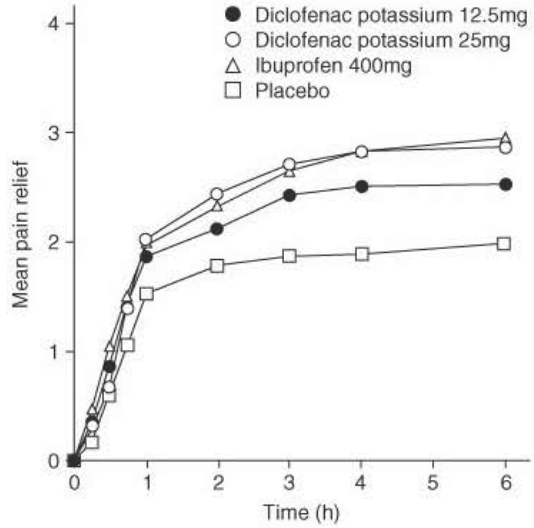

Fig. 5. Mean relief of headache with diclofenac potassium 12.5mg, diclofenac potassium 25mg, ibuprofen 400mg or placebo at different timepoints after initial dosage in study P35.[53] The pain relief scores for ibuprofen were significantly higher than for placebo at 15 minutes' post-dosing and onwards ($p \leq 0.01$). The pain relief scores for diclofenac potassium 12.5 and 25mg were significantly higher than for placebo at 45 minutes post-dosing and onwards ($p \leq 0.02$). The pain relief score for ibuprofen was significantly higher than for diclofenac potassium 25mg at 30 minutes ($p = 0.002$). Pain relief scale is: 0 = no relief; 1 = a little; 2 = some; 3 = a lot; 4 = complete.

In study P38, the relative efficacies of single oral doses of diclofenac potassium 6.25, 12.5 or 25mg were compared with paracetamol 1000mg and placebo in patients with an oral temperature of ≥38°C and a sore throat (n = 343).[58] Antipyresis was measured as area under the fever reduction-versus-time curve from 0 to 4 hours post-dose (AUC_{0-4}). Analgesia was measured as TOTPAR-4, the time-weighted sum of pain scored at 0, 2 and 4 hours. The antipyretic effects of all four active treatments (paracetamol 1000mg, diclofenac potassium 6.25, 12.5 and 25mg) were significantly superior to placebo, and all active treatments reduced oral tempera-

ture significantly more than placebo (secondary variable). Diclofenac potassium 12.5 and 25mg and paracetamol also produced significant relief of spontaneous sore throat pain and pain on swallowing compared with placebo (TOTPAR-4). Diclofenac potassium 25mg was significantly more effective than diclofenac potassium 6.25mg. Greater percentages of patients in the diclofenac potassium 12.5mg (42.4%) and 25mg (49.2%) groups rated the treatment as 'good' or 'very good' compared with diclofenac potassium 6.25mg (32%), paracetamol (26.8%) or placebo (22.9%).

In studies P36 and P37, diclofenac potassium was compared with ibuprofen or placebo in patients with influenza-like symptoms, using a flexible dosing regimen.[56,57] The primary outcome for first-dose efficacy was the timepoint-by-timepoint comparison of oral temperature. The primary outcome for overall efficacy of the regimen was the end-of-study global evaluation of overall symptom relief (fever, aches and pains). In study P37, in which patients (n = 356) were required to have a fever of ≥38°C, oral temperature in both active groups was significantly lower than in the placebo group at all timepoints from 30 minutes through to 6 hours ($p < 0.01$) [figure 6].[58] After the first dose, higher percentages of patients using diclofenac potassium or ibuprofen rated their feverishness, headache and muscle/joint aches as 'good', 'very good' or 'excellent' than in the placebo group (table IV). The end-of-study global evaluations of overall relief over the 3-day treatment period and time to rescue medication were similar in both active treatment groups and were significantly superior to placebo ($p < 0.01$).

Study P36 included a more heterogeneous population (n = 345), consisting of patients with either a common cold or influenza-like symptoms and therefore with or without a fever of ≥38°C; 30% had baseline oral temperatures of ≥38°C.[56] In this pyretic subpopulation, the first dose of diclofenac potassium (2 × 12.5mg) rapidly and progressively decreased oral temperature from a mean of 38.4°C to the lowest value of 37.3°C (mean decrease of 1.14°C) 4 hours' post-dose. A similar decrease was produced by the first dose of ibuprofen (2 × 200mg). The mean oral temperatures for patients receiving diclofenac potassium and ibuprofen were significantly lower than those for patients receiving placebo at 1, 2 and 4 hours ($p < 0.01$). The percentage of patients rating their first-dose global efficacy assessment (overall, feverishness, headache and muscle/joint aches) as 'good,' 'very good' or 'excellent' was much higher in the diclofenac potassium and ibuprofen-treatment groups than in the placebo group (table IV). The end-of-study global evaluation for overall relief over the 3-day treatment period was significantly superior to placebo for both diclofenac potassium and ibuprofen ($p < 0.05$).

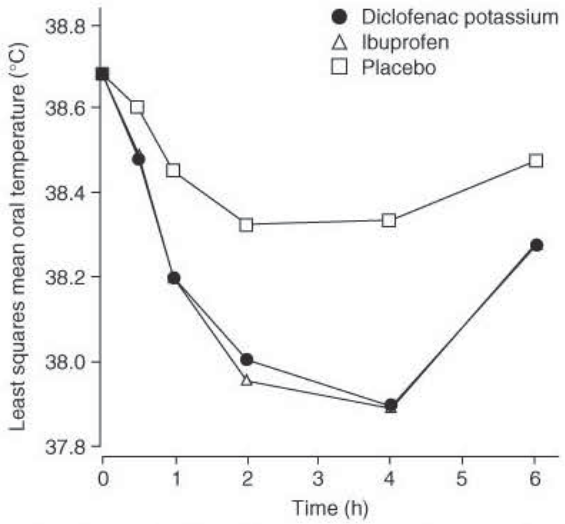

Fig. 6. Antipyretic effect (least squares mean oral temperature) of diclofenac potassium, ibuprofen or placebo at different timepoints after initial dosage in patients with influenza/influenza-like symptoms in study P37.[57] The oral temperatures in both active groups were significantly higher than in the placebo group at all timepoints ($p < 0.01$).

4.5 Menstrual Pain

One clinical trial (study P26) has been conducted in 156 women with mild to moderate pain associated with primary dysmenorrhoea in a randomised, double-blind, three-way crossover, double-dummy study

Table IV. Efficacy of diclofenac potassium vs ibuprofen or placebo in patients with influenza-like symptoms (studies P36, P37).[56,57] Values are first-dose evaluations and represent the combined percentages of patients rating a treatment as 'good', 'very good' or 'excellent'

Study	Diclofenac potassium 2 × 12.5mg	Ibuprofen 2 × 200mg	Placebo
Overall relief			
P36[56]	56.0[a]	65.5[a]	36.6
P37[57]	56.2[a]	55.1[a]	23.9
Fever/feverishness			
P36[56]	65.5[a]	70.7[a]	40.5
P37[57]	58.9[a]	60.0[a]	22.1
Headache			
P36[56]	55.2[a]	69.8[a]	39.3
P37[57]	60.5[a]	71.7[a]	18.6
Muscle/joint aches and pain			
P36[56]	53.5[a]	69.0[a]	39.3
P37[57]	56.3[a]	64.2[a]	20.4

a $p < 0.05$ vs placebo; no statistically significant differences between active treatments.

comparing a flexible dosing regimen of diclofenac potassium 12.5mg to a maximum 75 mg/day with ibuprofen 200mg to a maximum 1200 mg/day and placebo (table II).[60]

The first dose of study medication was two tablets (diclofenac potassium 25mg vs ibuprofen 400mg vs placebo), after which one or two tablets of the study medication were taken every 4–6 hours for 3 days, with a maximum daily dose of six tablets per day (diclofenac potassium 75mg or ibuprofen 1200mg, respectively).[60] This study showed that a single dose of diclofenac potassium 25mg and a flexible dosing regimen of diclofenac potassium 12.5mg tablets effectively treated mild to moderate pain of primary dysmenorrhoea.

Thirty minutes after administration of either active drug the pain relief scores were superior to placebo.[60] No significant difference was found between the two active treatment groups for the primary efficacy outcome. For all secondary first-dose outcomes (TOTPAR-3, SPID-3, time to either rescue or re-medicate and end-of-first-dose global efficacy assessment), diclofenac potassium and ibuprofen were significantly superior to placebo, and similar to each other.

Multiple doses of diclofenac potassium and ibuprofen provided consistently better analgesia than placebo over the 3 days of treatment; the percentage of patients taking rescue medication was at least 2-fold higher in the placebo cycle (34%) than in either the diclofenac potassium (17.4%) or the ibuprofen (8.6%) cycles.[60] Both diclofenac potassium and ibuprofen were superior to placebo in the end-of-study global assessment and similar to each other.

4.6 Summary of Efficacy Results

The key efficacy findings for studies of diclofenac potassium are:

- The onset of analgesic and antipyretic activity of diclofenac potassium 12.5mg taken as one or two tablets was mostly within 30 minutes. The duration of activity was 4–6 hours, depending on the indication and the dose. Repeated use resulted in prolonged analgesia.
- Diclofenac potassium was consistently superior to placebo in all pain models tested.
- Diclofenac potassium 12.5 or 25mg was as effective as ibuprofen 200 or 400mg in traditional OTC indications, for example acute lower back pain, tension-type headache, symptoms of cold

Table V. Dosing patterns by day in studies of diclofenac potassium (Diclo-K) flexible multiple-dose regimens (studies P26, P34, P36, P37, P40)[48,56,57,59,60]a

Days	Study P26[60] (dysmenorrhoea)		Study P34[48] (dental pain)		Study P36[56] (fever and influenza-like symptoms)		Study P37[57] (fever and influenza-like symptoms)		Study P40[59] (lower back pain)	
	Diclo-K	Ibu 200mg	Diclo-K	Par 500mg	Diclo-K	Ibu 200mg	Diclo-K	Ibu 200mg	Diclo-K	Ibu 200mg
1	100 [4.2 (2.0)]]	100 [4.1 (1.9)]	100 [3.7 (1.5)]	100 [3.8 (1.7)]	100 [5.7 (1.0)]	100 [5.8 (0.8)]	100 [5.4 (1.1)]	100 [5.6 (1.2)]	100 [6.0 (1.8)]	100 [6.1 (1.6)]
2	47.8 [1.3 (1.7)]	50 [1.5 (2.0)]	43.3 [0.8 (1.2)]	28.2 [0.6 (1.2)]	90.7 [4.5 (1.8)]	97.3 [4.9 (1.4)]	95.0 [4.5 (1.8)]	97.5 [4.5 (1.6)]	89.5 [3.9 (1.4)]	91.8 [4.0 (1.6)]
3	21.1 [0.6 (1.3)]	23.5 [0.5 (1.2)]	4.8 [0 (0.2)]	2.6 [0 (0.2)]	83.1 [3.8 (2.2)]	93.8 [4.5 (1.6)]	91.7 [4.0 (1.8)]	90.8 [4.1 (1.8)]	81.5 [3.8 (1.6)]	84.4 [3.8 (1.6)]
4	–	–	–	–	16.1 [0.2 (0.6)]	15.9 [0.2 (0.6)]	9.9 [0.1 (0.5)]	5.0 [0.1 (0.3)]	75.0 [3.1 (1.5)]	75.4 [3.6 (1.6)]
5	–	–	–	–	–	–	–	–	63.7 [3.1 (1.4)]	68.9 [3.4 (1.6)]
6	–	–	–	–	–	–	–	–	54 [3.0 (1.5)]	59.8 [3.1 (1.6)]
7	–	–	–	–	–	–	–	–	36.3 [2.1 (1.2)]	42.6 [2.0 (0.9)]

a Values shown are the percentages of patients taking medication on successive study days, with mean (SD) number of tablets taken per 24h period in brackets. The mean and SD of number of tablets for each day is for the population that was administered the drug on that day.

Ibu = ibuprofen; **Par** = paracetamol. – indicates no intake.

and influenza (headache, muscle/joint aches and pain, and fever), and dysmenorrhoea. Suggestions of greater efficacy or faster onset of action than standard ibuprofen in a subset of efficacy outcomes in certain circumstances could warrant further exploration.

- Diclofenac potassium 12.5 or 25mg was comparable to paracetamol 1000mg in relieving acute pain after dental surgery or sore throat. Similarly, these doses of diclofenac potassium had a quicker onset and longer duration of antipyretic and analgesic efficacy than paracetamol 1000mg.
- The flexible dosing regimen allows optimised exposure to the drug while permitting maximum symptom relief. The number of tablets taken and the pattern of use of the flexible dosing regimen of diclofenac potassium 12.5mg tablets were broadly similar to usage of the OTC drugs ibuprofen 200mg and paracetamol 500mg in the PAIN (Paracetamol Aspirin Ibuprofen New tolerability) study.[63] A recent pharmacy-based cohort study of OTC diclofenac potassium[64] has confirmed that this agent is commonly used in accordance with the labelling instructions, and in the same way as in clinical trials (table V).

5. Safety

The safety and tolerability profile of low-dose diclofenac potassium (either single doses ≤25mg or a flexible dosing regimen from 25mg to a maximum 75 mg/day) has been evaluated in 2377 patients as short-term treatment (for up to 7 days) in acute conditions (headache, dental pain, acute lower back pain, influenza-like symptoms, fever, dysmenorrhoea). Supportive data are also available from an additional 2430 patients administered single high doses (>25mg) of diclofenac potassium (n = 765) or short-term multiple high doses of diclofenac potassium (>75 mg/day) for up to 14 days (n = 794) in indications such as dysmenorrhoea, ankle sprain/strain or post-surgical pain. Patients with chronic

conditions (osteoarthritis [OA] of the knee) were administered long-term low-dose (37.5 and 75 mg/day) or high-dose (150 mg/day) diclofenac potassium over 3 months (n = 871).[65]

These patients are compared with 1297 patients treated with ibuprofen, the reference drug with the highest number of trials and the largest number of patients exposed, and to >2000 patients treated with placebo. Low-dose ibuprofen was defined as single doses of ≤400mg (n = 374) or a flexible dosing regimen of 400mg up to a maximum of 1200 mg/day (n = 873). High-dose ibuprofen (n = 247) was defined as multiple doses of >1200 mg/day.

A separate endoscopy trial,[66] in which healthy volunteers received low-dose diclofenac potassium (n = 13), is included in this review. Laboratory data on hepatic safety were collected in the 3-month trial of patients with OA (study P29), which included both low- and high-dose diclofenac potassium and low-dose ibuprofen.[65] A discussion of the findings of epidemiology studies is also included.

5.1 Demographic Data

The demographic pattern of patients receiving single doses of diclofenac potassium was similar across all treatment groups. More than 80% of individuals were aged <50 years, with most aged 21–30 years. This is explained by indications such as post-surgical pain arising from removal of impacted third molars, tension-type headache and post-gynaecological surgery. In all groups there were more women than men.

In the multiple-dose groups, the distribution of age in the low-dose diclofenac potassium and ibuprofen groups was similar, with approximately 50% of individuals aged <50 years. In the high-dose supportive diclofenac potassium group, there were more individuals (77.4%) aged <50 years. In all groups, approximately two-thirds of patients were women.

The demographics of the patients enrolled in the clinical trials were very similar to those of patients enrolled in the large-scale, real-life setting PAIN study[63] and in the observational Norwegian OTC pharmacy-based use cohort,[64] which suggests that the trial populations were probably representative of actual user populations.

5.2 Adverse Events

An International Medical Nomenclature dictionary similar to COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) was used to categorise adverse events by body system and medical term within each body system. Adverse events from 34 randomised phase I–IV trials, in which 4807 patients were treated with diclofenac potassium, were pooled in a standardised adverse event database (table VI). Among these were 20 single-dose studies (n = 2532), including 13 studies in acute pain conditions in which low-dose (≤25mg) diclofenac potassium was administered and 11 studies in pain conditions in which high-dose (>25mg) diclofenac potassium was administered. Therefore, in four of the studies, both low and high doses of diclofenac potassium were administered. There were 13 short-term multiple-dose studies (n = 1404), including five low-dose studies for non-prescription indications in acute pain conditions in which diclofenac potassium was taken at doses of 25mg up to 75 mg/day for up to 7 days, and eight high-dose studies for indications in which diclofenac potassium was taken in doses up to 150 or 200 mg/day for up to 14 days. Finally, there was one multiple-dose study of low-dose diclofenac potassium in a chronic indication (OA) [n = 871], in which patients were treated with either low or high doses of diclofenac potassium for up to 3 months.[65] This study provided information on the safety of long-term use of low-dose diclofenac potassium as well as information on use in patients with a chronic condition and prior use of NSAIDs.

Table VI. Number of trials and number of subjects pooled in the adverse events database

Variable	Low-dose diclofenac potassium (n = 3064)				High-dose diclofenac potassium (n = 1743)			
	SD	MD: ACs (≤7d)	MD: CC (OA) [3mo]		SD	MD: ACs (≤14d)		MD: CC (OA) [3mo]
No. of trials	13	5	1		11	8		1
No. of pts	1767	610	687		765	794		184
Dose (mg)	6.25	12.5	25	37.5	50	100	200	150
No. of pts	222	689	856	342	436	329	50	184

ACs = acute conditions; **CC** = chronic condition; **MD** = multiple dose; **OA** = osteoarthritis (of the knee); **pts** = patients; **SD** = single dose.

5.2.1 Adverse Events with Single Doses

Few adverse events were reported with a single low dose of diclofenac potassium ≤25mg: the incidence rate and the overall frequencies of adverse events by body system were similar to placebo (table VII).

Incidence rates of adverse events were comparable among all treatment groups for all body systems except for the GI and nervous systems. Rates of GI adverse events ranged from a low of 1.7% in the low-dose diclofenac potassium group to a high of 4.5% in the aspirin 650mg group. Common GI adverse events included nausea, vomiting, dyspepsia, abdominal pain and gastritis. The incidence of adverse events in the nervous system was in the range of 4–6% in all treatment groups except for paracetamol 1000mg, in which a low incidence of 1% was observed. Common nervous system adverse events included headache, dizziness, somnolence, insomnia and anxiety. No premature study withdrawals because of GI symptoms were reported with single doses of diclofenac potassium ≤25mg, ibuprofen ≤400mg or paracetamol 1000mg. There were two premature study withdrawals because of GI symptoms with single doses of aspirin 650mg and three withdrawals in the placebo group. However, only one placebo case (due to nausea and vomiting) was considered at least possibly study drug related. No serious GI adverse events or related deaths occurred in any of the treatment groups.

5.2.2 Adverse Events with Multiple Doses

The reference drug taken by the largest number of individuals was ibuprofen. The overall tolerability of low-dose OTC ibuprofen has been demonstrated to be equivalent to that of paracetamol and better than that of aspirin in a large-scale study.[63]

The highest rates of adverse events were observed in the body as a whole and in the GI and nervous systems (table VIII). The frequencies observed by body systems were similar for low-dose diclofenac potassium and ibuprofen in exposures for

Table VII. Frequency of adverse events (AEs) reported during single-dose studies of diclofenac potassium (Diclo-K) vs active comparators and placebo

Adverse event (frequency [%])	Diclo-K ≤25mg (n = 1767)	Diclo-K >25mg (n = 765)	IBU ≤400mg (n = 374)	ASA 650mg (n = 376)	PAR 1000mg (n = 196)	Placebo (n = 1013)
Any AE	9.4	10.2	10.2	10.6	6.6	9.2
Blood/lymphatic	0.1	0.1	0	0	0	0
Body as a whole	0.8	0.7	1.9	0.8	1.0	1.1
Cardiovascular	0.2	0.5	0	0.3	0	0.1
Gastrointestinal	1.7	3.7	2.4	4.5	3.6	3.3
Infections	0	0	0	0	0.5	0
Musculoskeletal	0.4	0	0	0	0.5	0.2
Nervous system	5.8	6.1	4.0	5.9	1.0	4.0
Respiratory system	0.9	0.4	1.9	0	0.5	0.6
Skin/appendages	0.2	0	0	0	0	0.2
Special senses	0.3	0	0	0	1.5	0.4
Urogenital system	0.2	0	0.3	0	0.5	0.2

ASA = aspirin (acetylsalicylic acid); **IBU** = ibuprofen; **PAR** = paracetamol.

up to 7 days, and comparable to placebo. These rates were much lower than those observed in high-dose diclofenac potassium and ibuprofen groups in exposures for up to 14 days. The adverse event rates in the low-dose diclofenac potassium and ibuprofen groups were generally comparable to those in the study cited above,[63] in which low-dose aspirin, ibuprofen or paracetamol were taken for up to 7 days. A high overall rate of adverse events was reported in that study, with incidence rates in the ibuprofen group of 19.5% for any adverse event, 4% for GI adverse events and 1.9% for nervous system adverse events.

With multiple dosing for 3 months in the OA study,[65] the incidence of any adverse event exceeded 50% in all treatment groups (table IX). The highest rates by body system were seen in the GI, respiratory and nervous systems and in the body as a whole. Incidence rates for low-dose diclofenac potassium and ibuprofen were very similar in that

Table VIII. Frequency of adverse events (AEs) reported during short-term (≤14d) multiple-dose studies of diclofenac potassium (Diclo-K) vs ibuprofen (Ibu) and placebo

Adverse event	Low dose (≤7d)			High dose (≤14d)		
(frequency [%])	Diclo-K ≤75mg (n = 610)	Ibu 1200mg (n = 523)	placebo (n = 599)	Diclo-K >75mg (n = 794)	Ibu 2400mg (n = 50)	placebo (n = 423)
Any AE	13.9	13.0	10.5	37.2	30.0	29.6
Blood/lymphatic	0.2	0.2	0	0.1	0	0
Body as a whole	2.3	0.8	1.0	6.4	2.0	4.3
Cardiovascular	0.3	0.2	0.3	1.3	0	0.5
Gastrointestinal	6.7	6.5	4.2	19.9	18.0	10.2
Infections	0	0	0.2	0	0	0
Metabolic/ nutritional	0	0	0	0.3	0	0.1
Musculoskeletal	1.1	1.1	0.7	3.0	4.0	2.1
Nervous system	4.4	2.7	3.8	14.5	8.0	14.9
Respiratory system	1.0	1.5	1.3	8.2	2.0	5.2
Skin/appendages	1.0	1.0	0.3	2.3	0	0.2
Special senses	0.8	0.4	0.2	1.4	2.0	0.7
Urogenital system	0.8	0.6	0.7	2.6	4.0	3.3

Table IX. Frequency of adverse events (AEs) reported in a 3-month study of diclofenac potassium vs low-dose ibuprofen and placebo in patients with osteoarthritis[65]

Adverse event (frequency [%])	Diclofenac potassium ≤75mg (n = 687)	Ibuprofen 1200mg (n = 350)	Diclofenac potassium 150mg (n = 184)
Any AE	55	57.1	63.6
Blood/lymphatic	0.7	0.3	0.5
Body as a whole	13.0	15.4	16.3
Cardiovascular	2.9	3.1	2.2
Gastrointestinal	23.4	25.1	31.5
Laboratory abnormality	0.1	0.6	0.5
Metabolic/nutritional	0.3	0.6	0
Musculoskeletal	8.4	5.7	12.0
Nervous system	14.0	14.0	17.4
Respiratory system	16.4	16.9	18.5
Skin/appendages	5.8	8.3	1.6
Special senses	3.6	2.9	3.3
Urogenital system	5.2	8.0	7.6

study and generally somewhat lower than in the high-dose diclofenac potassium group. Low frequencies of melaena (0.3%) and gastric ulcer (0.1%) were noted in this study. However, individuals with OA are known to be at risk for these events.

Comparing within and across groups, adverse event incidence rates are seen to increase as one progresses from a single dose (table VII) to multiple doses of up to 7 days, then to multiple doses of up to 14 days (table VIII), and finally to multiple doses over 3 months (table IX). However, rates of adverse events were similar between low-dose diclofenac potassium and low-dose ibuprofen over all durations of dosing (table X). Within each group of studies, adverse event rates were greater in the high-dose diclofenac potassium group compared with the low-dose group.

Low-dose diclofenac potassium given in a flexible dosing regimen of 25–75 mg/day in acute indications, which may be treated with OTC pain relievers, has a safety profile comparable to that of similarly used ibuprofen (400–1200 mg/day) and placebo.[68-70]

5.2.3 Severity of Adverse Events

A severity rating (mild, moderate, severe) for individual symptoms was recorded by the investigators during clinical trials. In single-dose studies, adverse event rates were similar not only in frequency but also in distribution of severity among patients receiving diclofenac potassium ≤25mg, ibuprofen ≤400mg or placebo. The two body systems with the greatest frequency of adverse events were the GI and nervous systems (table VII). In both systems, the small number of adverse events (ranging from 1% to 3% of patients) in the low-dose diclofenac potassium group, the ibuprofen group and the placebo group were either of mild or moderate severity in varying relative proportions, with very few severe adverse events reported.

In patients taking multiple doses of low-dose diclofenac potassium (≤75 mg/day) for up to 7 days' intake or high-dose diclofenac potassium for up to 14 days, adverse events were again most common in the GI and nervous systems (table VIII). Of those who experienced a GI or nervous system adverse event in the low-dose diclofenac potassium and low-dose ibuprofen (≤1200 mg/day) groups, 50–70% experienced only adverse events of mild severity and <10% experienced any severe adverse events. A similar distribution was seen in the high-dose diclofenac potassium group. Typically there were slightly fewer adverse events in the placebo group in

Table X. Incidence rates of total adverse events per 100 patients (95% CI) in multiple-dose studies by dose, treatment duration and indication

Variable	Diclo-K ≤75mg	Ibuprofen ≤1200mg	Placebo	Diclo-K >75mg	Ibuprofen >1200mg	Placebo
No. of pts	610	523	599	794	50	423
Short-term[a] acute indications	13.9 (11.1, 17.2)	13.0 (10.1, 16.5)	10.5 (8.1, 13.5)	37.2 (33.8, 40.5)	30.0 (16.8, 49.5)	29.3 (25.2, 33.9)
No. of pts	687	350	–	380	197	–
Short-term[b] chronic indications	30.7 (27.3, 34.2)	33.4 (28.5, 38.4)	–	42.4 (37.4, 47.3)	45.7 (38.7, 52.7)	–
No. of pts	687	350	–	380	197	–
3–6mo[c] chronic indications	55.0 (51.3, 58.7)	57.1 (52, 62.3)	–	72.4 (67.9, 76.9)	77.7 (71.8, 83.5)	–

a Short-term: 2–7d exposure. Acute indications: dental pain, headache, dysmenorrhoea, symptoms of colds and flu and acute lower backache.

b Short-term, chronic indication: first 14d in pts with OA: studies P29 (study P29[65] was a randomised, single-blind, parallel-group, reference-controlled study comparing daily fixed doses of Diclo-K 37.5mg [n = 342], 75mg [n = 345] and 150mg [n = 184], ibuprofen 1200mg [n = 350], and open-label diclofenac sodium [sustained-release] 300mg [n = 116] over 3mo in pts with OA of the knee) and P8 (study P8[67] was included as supportive data for high-dose treatment; this study was a randomised, double-blind, double-dummy, parallel-group, reference-controlled study comparing daily fixed doses of Diclo-K 150mg [n = 196], diclofenac sodium 150mg [n = 197] and ibuprofen 1200mg [n = 197]) over 6mo in pts with OA of the knee.

c Long-term: 3–6mo in pts with OA (studies P29 and P8).

Diclo-K = diclofenac potassium; **OA** = osteoarthritis; **pts** = patients. – indicates no data.

these studies, but these tended towards greater severity. Of patients in the placebo group who experienced an adverse event in the GI or nervous systems, ≤20% experienced at least one event that was considered severe.

Of those who experienced an adverse event following long-term exposure over 3 months in the safety study P29,[65] adverse events were rated as only mild in 30–50% in each treatment group. Only 10–20% of patients experienced at least one adverse event considered to be severe. This pattern repeated itself in the distribution of severity within those individual body systems in which adverse events were most common (GI, respiratory, nervous system, and body as a whole) [table IX].

Consideration of the severity of adverse events over the entire range of studies indicates that there was a greater but not overwhelming tendency towards moderate severity as the duration of dosing increased. Severe adverse events were generally uncommon in all treatment groups regardless of dosing duration. Among patients experiencing adverse events, the highest frequency of those experiencing a severe adverse event was in the placebo group in short-term multiple-dose studies. Severity of adverse events was generally similar in patients taking low-dose diclofenac potassium or ibuprofen with all dosing durations.

5.2.4 Discontinuations Because of Adverse Events

Among patients treated with single low doses of diclofenac potassium, only one patient experienced an adverse event, i.e. mild rash. There were no adverse events among patients treated with low-dose ibuprofen; two patients in the aspirin treatment group presented with nausea and vomiting, and seven patients in the placebo group experienced fever, flatulence, nausea, vomiting and headache. These numbers represent <1% of randomised patients.

Of patients taking multiple doses of up to 7 days' duration, 1.5–1.7% discontinued because of an ad-

verse event in the low-dose diclofenac potassium, ibuprofen and placebo groups. In the high-dose diclofenac potassium and ibuprofen groups, with exposures of up to 14 days, these rates increased to 3–4%. Much of the increase was associated with GI adverse events.

In the 3-month safety study,[65] the frequency of patients discontinuing because of an adverse event increased to 8.3% in the low-dose diclofenac potassium group, 10.3% in the high-dose diclofenac potassium group and 12.0% in the low-dose ibuprofen group. Many of these discontinuations were because of GI adverse events, i.e. 4.1% in the low-dose diclofenac potassium group, 6.5% in the high-dose diclofenac potassium group and 4.9% in the low-dose ibuprofen group.

5.2.5 Serious Adverse Events

No serious adverse event or reaction occurred with either low- or high-dose diclofenac potassium in any single-dose or short-term multiple-dose trials of up to 14 days of treatment. In the long-term trial in patients with OA (study P29),[65] there were three reports of serious adverse events that were considered possibly study-drug related among 687 patients treated with low-dose diclofenac potassium. All three occurred >30 days after the start of treatment.

No study drug-related deaths were reported during short-term, low- or high-dose treatment in any diclofenac potassium clinical trials. Two deaths, both considered not related to the study drug, were reported in the long-term study (study P29)[65] in the low-dose diclofenac potassium group; one secondary to GI haemorrhage in a patient with haemorrhagic adenocarcinoma of the stomach, and the second due to metastatic prostate cancer.

5.3 Gastrointestinal Safety

Although NSAIDs are generally well tolerated, they have been associated with adverse effects such as damage to the GI tract. This risk varies widely depending on the individual drug, its dose and intake duration, concomitant medication and the individual's risk factors, such as a previous history of peptic ulcer.[71] The GI safety data available for low-dose diclofenac potassium includes pooled data from clinical studies, a specific endoscopy study and several large epidemiological studies.

When calculating the incidence rates of total GI events reported in the reviewed clinical trials an obvious relationship between dose, treatment duration and indication can be seen (table XI). No differences in incidence of GI events were observed between diclofenac potassium and ibuprofen at each dose level of observation: short-term low dose in acute conditions, short-term high dose in chronic conditions and long-term high dose in chronic conditions.

An endoscopy study showed that short-term intake of low-dose diclofenac potassium produced little or no injury to the gastric mucosa.[66] Low-dose diclofenac potassium 75 mg/day, low-dose ibuprofen 1200 mg/day and aspirin 3000 mg/day were given for 2 days to 12 healthy volunteers in this randomised, single-blind crossover study. The effects on the gastric mucosa were quantified as Lanza gastric scores, where scores <grade 1 are considered very mild, scores of grade 1–1.5 as mild and scores of 1.5–2 as clinically relevant.[72] The mean score in the low-dose diclofenac potassium group (0.33 ± 0.5) was similar to that in the low-dose ibuprofen 1200 mg/day group (0.42 ± 0.7), and significantly lower than that in the aspirin 3000 mg/day group (2.67 ± 0.9) [figure 7].[66] Moreover, such low scores approach those observed with placebo, which range from 0.13 to 0.25.[72,73] The mean gastric score with low-dose ibuprofen was in the same range as those published previously after a single dose of 200mg[74] or after multiple doses of ≤1200 mg/day.[72,75]

Pharmacoepidemiological studies complement clinical study safety data as they permit quantification of a risk or its absence under real-life conditions. Five cohort studies investigated the risk of dif-

Table XI. Incidence rates of total gastrointestinal adverse events (whether or not drug-related) per 100 patients (95% CI) in multiple-dose studies by dose, treatment duration and indication

Variable	Diclo-K ≤75mg	Ibuprofen ≤1200mg	Placebo	Diclo-K >75mg	Ibuprofen >1200mg	Placebo
No. of pts	610	523	599	794	50	423
Short-term[a] acute indications	6.7 (4.8, 9.1)	6.5 (4.5, 9.1)	4.2 (2.7, 6.2)	19.9 (17.1, 22.7)	18 (8.2, 34.2)	10.2 (7.4, 13.7)
No. of pts	687	350	–	380	197	–
Short-term[b] chronic indications	13.5 (10.9, 16.6)	15.1 (11.3, 19.8)	–	21.8 (17.4, 27.1)	25.9 (19.3, 34)	–
No. of pts	687	350	–	380	197	–
3–6mo[c] chronic indications	23.4 (20.3, 26.6)	25.1 (20.6, 29.7)	–	40 (35.1, 44.9)	49.8 (42.8, 56.7)	–

a Short-term: 2–7d exposure. Acute indications: dental pain, headache, dysmenorrhoea, symptoms of colds and flu and acute lower backache.

b Short-term, chronic indication: first 14d in pts with OA: studies P29 (study P29[65]) was a randomised, single-blind, parallel-group, reference-controlled study comparing daily fixed doses of Diclo-K 37.5mg [n = 342], 75mg [n = 345] and 150mg [n = 184], ibuprofen 1200mg [n = 350], and open-label diclofenac sodium [sustained-release] 300mg [n = 116] over 3mo in pts with OA of the knee) and P8 (study P8[67] was included as supportive data for high-dose treatment; this study was a randomised, double-blind, double-dummy, parallel-group, reference-controlled study comparing daily fixed doses of Diclo-K 150mg [n = 196], diclofenac sodium 150mg [n = 197] and ibuprofen 1200mg [n = 197]) over 6mo in pts with OA of the knee.

c Long-term: 3–6mo in pts with OA (studies P29 and P8).

Diclo-K = diclofenac potassium; **OA** = osteoarthritis; **pts** = patients. – indicates no data.

Fig. 7. Mean (± SD) Lanza gastric injury scores after 2 days of treatment with diclofenac potassium, ibuprofen or aspirin (acetylsalicylic acid) in a single-blind, three-way crossover, endoscopy study.[66] **tid** = three times daily.

ferent NSAIDs (including low doses of diclofenac) for inducing GI complications such as GI bleeding.[76-80] The ranking for GI complications in patients aged >70 years was ibuprofen < diclofenac < naproxen. However, in all countries where these studies were conducted, ibuprofen was freely available as an OTC medication whereas diclofenac was available only on prescription. This could have resulted in an inadequate comparison of OTC and prescription doses, and of drugs used in different indications. When only low (OTC) equivalent doses are compared there seems to be no difference in the risk of GI bleeding or other GI events between diclofenac and the reference ibuprofen.

It can be concluded that for the same indication and duration, and when both medications are given at low doses, there is no difference in the incidence or relative risk of GI events generally, or of severe GI events in particular, between diclofenac and ibuprofen.

5.4 Hepatic Safety

Diclofenac has an unfortunate reputation of being mildly hepatotoxic, which may be related to a misunderstanding of the combination of frequent dose- and duration-dependent increases in transaminases and rare reported cases of sometimes serious acute hepatotoxic reactions in treated patients.

Asymptomatic increases in serum transaminases that are dose and duration related are well known

with diclofenac but are not considered to be clinically significant[65,81,82] or predictive of hepatic injury.[83]

Many drugs can cause acute hepatic injury, including antihypertensive, antimicrobial, cardiovascular and psychotropic agents, as well as NSAIDs.[84,85] Hepatotoxicity could be considered a class characteristic of NSAIDs[86-90] and has been reported for the other OTC analgesics, including ibuprofen,[91-98] naproxen,[98-100] ketoprofen,[101] aspirin[87] and paracetamol.[84,102] The risk of drug-related hepatotoxicity is increased with concomitant medication, older age and certain diagnoses such as inflammatory diseases, especially rheumatoid arthritis, a common indication for prescription of diclofenac.

However, *in vitro* and *in vivo* animal studies do not indicate that diclofenac is hepatotoxic. These findings do not explain rare hepatic reactions in humans, but rather support the clinical and epidemiological evidence that diclofenac is as safe as other NSAIDs. *In vitro* studies with hepatocytes showed diclofenac protein binding, an event commonly found with other NSAIDs and other drugs.[103,104] The CYP3A4 isoform that activates diclofenac (5′-hydroxylation) does not act at low concentrations.[105,106] 5-Hydroxydiclofenac is a minor metabolite. Protein binding may occur when the normal glutathione defences are overwhelmed,[105] so that hepatic injury, if any, would be expected to occur mainly in quite specific circumstances such as prolonged use, high doses or in the presence of glutathione depletion. The same could be expected in similar circumstances with other drugs commonly used for pain relief such as ibuprofen, and especially with paracetamol, which is known to be quite hepatotoxic in exactly these circumstances (high doses and/or glutathione depletion). Chronic inflammatory diseases, which are associated with the combination of use of higher doses of NSAIDs, use of many concomitant often hepatotoxic drugs and chronic glutathione depletion because of a chronic hyperoxidative inflammatory state, are a prime setting for hepatotoxic reactions. This is not usually the case in patients treated with OTC analgesia, who are generally otherwise healthy young individuals who require treatment only for an acute painful episode.

In the 34 randomised phase I–IV studies reviewed for this paper, no serious hepatic reaction was reported in >2500 patients who were given single low- or high-dose diclofenac potassium and >1400 patients given multiple low- or high-dose diclofenac potassium in the short term (up to 14 days). Since serious hepatic reactions are extremely rare, they were not expected to occur.

Laboratory data are available from study P29, in which patients with OA of the knee were randomised to treatment with several doses of diclofenac potassium (3 × 12.5, 25, or 50 mg/day) or ibuprofen (3 × 400 mg/day) for 3 months.[65] A small subset of patients with severe OA took sustained-release diclofenac sodium 300 mg/day. Haematological, hepatic and renal profiles were assessed from blood samples obtained at 10–13 days, 28 days and periodically thereafter for up to 12 weeks. Diclofenac potassium had no clinically significant effect on complete blood count, platelets, alkaline phosphatase, bilirubin or creatinine levels. After 25–31 days of treatment, two patients (0.3%) taking diclofenac potassium up to 75 mg/day experienced an increase in transaminase levels to >3 × ULN (upper limit of normal). None occurred before day 25 of treatment. Over the 3-month study, six patients (1.8%) in the diclofenac potassium 37.5mg group experienced moderate/marked transaminase elevations (>3 × ULN) and all were asymptomatic. Of these six patients, one patient had a history of alcohol consumption, while another patient with marked elevations (>8 × ULN) was diagnosed with hepatitis A. In the 75mg group, none of the five patients (1.4%) with moderately elevated enzymes over the 3-month study showed symptoms of liver injury. During the

evaluation of the transaminase elevation, one of these patients was diagnosed with prostatic cancer with liver metastases, which probably explained his abnormal values. Of the eight patients (4.3%) in the diclofenac potassium 150mg group and seven patients (6%) in the diclofenac potassium 300mg group with enzyme elevations >3 × ULN during the 3-month study, none had symptoms suggestive of liver injury. None of the 26 patients (over all diclofenac groups) with transaminase elevations mentioned here had significantly increased bilirubin levels or any other clinical signs of liver injury. The transaminase elevations were reversible after treatment cessation.

The increases in transaminases seen in this study[65] were clearly dose- and duration-dependent. There was no increase in plasma transaminase to 3 × ULN during the 10-day period in which one would typically use OTC analgesics, even in this high-risk population. It is therefore unlikely that patients using OTC diclofenac potassium would have a significantly increased risk of elevated transaminase levels. Nevertheless, if this occurred, transaminase levels would return to normal on cessation of treatment, as is already the case for the higher doses of diclofenac that are routinely used in millions of patients on a yearly basis.

Currently available epidemiological information does not separate diclofenac from other conventional NSAIDs with regard to its hepatic safety profile. A comparison of the incidence of hepatotoxic reactions reported in large cohort studies[81,95,96,107-110] (table XII) reveals no difference between ibuprofen and naproxen. De Abajo et al. have confirmed that, in contrast with most other drugs, NSAID- and diclofenac-related hepatotoxicity is dose- and duration-related, another indication of the safety of these OTC medications.[81]

Table XII. Epidemiological data on liver safety of NSAIDs and paracetamol[a]

Drug	Garcia et al.[107]	Jick et al.[109]	Garcia et al.[108]	Lanza et al.[110]	de Abajo et al.[81]	Traversa et al.[97]	Bareille et al.[98]
Cohort size	**228 392**	**102 644**	**625 307**	**68 028**	**1 636 792**	**835 000**	**42 913**
NSAIDs	3.9 (2.3, 6.1)					1.4 (0.9, 2.1)	0.4 (0.4, 0.5)
NSAID non-users	9.0 (5.2, 14.6)	10.3 (4.7, 19.5)					
Diclofenac[b]	8.8 (0.3, 8.7)	2.7 (0.1, 14.8)	6.6 (1.8, 16.6)		6.3 (3.0, 11.7)	1.5 (0.7, 3.2)	0.4 (0.3, 0.6)
Ibuprofen[b]	8.8 (0.3, 8.7)		4.2 (1.4, 9.9)	17.7 (0.5, 98.7)		3 (0.7, 12.4)	0.3 (0.2, 0.5)
Naproxen	9.6 (2.0, 28.0)		8.9 (2.4, 22.8)	55.5 (31.1, 91.6)		0.9 (0.1, 6.2)	0.6 (0.3, 1.2)
Ketoprofen						1.4 (0.5, 3.8)	0.4 (0.3, 0.6)
Paracetamol							2.1 (1.9, 2.3)

a Values are the incidence rates (95% CI) of acute hepatic injuries caused by NSAIDs (per 100 000 patient treatment-years).

b Data from large cohort studies (high dose) document that there is no difference between ibuprofen and diclofenac with regard to hepatotoxic potential.

5.5 Cardiovascular Safety

The withdrawal from the market of rofecoxib because of a suspicion of increased cardiovascular risk is the result of a chain of events that began with the publication of the VIGOR (Vioxx GI Outcomes Research) study in 2000[111] and was followed by various related population-based studies and clinical trials. These studies led to an increased suspicion of cardiovascular risk with all NSAIDs, related to a direct prothrombotic effect suspected to be a property of COX-2-preferring inhibitors or to an interaction with the antiplatelet effects of aspirin.

In 2001, Catella-Lawson et al., exploring a possible interaction between rofecoxib or celecoxib and aspirin, also confirmed an interaction between ibuprofen and aspirin first described >20 years ago.[112] However, no interaction was found between diclofenac and aspirin. More specifically, diclofenac did not antagonise the aspirin-induced inhibition of platelet aggregation. In a population-based study, MacDonald and Wei reported that patients taking aspirin and ibuprofen had an increased risk of all-cause and cardiovascular mortality.[113] In contrast, no increase in hazard was observed in patients combining aspirin with diclofenac. Thus, these investigators suggested that diclofenac might be preferred to ibuprofen in cardiac patients or those taking aspirin.

Several hypotheses for the absence of an interaction between aspirin and diclofenac have been suggested. For example, in one study, when diclofenac was administered at a low dose (25mg), thromboxane B_2 inhibition was about 87% after dosing and decreased to 55% within 6 hours.[112] In contrast, inhibition of thromboxane B_2 by ibuprofen was more pronounced (almost 100%) and sustained for 6 hours after administration. Another possible explanation could be found in the binding characteristics of the two drugs. While ibuprofen binds COX-1 in a superimposable configuration,[114] the binding of diclofenac may be spatially segregated from the ibuprofen binding site in the hydrophobic channel.[115]

Although NSAIDs in general have long been considered as rather cardioprotective, recently there have been concerns about their real cardiovascular risks, culminating in the withdrawal of rofecoxib from the market in September 2004. The first indications were the observation in the VIGOR study of an excess risk of cardiovascular mortality in the rofecoxib arm. This was initially attributed to a lower risk in the naproxen arm, but further epidemiological studies[116] and a clinical trial[117] showed that there appeared to be an increased risk of thrombotic cardiac events with rofecoxib at dosages of ≥50 mg/day. These findings led to withdrawal of the drug from the market. During the exploration of the potential cardiovascular risk of rofecoxib, a series of population-based studies showed that in fact the risk seemed rather low, with an odds ratio of about 1.2 for standard doses of rofecoxib (25 mg/day), and that this slight increase in risk seemed common to all NSAIDs (except celecoxib[118]), a finding contrary to those of many previous studies that had found no effect or a cardioprotective effect with most NSAIDs (and especially aspirin). These results persuaded the European Medicines Agency to contraindicate the use of COX-2 selective inhibitors in patients with coronary heart disease and post-stroke patients.[119]

Since diclofenac and other non-selective NSAIDs inhibit both COX-2 and COX-1, concerns were recently raised about a possible increased risk of similar cardiovascular events with use of non-selective NSAIDs. In a recent study,[120] diclofenac appeared to be associated with higher odds of myocardial infarction, but a channelling bias related to previous indications of lack of interaction with aspirin cannot be excluded, especially given the low grade of the association. In this publication, the investigators of an observational, nested case-control study evaluating data from 367 UK general

practices (QRESEARCH database) on the comparative risk of first time myocardial infarction in patients receiving COX-2 selective inhibitors and other NSAIDs, reported an increased risk associated with the use of rofecoxib, as well as diclofenac and ibuprofen. Odds ratios varied over a wide range between 0.65 and 3.08 and were 0.96 for naproxen, 1.16 for ibuprofen and 1.23 for diclofenac. However, given the low cardiovascular risk described, and the possible channelling of diclofenac to high-risk patients related to previous publications showing no interaction between diclofenac and aspirin, the meaning of these studies is still unclear. General limitations of observational analyses and several shortcomings (incomplete cardiovascular risk factors and potential confounders, uncertainties about actual drug exposure, contradictory finding with naproxen and aspirin) mandate caution over interpretations of cardiovascular risk in this context.

Several epidemiological studies have evaluated use of NSAIDs, including diclofenac, and cardiovascular risk.[121-126] Additional information is available from prospective clinical trials of celecoxib or etoricoxib in which diclofenac was used as the reference drug.[127-129]

The epidemiological studies varied with respect to their patient populations, sample sizes, definitions of events used and controls for confounding factors. However, when the data are considered overall, there is no consistent evidence that exposure to diclofenac poses a significant risk for cardiovascular events, including myocardial infarction, stroke or hypertension, compared with no exposure or exposure to comparators.

There is also no evidence from clinical trials that low-dose diclofenac potassium or ibuprofen poses any cardiovascular risk when given over short periods (tables VII and VIII) or for a longer period (table IX). Neither myocardial infarction nor stroke occurred in any of these studies.

Recent publications have further analysed the risk of cardiovascular problems (myocardial infarctions) in a subset of observational and epidemiological studies of traditional NSAIDs and COX-2 inhibitors.[130-132] McGettigan and Henry investigated the reported cardiovascular events with either COX-2 inhibitor or NSAID use in 17 case-control and six cohort-design studies.[130] This analysis, which was based exclusively on epidemiological studies, indicated that among NSAIDs, diclofenac had the highest risk with a summary relative risk of 1.40 (95% CI 1.16, 1.70), while the relative risk for ibuprofen was 1.07 (95% CI 0.97, 1.18), for piroxicam 1.06 (95% CI 0.70, 1.59) and for naproxen 0.97 (95% CI 0.87, 1.07). Singh et al. conducted a meta-analysis on 14 studies containing data on the risk of acute myocardial infarction in NSAID users, with a focus on confirmed myocardial infarctions.[131] These authors concluded that based on the limited current data there could be a general direction of effect for traditional NSAIDs as a class to be associated with an increased risk of acute myocardial infarction (1.19; 95% CI 1.08, 1.31). This meta-analysis did not separate out diclofenac versus other NSAIDs or COX-2 selective inhibitors. However, the diclofenac risk ratio (1.38; 95% CI 1.22, 1.57) was described as being similar to that observed for NSAIDs overall (1.19) and ibuprofen (1.11) but lower than that for naproxen (0.99).

In their epidemiological study, Jick et al. investigated if the risk for myocardial infarction increases with the number of NSAID prescriptions in patients with low-to-moderate cardiovascular baseline risk.[132] The risk of myocardial infarction in patients with a single NSAID prescription (corresponding to a 1-month supply) was considered by the authors as being neutral. An increased risk was noted in patients who received ten or more prescriptions for rofecoxib, celecoxib or diclofenac, but no elevation of risk according to the number of prescriptions was observed for ibuprofen or naproxen. These studies

were unable to control for dose effects since the available information indicated that the median daily doses were comparatively low (from an equipotency perspective) in the ibuprofen, rofecoxib and celecoxib groups compared with diclofenac. The large-scale study by Singh et al. found no increased risk of heart attack with diclofenac when given at the recommended prescription doses (substantially higher than the approved OTC dose of up to 75 mg/day)[131] and the study by Jick et al. indicated that there is a risk with ten prescriptions or more,[132] a treatment duration much longer than the recommended OTC medication (<1 week).

Collectively these meta-analyses do not provide more information than the individual large-scale studies. There may be a slightly higher-grade association of diclofenac with myocardial infarction than some other NSAIDs. This association is around 1.4–1.6, compared with 1.2–1.4 with other NSAIDs, which is compatible with a number of biases, including a prescription or channelling bias related to publications stating that diclofenac does not interfere with the cardioprotective effect of aspirin,[107,108] especially since most of the epidemiological studies were performed after these publications. Most studies do not control for the concomitant use of aspirin, especially low-dose aspirin. There also appear to be indications of dose and duration effects in the cardiovascular risk profiles associated with NSAIDs, which again raises the question of the relevance of the results of long-term, high-dose studies to short-term, low-dose use of diclofenac for common pain.

In 2005 the European Medicines Agency completed an assessment of the available evidence on the cardiovascular safety of NSAIDs and recommended no changes be made to advice given to patients and prescribers.[133]

5.6 Summary of Comparative Safety and Tolerability

The type and frequency of adverse events, including GI adverse events, in almost 2400 patients given low-dose diclofenac potassium 12.5mg in single or multiple doses for up to 7 days were similar to those of low-dose ibuprofen 200mg and comparable to placebo. The percentages of patients with low-dose diclofenac potassium discontinuing treatment because of GI adverse events were similar to those taking low-dose ibuprofen and placebo. No serious adverse events or deaths occurred in short-term trials (of up to 7 days) with low-dose diclofenac potassium 12.5mg.

A long-term, randomised, single-blind trial in 1221 patients with OA compared two low doses of diclofenac potassium (37.5mg and 75 mg/day) and high-dose diclofenac potassium (150 mg/day) to low-dose ibuprofen (1200 mg/day) given daily for 3 months.[65] No difference in safety and tolerability between low-dose diclofenac potassium and low-dose ibuprofen was demonstrated with respect to type and frequency of adverse events and number of premature discontinuations because of adverse events.

Only three drug-related serious adverse events occurred with low-dose diclofenac potassium, two of which were GI complications; none occurred before 1 month of treatment (range 30–70 days). No drug-related deaths because of GI complications occurred in the 3-month trial with low- or high-dose diclofenac or low-dose ibuprofen.[65]

The GI safety profile of low-dose diclofenac potassium 12.5mg has been confirmed in a low-dose endoscopy trial[66] in which multiple doses over 2 days produced similar GI scores to low-dose ibuprofen, and significantly better scores than aspirin.

There were no hepatic adverse events in short- and long-term trials of low-dose diclofenac potassium for up to 3 months. In a specific hepatic safety

trial performed in patients with OA, no clinically relevant elevations in ALT and/or AST occurred in the first 2 weeks of treatment.[65] Only 2 of 687 patients (0.3%) receiving low-dose diclofenac potassium had a clinically relevant elevation of liver transaminase levels (>3 × ULN) after 28 days of treatment (range 25–31 days).

There were no clinically relevant cardiovascular safety-related events.

6. Conclusion

The analgesic and antipyretic efficacy of diclofenac potassium 12.5mg is demonstrably superior to placebo and at least as good as standard OTC reference drugs in a range of painful and febrile conditions, i.e. dental pain, headache, fever and painful symptoms of cold and influenza, acute lower back pain and dysmenorrhoea. In the pooled clinical trials with immediate-release formulations of low- or high-dose diclofenac potassium, the most common adverse events, including GI events, were dependent on dose (low vs high) and treatment duration (single dose vs short term, i.e. 1–2 weeks, vs long term, i.e. 3 months), and indication. The adverse event profile of low-dose diclofenac potassium was similar to that of low-dose ibuprofen regardless of the duration of treatment. Therefore, it is likely that in normal OTC use, the tolerability profile of diclofenac would be very similar to that of ibuprofen, the reference for drug safety in OTC analgesia, with the added benefit of a lack of interference with the cardioprotective effect of aspirin.

Patients are generally capable of taking diclofenac potassium 12.5mg in an appropriate way. Its efficacy and safety/tolerability profile as demonstrated in clinical trials for short-term use, i.e. 5 days for pain and 3 days for fever, support its use as an OTC agent.

Acknowledgements

The author would like to thank Novartis Consumer Health for providing the data used to prepare this review, and Drs Ackerman, Unkauf and Farrenkopf for their assistance in preparing the manuscript. The persons acknowledged here are employees of Novartis or were commissioned by Novartis to provide the data used in this review. The author received no funding in relation to the preparation, submission or acceptance of this paper. The author has no conflicts of interest that are directly relevant to the contents of this review.

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