REVIEW ARTICLE

Review of Safety and Efficacy of Polmacoxib: A Novel Dual Inhibitor of Cyclo-oxygenase 2 and Carbonic Anhydrase in Osteoarthritis and Acute Painful Conditions

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Received: 28 April 2025; *Accepted:* 10 June 2025

Abstract

Osteoarthritis (OA) is a chronic degenerative joint disorder and a leading cause of pain and disability among the elderly. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), though effective in symptom relief, pose significant risks of gastrointestinal, cardiovascular, and renal complications, especially in long-term use. Polmacoxib (CG100649) is a newer NSAID with its dual inhibitory role on cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA), planned to offer higher therapeutic efficacy and safety. This review critically examines the pharmacodynamic and pharmacokinetic properties of polmacoxib, along with its clinical efficacy and safety in OA and acute pain conditions. Clinical trials across phases I–III consistently show polmacoxib to be well tolerated and effective in pain relief and efficient improvement of the joint, with a safety profile comparable to or better than traditional COX-2 inhibitors like celecoxib. Recent trials also explore its role in combination therapies for acute pain management, including dental and postoperative settings, showing noninferiority to standard regimens and fewer adverse events. Its innovative mechanism and pharmacological profile support its potential as a next-generation NSAID for OA and pain management, particularly in populations at high risk for NSAID-induced adverse effects. Further larger long-term studies are warranted to confirm its medical benefits and broader therapeutic applications.

Journal of The Association of Physicians of India (2025): 10.59556/japi.73.1180

Introduction

Osteoarthritis (OA) is the most common type of arthritis leading to chronic pain and long-term disability in adults. It is associated with articular cartilage loss and hypertrophic bone. It predominantly affects load-bearing joints such as the hips and knees.[1] The World Health Organization (WHO) Global Ageing and Health Report (2015) underscores it as the fourth leading cause of disability among adults aged 60 years and older.[1,2] In 1990 nearly 23.46 million Indians were affected by OA, while by 2019 it had risen to 62.35 million.[3] OA can be categorized into two types: primary OA, which arises without an identifiable cause, and secondary OA, which develops due to factors such as injury or underlying medical conditions. Risk factors for OA include advancing age, female sex, obesity, certain anatomical traits, muscle weakness, and joint injuries, particularly those resulting from occupation-related activities or sports.[4]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been the cornerstone of symptomatic treatment for OA, helping to alleviate pain and inflammation. However, traditional NSAIDs, while effective, are associated with significant adverse effects, including gastrointestinal (GI) toxicity, cardiovascular (CV) risk, and renal impairment, which limit their long-term use, especially in older adults.[5]

Recent therapeutic advancements have aimed to develop safer alternatives with improved efficacy and reduced side effects. Polmacoxib is an innovative dual inhibitor of cyclooxygenase-2 (COX-2) and carbonic anhydrase (CA), a promising new class of NSAID that has garnered attention for its potential to provide effective pain relief with a more favorable safety profile.[6] Its dual mechanism of action targets both the inflammatory pathway mediated by COX-2 and the dysregulated CA enzyme activity often seen in OA, offering a more comprehensive approach to managing the disease.

This review aims to critically appraise the safety and efficacy of polmacoxib in the treatment of OA. We will explore preclinical and clinical studies, focusing on its pharmacokinetics (PK), pharmacodynamics (PD), clinical outcomes, and adverse event profile. By comparing polmacoxib to traditional NSAIDs and other novel treatments, this review seeks to provide a comprehensive understanding of its role as a next-generation therapeutic option for OA.

Polmacoxib (CG100649)

Polmacoxib is a synthetic novel NSAID inhibiting both COX-2 and CA enzymes. It was developed by CrystalGenomics Inc. and first approved in South Korea in 2015 for the treatment of colorectal cancer and OA.[7] On 14th February 2023, the Drug Controller of India approved polmacoxib for the management of idiopathic primary OA of the hip and knee.[8] Its chemical structure and pharmacological properties are shown in Figure 1 and Table 1, respectively.

Pharmacodynamics of Polmacoxib

NSAIDs are a class of drugs commonly used to relieve pain, control inflammation, and reduce fever. They act through cyclooxygenase (COX) enzyme inhibition. There are two types of COX isoenzymes: COX-1, which is constitutively expressed and plays a protective role in the gastric mucosa and platelet function, and COX-2, which is induced in inflammation and is responsible for producing prostaglandins mediating pain and inflammation.[10] Most traditional NSAIDs are nonselective,

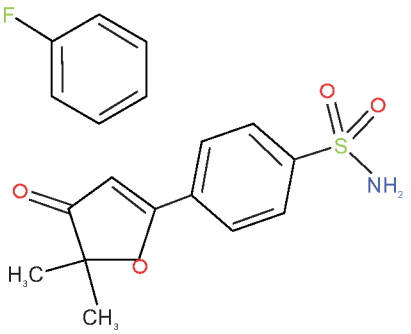

Fig. 1: Chemical structure of polmacoxib

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How to cite this article: Gunjal VS, Pawar RR, Sharma AD. Review of Safety and Efficacy of Polmacoxib: A Novel Dual Inhibitor of Cyclo-oxygenase 2 and Carbonic Anhydrase in Osteoarthritis and Acute Painful Conditions. J Assoc Physicians India 2025;73(10):88–92.

Table 1: Features and properties of polmacoxib[9]

Alternative names	CG100649, CG-100649, Acelex®, Polmakem™
Class	Nonsteroidal anti-inflammatory drugs
Route of administration	Oral
Recommended dosage	2 mg once daily after a meal. The dose should not exceed 2 mg/day
Pharmacodynamics	Dual inhibitor of cyclo-oxygenase 2 and carbonic anhydrase
Pharmacokinetics	Mean T_{max}: 5.6 hours; mean C_{max}: 3.5 ng/mL; mean $t_{1/2}$: 131 hours; Excretion: primarily *via* the fecal route
Approved therapeutic indication	OA of the hip or knee
Adverse events	Epigastric pain, diarrhea, indigestion, nausea, abdominal pain, chest discomfort, facial swelling, edema, peripheral swelling
WHO ATC code	M01AH07
Molecular formula	$C_{18}H_{16}FNO_4S$
CAS registry number	301692-76-2

CAS, chemical abstracts service; WHO ATC, World Health Organization Anatomical Therapeutic Chemical

inhibiting both COX-1 and COX-2, and can lead to GI adverse effects. Selective COX-2 inhibitors specifically target the COX-2 isoenzyme, reducing GI damage but sparing the gastroprotective effects of COX-1.[11] Hence, it is usually recommended to use selective COX-2 inhibitors over nonselective NSAIDs for patients with OA and GI comorbidities.[12] However, certain COX-2 inhibitors, such as rofecoxib and valdecoxib, have been withdrawn from the market due to concerns about increased CV risks linked to their inhibition of COX-2 in the circulatory system.[13]

Polmacoxib stands out from other NSAIDs due to its dual mechanism of action, which includes both COX-2 inhibition and inhibition of CA-I and CA-II. Unlike most conventional COX-2 inhibitors, which do not significantly affect CA activity, polmacoxib shows a higher affinity for CA than COX-2, particularly in CV tissues. This dual inhibition reduces COX-2 activity in the CV system, potentially minimizing the CV risks typically seen with selective COX-2 inhibitors.[14] Moreover, low-dose administration has negligible impact on overall CA function in the CV system. In contrast, inflamed tissues, which have low CA levels and elevated COX-2 expression, benefit from its ability to effectively inhibit COX-2, thus reducing inflammation and pain, particularly in conditions like OA.[14]

Pharmacokinetics of Polmacoxib

The transport of polmacoxib across the biological membrane principally involves red blood cells (RBCs). RBCs act as a reservoir, carrying the drug in an inactive form to tissues with low CA activity, for example, inflamed joints in OA. The drug concentration in RBCs is 85- to 100-fold higher than in plasma, where CA is absent.[15] This unique transport system ensures that polmacoxib remains active in the inflamed joints while minimizing systemic exposure, thereby reducing its potential impact on the CV, renal, and GI systems. Pharmacokinetic data show that after oral administration of polmacoxib at 2 and 8 mg doses, maximum plasma concentrations (Cmax) were 3.5 and 14.1 ng/mL, respectively, with elimination half-lives of 131 hours and 127 hours.[15] Polmacoxib also demonstrates a longer retention time in the inflamed joint tissues compared to blood, suggesting its sustained therapeutic effect at the target site while limiting prolonged exposure to other body systems. Polmacoxib is metabolized by the hepatic microsomal enzyme CYP3A4 and is principally excreted in the feces, with only traces found in the urine. Any impairment in liver function could potentially affect its clearance.[14]

Preclinical Pharmacology

Lee et al. (2008) conducted an experimental *in vivo* and *in vitro* evaluation of polmacoxib.[16] The study reported that polmacoxib has moderate selectivity for COX-2 compared to COX-1, with selectivity ratios ranging from 15-fold in human cells (whole blood, macrophages, and platelets) to 45-fold in mouse peritoneal macrophages. In *ex vivo* assays (rat whole blood), it showed a lower COX-1 inhibition potential compared to indomethacin. It showed potent anti-inflammatory effects in animal models, with paw swelling ED_{50} of 0.10 and 0.22 mg/kg/day in adjuvant-induced and collagen-induced arthritis in Lewis rats, respectively. Indomethacin and polmacoxib exhibited parallel efficacy in rat paw edema and mouse acute air pouch models, but the latter was 5 times more potent compared to indomethacin in a thermal hyperalgesia rat model and displayed higher antipyretic activity than ibuprofen. Polmacoxib inhibited human CA I and II with IC_{50} values of 0.336 µM and 0.062 µM, respectively, compared to acetazolamide (0.68 µM and 0.0091 µM). The CA-blocking activity of polmacoxib likely does not interfere with its therapeutic effects, as it is believed to detach from CA and concentrate in tissues with low CA activity (inflamed joints). However, its high affinity toward CA may influence its tissue distribution, potentially reducing COX-2 inhibition in CA-rich tissues like the GI tract, blood, and kidneys, thereby mitigating NSAID-associated toxicities in these organs. Additionally, its CA-binding affinity could lead to blood pressure reduction, similar to the effects of acetazolamide, a potent CA inhibitor.[16]

Clinical Pharmacology

A phase I clinical trial conducted by Hirankarn et al. (2013) characterized the pharmacokinetics (PK) of polmacoxib in healthy volunteers. After single oral doses of 2 mg or 8 mg, polmacoxib exhibited long half-lives in whole blood and plasma (mean ± SD: 127 ± 33 hours and 131 ± 19 hours, respectively) and a high whole blood-to-plasma concentration ratio (78 ± 23), indicative of biodistribution similar to other strong CA inhibitors. While absorption rate constants between plasma and whole blood were comparable, significant differences were observed in clearance (3.29 vs 0.04 L/hour/70 kg) and in volume of distribution (559 vs 7.6 L/70 kg). These findings highlight unique pharmacokinetic parameters of polmacoxib compared to other COX-2 inhibitors, warranting further studies to explore its clinical implications.[17]

Similarly, a randomized, placebo-controlled, double-blind, multiple ascending dose (MAD) study was conducted by Kim et al. (2015)[18] and evaluated polmacoxib's safety, PK, and PD. This study included 48 healthy Korean volunteers (8 males and 8 females in each dose cohort). Participants received either polmacoxib—administered as loading doses of 8, 10, or 12 mg followed by 2, 4, or 8 mg daily for 6 days—or a placebo. Results showed that polmacoxib achieved significantly higher whole blood concentrations (50–70 times plasma levels), with a median T_{max} of 3–10 hours and a terminal half-life of 121–203 hours in blood. Adverse events were mild, with no significant changes in blood pressure. The

study concluded that polmacoxib was well tolerated and effective in suppressing COX activity markers at multiple doses.[18]

A phase II double-blind randomized controlled trial (RCT) (NCT00530452)[19] was conducted by CrystalGenomics Inc. to study the safety and efficacy of polmacoxib in treating OA pain over 21 days. This placebo-controlled study randomized eligible participants, who recorded an average daily pain intensity (DPI) of 4–8 during a washout period, to receive one of three dose levels of polmacoxib or placebo. Participants were prohibited from using other NSAIDs, COX-2 inhibitors, opioids, or corticosteroids during the study, with acetaminophen allowed for breakthrough pain. Efficacy was assessed using differences in the Western Ontario and McMaster Universities OA (WOMAC OA) index at baseline and days 7, 14, 21, 28, and 35, along with DPI, functional interference–Brief Pain Inventory (BPI) scales, and pain relief evaluations recorded in subject diaries at scheduled visits. The study findings are not available in the public domain but are suggestive of promising efficacy and safety of polmacoxib.[19]

Later, a phase IIa randomized double-blind trial conducted by Schmidt et al. (2009)[20] evaluated the efficacy and safety of polmacoxib. The study involved 248 male patients with OA across 25 sites in Germany, Ukraine, and Hungary. The participants received high (8 mg), medium (4 mg), or low doses (2 mg) of either polmacoxib or placebo over a 21-day treatment period. The 8 mg group showed more than twice the improvement in WOMAC scores compared to the placebo group (37 vs 17%; $p = 0.01$), with significant benefits observed across pain, stiffness, and physical function subscales ($p < 0.05$) throughout the treatment as well as during the follow-up periods. Early and sustained pain relief was evident by day 7 and persisted through day 28. Importantly, polmacoxib showed no treatment-related changes in blood pressure, electrocardiogram (ECG) parameters, or GI bleeding across all doses, highlighting its safety profile. The study concluded that polmacoxib provides significant analgesic and functional benefits as a dual COX-2 and CA inhibitor and lacks GI or CV adverse effects.[20]

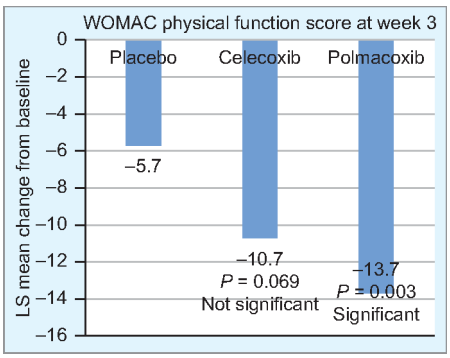

Fig. 2: WOMAC physical function score

In 2017, Lee et al.[21] reported the study findings of a phase III RCT of 6 weeks, followed by an open-label extension study (for 18 weeks) which evaluated the safety and efficacy of polmacoxib compared to placebo (superiority) and celecoxib (noninferiority) in patients with OA. Of 362 patients randomized, 324 completed the 6-week treatment phase, and 220 continued into the extension. Polmacoxib (2 mg) demonstrated significantly greater pain reduction than placebo, as reflected by the WOMAC pain subscale (mean difference: –2.5; 95% CI: –4.4 to –0.6; $p = 0.011$), and was found to be noninferior to celecoxib 200 mg (mean difference: 0.6; 95% CI: –0.9 to 2.2; $p = 0.425$). Additionally, physician assessments indicated that a higher proportion of patients treated with polmacoxib were rated as "much improved" by week 3. Surprisingly, polmacoxib demonstrated statistically significant superiority over placebo ($p = 0.003$), whereas celecoxib did not show a statistically significant difference from placebo ($p = 0.069$) at week 3, as shown in Figure 2. Adverse events, particularly GI and general disorders, were more frequent with polmacoxib and celecoxib than with placebo. The study concluded that polmacoxib 2 mg is an effective and safer option for the treatment of OA, demonstrating a safety profile similar to that of celecoxib.[21]

Recently, in 2024, a phase III multicentric RCT by Sinha et al.[22] reported the efficacy and safety of polmacoxib (2 mg) vs celecoxib (200 mg) in 294 Indian adult patients with idiopathic knee or hip OA diagnosed per the American College of Rheumatology (ACR) criteria. Patients were randomized with an allocation ratio of 1:1 and received either polmacoxib or celecoxib. Pain assessment scores were recorded at weeks 3 and 6 using the WOMAC pain subscale, WOMAC OA index, and global evaluations by subjects and physicians. It demonstrated comparable improvements in pain scores for both groups, with mean changes of 4.88 (polmacoxib) vs 4.49 (celecoxib) in the ITT population and 4.90 vs 4.50 in the PP population ($p < 0.0001$). Of the 40 adverse events (AEs) reported, 30 were treatment related, with a slightly lower incidence in the polmacoxib group (13 AEs vs 17 AEs for celecoxib). The study concluded that polmacoxib is noninferior to celecoxib in terms of both safety and efficacy, potentially offering a safer alternative to traditional NSAIDs by reducing GI and CV side effects.[22]

The clinical evolution of polmacoxib is summarized in Table 2.

Clinical Evidence on Drug–Drug Interactions

A study was conducted by Choi et al. (2013)[23] to find the effect of a strong CYP3A inhibitor (ketoconazole) on the pharmacokinetics of polmacoxib. This was a randomized open-label two-period crossover trial involving 30 healthy Korean male volunteers. Participants received a single 6 mg dose of polmacoxib alone or in combination with 400 mg of ketoconazole, with a washout period of 42 days between the treatments. The results showed that concurrent ketoconazole administration increased the AUClast of polmacoxib by 29% (2074.0 vs 2685.8 ng·hour/mL; $p < 0.05$), while the Cmax values were comparable (10.7 vs 11.0 ng/mL). No significant differences were observed in safety outcomes, including vital signs, clinical laboratory results including ECGs, or adverse events (AEs), with 17 mild AEs reported and resolved without sequelae. The study concluded that although ketoconazole increases exposure to polmacoxib, the combination does not alter its safety profile, suggesting no need for dosage adjustments.[23]

Clinical Research with Concomitant Administration of Other Analgesics

A multicentric parallel RCT (CTRI/2023/11/060049)[24] evaluated the efficacy and safety of a fixed-dose combination (FDC) of polmacoxib (2 mg) and paracetamol (325 mg) vs an FDC of etoricoxib (60 mg) and paracetamol (325 mg) in Indian adults (18–65 years) experiencing acute pain following dental extraction. This study was conducted at 10–12 sites across India, and a total of 144 patients (72 per group) were randomized in a 1:1 ratio. The study reported noninferiority of polmacoxib + paracetamol to etoricoxib + paracetamol in percent change in mean pain intensity assessed by the Numeric Pain Rating Scale (NPRS) at 6, 24, and 48 hours. There was better control of pain at 24 and 48 hours in polmacoxib + paracetamol vs etoricoxib + paracetamol in mean pain relief (five-point scale), total pain relief, and Patient's Global Impression of Improvement (PGI-I). Of 25 AEs reported, only 6 were treatment related, with a lower incidence in the polmacoxib + paracetamol group (2 AEs vs 4 AEs for etoricoxib + paracetamol). All AEs were grade 1–1 and resolved without sequelae. The study concluded that polmacoxib + paracetamol is noninferior to etoricoxib +

Table 2: Summary of clinical trials

Phase	*Authors*	*Year*	*Study design*	*Population*	*Intervention*	*Efficacy*	*Safety*
I	Hirankarn et al.[17]	2013	Randomized, prospective, single dose pharmacokinetic (PK) study	*N* = 13 healthy human participants	Polmacoxib 2 and 8 mg	PK profile: Comparable absorption rate constants in plasma and whole blood High whole blood-to-plasma concentration ratio (78 ± 23) Volume of distribution –559 vs 7.6 L/70 kg) Clearance –3.29 vs 0.04 L/hour/70 kg) Half-lives in whole blood and plasma (mean ± SD: 127 ± 33 hours and 131 ± 19 hours, respectively)	
I	Kim et al.[18]	2015	Randomized, double-blind, placebo-controlled, multiple ascending dose study	*N* = 48 healthy Korean volunteers	Polmacoxib (8, 10, or 12 mg loading doses followed by 2, 4, or 8 mg daily for 6 days) or placebo	Suppressed serum thromboxane B2 (68–91%) and *ex vivo* lipopolysaccharide-stimulated prostglandin E2 (89–96%; $p < 0.001$) at all doses 8 mg dose also reduced urinary prostacyclin metabolite excretion by 64% ($p < 0.001$)	Adverse events (AEs) were mild, with no significant changes in blood pressure
II	NCT00530452[19]	2007	Randomized, double-blind, placebo-controlled study	*N* = 240 adult, normotensive patients of osteoarthritis (OA)	Polmacoxib 2, 4, or 8 mg daily for 21 days or placebo	Not yet publicly available	Not yet publicly available
IIa	Schmidt et al.[20]	2009	Randomized, double-blind, placebo-controlled study	*N* = 248 male patients with OA	Polmacoxib 2, 4, or 8 mg daily for 21 days or placebo	8 mg group showed >2 folds improvement in WOMAC scores compared to placebo (37 vs 17%; $p = 0.01$), with significant benefits observed across pain, stiffness, and physical function subscales ($p < 0.05$) throughout the treatment and follow-up periods	No treatment-related changes in blood pressure, ECG parameters, or gastrointestinal bleeding across all doses, highlighting its safety profile
III	Lee et al.[21]	2017	Randomized, double-blind trial of 6-week, followed by an open-label extension study (for 18 weeks)	*N* = 362 patients of OA	Polmacoxib 2 mg compared to placebo (superiority) and celecoxib 200 mg (noninferiority)	Polmacoxib showed superior pain reduction compared to placebo (WOMAC-pain subscale difference: –2.5; 95% CI, –4.4 to –0.6; $p = 0.011$) and was noninferior to celecoxib (difference: 0.6; 95% CI, –0.9 to 2.2; $p = 0.425$) Physician's assessments showed higher proportion of patients opted for "much improved" at week 3 with polmacoxib	AEs, particularly gastrointestinal and general disorders, were more frequent with polmacoxib and celecoxib than with placebo
III	Sinha et al.[22]	2024	Randomized, multicentric, double-blind, active-controlled study	*N* = 294 adult Indian patients with idiopathic knee or hip OA	Polmacoxib (2 mg) vs celecoxib (200 mg)	Improvements in pain scores (WOMAC pain subscale, WOMAC-OA index, and global evaluations by subjects and physicians) for both groups, with mean changes of 4.88 (polmacoxib) vs 4.49 (celecoxib) in the ITT population and 4.90 vs 4.50 in the PP population ($p < 0.0001$)	Of the 40 AEs reported, 30 were treatment-related, with a slightly lower incidence in the polmacoxib group (13 AEs vs 17 AEs for celecoxib)

AEs, adverse events; CI, confidence interval; ITT, intention to treat; OA, osteoarthritis; PK, pharmacokinetics; PP, per protocol; WOMAC, Western Ontario and McMaster Universities Arthritis Index

paracetamol in terms of both safety and efficacy, potentially offering a safer and more efficacious alternative in acute pain.[24] Based on the study findings, the fixed-dose combination (polmacoxib 2 mg plus paracetamol 325 mg) received marketing approval for short-term use in acute somatic mild-to-moderate painful inflammatory conditions by DCGI on 6th August 2024.[25]

Another randomized parallel controlled clinical trial was initiated in August 2024, evaluating the efficacy of concomitant administration of polmacoxib 2 mg once daily with Ultraset ER Semi [containing tramadol (18.75 mg) + paracetamol (162.5 mg), as required] vs Ultraset ER Semi perioperatively in 150 patients with OA undergoing surgery for rotator cuff tear. The primary endpoint is cumulative administration frequency of narcotic analgesics at postoperative day 3. The secondary endpoints are cumulative number of doses of nonopioid analgesics excluding NSAIDs, range of motion, pain scores [Visual Analog Score, American Shoulder and Elbow Surgeons Score, and University of California, Los Angeles (UCLA) Score] perioperatively, and rotator cuff retear status at 12 weeks

postsurgery. The estimated study completion is August 2025.[26]

Finally, to summarize, polmacoxib is an innovative first-in-class orally administered NSAID with dual inhibition of COX-2 and CA enzymes. Being a selective COX-2 inhibitor, it reduces the risk of GI side effects typically seen with traditional nonselective NSAIDs. Clinical studies indicate that polmacoxib delivers significant analgesic and functional benefits, making it a promising option for effective and well-tolerated long-term pain relief in OA management as well as effective in acute painful conditions such as toothache. Additionally, its unique tissue-specific transport mechanism may help reduce the CV risks often linked to COX-2 inhibition. However, further larger RCTs are necessary to comprehensively assess its long-term safety and efficacy.

Conclusion

In conclusion, polmacoxib emerges as a promising dual-action NSAID with distinct advantages for managing osteoarthritis and acute painful conditions. By selectively inhibiting both COX-2 and carbonic anhydrase enzymes, polmacoxib offers a targeted mechanism that minimizes gastrointestinal, cardiovascular, and renal side effects commonly associated with traditional NSAIDs. Clinical studies across phases I–III consistently demonstrate its noninferiority to established treatments like celecoxib, with favorable safety and efficacy profiles. Its pharmacokinetic properties—including prolonged half-life and red blood cell-mediated tissue-specific delivery—enable sustained therapeutic effect while reducing systemic toxicity. Moreover, recent data from Indian and international trials underscore its potential utility not only in chronic OA management but also in acute pain scenarios such as postoperative and dental pain. The availability of fixed-dose combinations further enhances its clinical versatility. While current findings are encouraging, further long-term multicenter studies are essential to substantiate its safety and broaden its therapeutic applications across diverse patient populations.

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