EFFICACY AND SAFETY OF **S-ETODOLAC 300 mg** PROLONGED RELEASED TABLETS IN TREATMENT OF OSTEOARTHRITIS

Content

Background and Objective of the Survey

S-Etodolac 300mg prolonged-release tablets have shown promising efficacy and safety in the treatment of osteoarthritis (OA), providing relief from pain and inflammation associated with this degenerative joint disease.

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that works by inhibiting the production of prostaglandins, which are chemical messengers involved in pain and inflammation. The prolonged-release formulation of S-etodolac allows for sustained release of the medication over an extended period, providing continuous pain relief and improved patient adherence due to less frequent dosing.

Several clinical studies have demonstrated the efficacy of S-etodolac prolonged-release tablets in reducing pain and improving physical function in patients with OA. These studies have shown that S-etodolac provides significant pain relief compared to placebo and is non-inferior to other NSAIDs commonly used in the treatment of OA, such as naproxen and diclofenac.

In addition to its pain-relieving effects, S-etodolac has been shown to reduce inflammation and improve joint function in patients with OA. This can lead to enhanced mobility, increased range of motion, and improved quality of life for individuals affected by this chronic condition.

Furthermore, the prolonged-release formulation of S-etodolac may offer advantages in terms of safety and tolerability compared to immediate-release NSAIDs. By providing a steady and controlled release of the medication, S-etodolac prolonged-release tablets may help minimize gastrointestinal side effects such as dyspepsia, gastritis, and peptic ulcers, which are commonly associated with NSAID use.

The objective of the survey is:

To evaluate the efficacy and safety of S-etodolac 300mg prolonged released tablets in treatment of osteoarthritis

Methodology of the Survey

A survey was conducted to evaluate the efficacy and safety of S-etodolac 300mg prolonged released tablets in treatment of osteoarthritis. A total of 125 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Etodolac
- Pharmacokinetic Properties
- Pharmacokinetic Profile in Special Populations
- Tolerability
- Drug-drug interactions
- Studies on Etodolac
- Clinical Applications
- Abstracts on S-etodolac

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Anti-inflammatory, analgesic medications, including aspirin, are widely used agents that are effective in the treatment of arthritic conditions. Clinicians have found, however, that patients with arthritis have varied responses to the currently available compounds in terms of relief of symptoms and the side effects produced, and often must try alternative compounds to ascertain the most favorable treatment for an individual patient. Etodolac is a new nonsteroidal anti-inflammatory drug (NSAID) that has become available recently for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA), and mild to moderate pain in the United Kingdom and in many other countries.

Efficacy in OA and RA is measured by relief of pain and stiffness, reduction of swelling, and improvement in joint function, among other assessments. Safety evaluation is based on the frequency and severity of adverse events, both in controlled clinical trials and in clinical practice. Another important aspect of safety is drug interaction. In clinical practice, a patient may be under treatment for more than one condition, and may be receiving other drug therapies. Etodolac, like other NSAIDs, is highly (> 99%) bound to serum protein(l). It is therefore important to rule out possible interactions with other highly protein-bound drugs.

Etodolac[2]

Etodolac is marketed in Canada by Procter & Gamble under the name of Ultradol and in some other countries by Wyeth-Ayerst as Lodine. The structural formula of etodolac is (+) 1,8-diethyl-l,3,4,9-tetrahydropyrano-(3,4,-b) indole-l-acetic acid. It is a peripherally acting drug with analgesic, antipyretic and anti-inflammatory properties. Etodolac has been extensively evaluated in the treatment of both inflammatory and degenerative forms of arthritis. It is not the intention of this review to examine those clinical trials which support the use of this effective and well-tolerated NSAID in the treatment of arthritis. Rather, the intent is to review other applications of etodolac in the management of various pain disorders. Etodolac has been

evaluated in patients with rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS) and gout.

It is superior to placebo and similar in efficacy and tolerability to other NSAIDs. In these studies, etodolac has been compared with a number of commonly prescribed NSAIDs (e.g. aspirin, diclofenac, naproxen, piroxicam, indomethacin, sulindac). Most studies employed a double-blind, randomized, parallel design and were of several weeks duration. Interested readers are referred to an extensive review by Balfour and Buckley for further information. In addition to the antiarthritic application of etodolac, clinical studies have also been conducted to evaluate the analgesic potential of etodolac in soft-tissue rheumatism, acute musculoskeletal injury, oral surgery, primary dysmenorrhoea, and following orthopaedic surgery, urological surgery and episiotomy.

Pharmacokinetic Properties

Absorption[3]

Peak plasma concentrations (Cmax) of etodolac are attained within 1 to 2 hours of administration of regular-release solid formulations. The time to achieve Cmax (tmax) of etodolac is most rapid when the drug is administered in solution, followed by solid regular-release formulations. As expected, tmax is longest when the drug is administered as a sustained release dosage form. After giving 4 individuals [^{14}C]etodolac 200mg, Ferdinandi et al. found Cmax values to range from 9.S to 22 mg/L. Interestingly, they suggested that this range of values was due to interindividual differences in first-pass metabolism, even though most NSAIDs undergo low hepatic extraction. Indeed, on the basis of animal studies, the absolute bioavailability of etodolac in humans was assumed to be near 1. However, a direct assessment of absolute bioavailability in humans has not been performed due to the lack of a suitable commercial intravenous formulation. Because etodolac is estimated to be nearly 100% bioavailable, a variation in Cmax due to firstpass metabolism alone is unlikely. The variation in Cmax may result from interindividual differences in the rates of absorption and/or volume of distribution (Vd) of the drug.

The relative bioavailability of sustained release etodolac was studied by Dey et al. in young male healthy volunteers. Two different sustained release formulations of etodolac were given; after 14 hours, 64 and 73% of the etodolac from these 2 formulations was released in an in

vitro dissolution test. The formulation giving the higher dissolution also had higher bioavailability in vivo than the formulation releasing less etodolac in vitro. Both sustained release formulations yielded a significantly lower bioavailability than an aqueous solution. The bioavailability of a sustained release formulation of etodolac is 78 to 84% of that of oral solutions.

Very recently, bioequivalence of an etodolac suppository has been assessed against a tablet formulation. Despite a 30% lower Cmax and somewhat slower absorption rate, the authors suggested that the suppository was bioequivalent to the tablet because area under the plasma concentration-time curve (AUC) and tmax values of the products were within 100 ± 20% of one another. Unfortunately, however, stereochemical aspects of etodolac pharmacokinetics were not taken into consideration.

In calculating the total body clearance (CL), Dey et al. assumed a value of 0.82 for bioavailability based on the recovery of radiolabelled drug in urine. However, when we reviewed the paper by Cayen et al. we could find no such value for bioavailability. Indeed, Ferdinandi et al. reported the urinary excretion of total radioactivity after administration of radiolabelled etodolac to be only 73%.

The effects of particle size, multiple-dose administration and dosage regimen on the pharmacokinetics of etodolac were studied by Kraml et al. in healthy human volunteers. The Cmax achieved following administration of etodolac as a tablet or capsule was 13 to 20% lower than that achieved after administration of the drug in solution ($p < 0.05$). Similarly, tmax was achieved earlier when the drug was given in solution than when it was administered in a solid dosage form. However, there was no difference in AUC values between the solid dosage forms and solution, indicating that the extent of absorption was not dependent on the dosage form used.

When capsules containing micronised etodolac were given (i.e. the particle size was smaller than that in other solid dosage formulations), the Cmax was significantly higher than that of a regular tablet. However, tmax, AUCO-48, and elimination half-life (v/2/3) were similar after administration of these 2 dosage forms. After repeated administration of etodolac (200mg daily or 100mg twice daily), there were no differences in the AUCO-24 of etodolac between that observed after the first dose and that observed after 7 days of administration. Therefore, etodolac does not appear to accumulate with repeated doses. Given that etodolac has a t'l2/3 of approximately 6 to 8 hours, this finding was unexpected. In contrast, Scatina et al. found a 13%

increase in AUCo-12 between the first and seventh dose of etodolac after administration of etodolac to a group of elderly volunteers.

With respect to stereoselectivity, the Cmax of Retodolac was significantly higher than that of Setodolac in young healthy volunteers given single doses of racemic etodolac 200mg. The tmax of both enantiomers, however, was similar. The S-enantiomer has a much higher CL and V d than the R-enantiomer, which explains its lower Cmax value. There has been no direct determination of the absolute bioavailability of the enantiomers in humans or animals. However, because of the much larger CL of the S-enantiomer, some difference in bioavailability between the enantiomers might be anticipated. By assuming an approximately lO-fold difference in the intrinsic clearance of the enantiomers, and by making some assumptions about the metabolism and excretion of etodolac, Brocks et al. have roughly estimated the bioavailability of the S-and R-enantiomers to be 0.73 and 0.97, respectively.

In assessing bioequivalence of racemic products, it is more meaningful to consider the concentration of the active enantiomer. This point is particularly important for etodolac because the concentration of the active enantiomer constitutes only 10% of the total drug concentration. Hence, non stereospecific data mainly reflect the time course of the inactive enantiomer, and any changes in the bioavailability of S-etodolac may remain unnoticed due to the lower statistical power of discrimination. This concern may become even more consequential when there exists a marginal difference in total plasma concentrations between the products. Indeed the insignificant differences between suppositories and tablets observed by Molina-Martinez et al. might have been significant if the plasma concentration of the S-etodolac had been measured.

Another important aspect of etodolac pharmacokinetics is the presence of substantial concentrations of the unstable glucuronidated drug in plasma. Spontaneous hydrolysis of these metabolites results in the release of parent etodolac if proper analytical procedures are not followed. Unfortunately, the assay described by Cosyns et al. and used by Molina-Martinez et al. in the study described above did not seem to involve precautions to prevent the spontaneous hydrolysis of the conjugated etodolac.

Table I. Mean pharmacokinetics of etodolac after single oral doses to healthy volunteers or patients

Study participants	Gender	No.	Age (y)	Weight (kg)	Dose (mg) [form]	C_{max} (mg/L)	t_{max} (h)	AUC_{0-t}[a] (mg/L • h)	$t_{½β}$ (h)	CL (ml/h/kg)	Vd/F (L/kg)	Presence of acyl-G tested
Nonstereospecific studies												
Healthy	M	28	26	78	200 (tab)	17.4	1.2	70.7[b]	6.0			No
	M	28	26	78	200 (cap)	15.9	1.4	71.6[b]	5.9			
	M	28	26	78	200 (sol)	20.0	0.5	67.9[b]	5.9			
Healthy	M	18	26	69	400 (mic)	28.6	1.4	115[c]	6.9			No
	M	18	26	69	400 (tab)	21.0	1.6	115[c]	6.5			
Healthy	M								7	40.8	0.41	No
Healthy	M	14	27		400 (sol)	36.8	0.55	133	6.0	36.3	0.31	No
	M	37	27	71	200 (cap)				8.4	38.5	0.47	
	M	37	27	71	200 (SR)	4.6	7.2	51.5[b]				
	M	37	27	71	400 (SR)	7.5	7.9	104[b]				
	M	37	27	71	600 (SR)	11.9	7.8	146[b]				
Healthy	M	4	23	68	200 (cap)	14.5	1.9	84	6.1			No
Healthy	M	20	27		200 (cap)	15.9	1.2	71.8	6.0			No
Healthy	M	24	76		200 (cap)	15.3	1.2	63.0	6.1			
Healthy	M	10			200 (cap)	15.4	1.4	63.9	5.7			No
Healthy	6M, 4F	10	27	69	200 (tab)	19.7	1.3	106	7.5			No
					200 (sup)	13.6	1.6	101	7.1			
Osteoarthritis	M	20	75		200 (cap)	16.7	1.3	74.6	6.5			
Cirrhosis	M	10			200 (cap)	17.4	1.1	67.4	6.0			No

Distribution[3]

Volume of Distribution

The mean apparent oral volume of distribution (V dIF) of etodolac calculated from oral doses is 0.3 to 0.5 L/kg. This value is higher than that of most other NSAIDs. In an animal study, Cayen et al. suggested that the high V d was due to the unbound fraction of etodolac in plasma (3.6 to 4.7%), which was apparently higher than that of other NSAIDs. However, in this study, the concentrations of etodolac used to spike the plasma were somewhat greater than those

encountered clinically. Later studies showed that the earlier value for unbound fraction reported by Cayen et al. was indeed larger than that seen at the concentrations encountered in vivo.

The mean V dIF of the S-enantiomer is 7- to 8-fold higher than that of the R-enantiomer. A small part of the difference can be attributed to the apparently lower bioavailability of the S-enantiomer. Nevertheless, when corrected using the estimated bioavailability of the enantiomers, 265 the V d of the S-enantiomer is still approximately 5-fold higher than that of its antipode. Indeed, the large VdIF of racemic etodolac is mainly due to the active S-enantiomer because R-etodolac has a V d/F similar to that reported for other NSAIDs. This extensive distribution of the S-enantiomer may have some interesting therapeutic relevance.

Protein Binding

Cayen et al. first reported the protein binding of etodolac in human serum samples spiked with either 20 or 100mg of the racemate. The binding was reduced with increases in serum concentration of drug; the unbound fraction at 100 mg/L was 1.35-fold greater than that at serum concentrations of 20 mg/L.

Using [^{14}C]etodolac, Ferdinandi et al. found that the protein binding of etodolac in human serum was extensive. Over a serum concentration range of 6 to 33 mg/L, the unbound fraction of etodolac in plasma was between 0.66 and 1.04%. The extent of binding of etodolac to proteins was independent of etodolac concentration within this range of drug concentrations. Ferdinandi et al. discounted the unbound fraction of etodolac reported by Cayen et al., but did not offer an explanation for the discrepancy in the results from the 2 studies. It is likely that the higher unbound fraction reported by Cayen et al. was at least partly due to the higher concentrations (100 mg/L) that were used. In common with the results of Ferdinandi et al., Scatina et al. found that the mean unbound fraction of etodolac in the serum of young individuals and elderly patients with osteoarthritis was 0.97 and 1.02% after single or multiple doses of 200mg etodolac. Albumin or total protein levels were similar in both groups of individuals. However, it is possible that there is an age-related change in the protein binding of the therapeutically active S-enantiomer.

The binding of etodolac to serum and synovial fluid after repeated administration was studied in patients with rheumatoid arthritis, but not receiving the drug. Samples were spiked with [^{14}C]etodoiac and equilibrium dialysis was used to assess binding. Etodolac was bound more

extensively in serum than in synovial fluid. There was a significant correlation between the extent of binding and total protein (r2 = 0.593) and albumin (r2 = 0.515) concentrations.

Using equilibrium dialysis of drug-spiked plasma and synovial fluid from patients with rheumatoid arthritis, Brocks et al. found that the R-enantiomer of etodolac was more highly bound than the S-enantiomer in both fluids. The plasma protein binding of the enantiomers in healthy individuals was similar to that observed in the plasma of patients with osteoarthritis or rheumatoid arthritis. These results were consistent with the observed higher V d/F of the S-enantiomer.

In a study involving the binding of etodolac enantiomers to human serum albumin, Muller et al. found a different extent of binding than that earlier reported by Brocks et al. in human plasma. As was recognised by Muller et al. plasma contains many endogenous components that might cause the binding in plasma to differ from that seen in a solution of albumin. Furthermore, Muller et al. used individual enantiomers to assess the extent of binding, whereas Brocks et al. spiked their plasma samples with racemate. Nevertheless, a higher binding of the R-enantiomer, as reported earlier, is quite consistent with the lower CL and Vd of R- than S-etodolac.

Table II. The in vitro protein binding of etodolac in serum from patients with osteoarthritis or rheumatoid arthritis

Reference	Specimen	Etodolac concentration (mg/L)	Unbound fraction (%)		
			S	*R*	racemate
Nonstereospecific					
Cayen et al. (1981)	Serum from healthy volunteers[a]	20			3.6
	Serum from healthy volunteers[a]	100			4.7
Ferdinandi et al. (1986)	Serum from healthy volunteers	6-33			0.66-1.04
Kraml et al. (1988)	Serum from patients with RA	0.1-20			0.93
	Synovial fluid from patients with RA	0.1-3.0			2.5
Scatina et al. (1986)	Serum from elderly patients with OA	2-15			0.97
	Serum from young healthy volunteers	2-15			1.02
Stereospecific					
Brocks (1993)	Plasma from young healthy individuals	10	0.85	0.47	
	Plasma from patients with RA and OA	10	0.90	0.51	
Brocks et al. (1991)	Plasma from patients with RA[a]	5	0.72	0.29	
	Plasma from patients with RA[a]	50	1.5	0.75	
	Synovial fluid from patients with RA	5	4.5	3.3	
Muller et al. (1992)	Human serum albumin solution (40 g/L)[b]	2	0.53	1.37	

a Samples 'spiked' with racemate.

b Samples 'spiked' with individual enantiomer.

Abbreviations: OA = osteoarthritis; RA = rheumatoid arthritis.

Distribution to Extrasynovial Tissues

Although there are no data available from humans, there are animal data describing the distribution of etodolac in extrasynovial tissues. In one study, the concentrations of radioactively labelled etodolac were highest in blood vessels, connective tissues and highly perfused organs such as kidney, liver and heart. The serum contained higher concentrations of etodolac than any of the tissues, but the elimination from tissues paralleled that in the serum. In a stereospecific tissue study, the ratio of AVC values of Sto R-enantiomers of etodolac in rat heart, liver, kidney and fat tissues was between 0.8 and 1.1. This was in contrastto the values seen in rat plasma, where the ratio of AVC values for the S- to R-enantiomer was 0.3. This finding complemented the plasma protein binding of etodolac enantiomers in the rat, because although the total concentration of S-etodolac was about one-third that of R-etodolac, the

unbound fraction of the S enantiomerwas 3- to 5-fold higher than that of the R enantiomer. Thus, the approximate I to 1 ratio of AVC values of the enantiomers in the tissues was explained. The large gap observed between the V d of the 2 enantiomers in animals and in humans is also explained, in part, by this observation.

Brocks and Jamali also studied the binding of etodo1ac enantiomers to rat tissues. A stereoselective binding of the enantiomers to each of the tissues was seen, with S to R AVCo-24 ratios ranging from 1.2 to 3.7. However, the absolute extent of the binding varied from tissue to tissue. After administering [^{14}C]etodolac, Ferdinandi et al. found that the blood clots remaining after separation of human serum contained almost no radioactivity indicating little orno uptake by the human blood cells.

Distribution into the Synovial Fluid

The synovial fluid has been proposed to be the primary site of action of NSAIDs. Therefore, the uptake of etodo1ac into the synovial fluid of patients has received some attention. Kraml et al. studied the etodolac concentration-time course in the synovial fluid of 5 patients (2 female, 3 male; age 35 to 71 years) with rheumatoid arthritis. The patients were given repeated doses of 200mg twice daily for 7 days. On the eighth day, etodolac 200mg was given, and serial serum and synovial fluid samples were collected for 32 hours. The mean Cmax of total etodolac (bound + unbound) in the synovial fluid 267 was lower (2.6 vs 15.6 mg/L), and the tmax was longer (3.2 vs 1.2 hours), than in the serum. This indicates that the entry of etodolac into the synovial fluid is delayed. The terminal decline in concentrations in both fluids was equivalent (t1\2β values were 6 hours in both fluids). However, neither the concentrations of the pharmacologically active S-enantiomer nor those of acyl glucuronidated etodo1ac were measured.

Kraml et al. found AVC values for total etodolac (bound + unbound) in the synovial fluid to be 67% of that in te serum, however, a substantially higher AVC for unbound etodolac (172%) was found in the latter. The investigators suggested that an active process for the transport of etodolac into synovial fluid may account for these observations.

Brocks et al. questioned the conclusions by Kraml et al., as these investigators had determined the unbound concentration of the drug using equilibrium dialysis of synovial fluid versus phosphate buffer. In vivo, however, synovial fluid is in equilibrium with plasma and not with

the buffer used. Hence, equilibrium is achieved only when free concentrations are equal in both sides of the synovium-plasma membrane. Therefore, as a result of the greater concentration of proteins in plasma compared with synovial fluid, the unbound fraction becomes influenced mainly by the extent of plasma protein binding. On the other hand, when synovial fluid is dialysed against buffer, plasma protein binding has no influence on the free concentration of drug in the synovial fluid. Consequently, if passive diffusion is assumed to exist, we would expect higher drug concentrations in the buffer side of dialysis cells that are equilibrated against synovial fluid than those placed against plasma. Hence, the difference in unbound drug concentration in the 2 fluids determined after equilibrium dialysis by Kraml and colleagues may have been solely due to different concentrations of albumin, the primary binding protein of NSAIDs.

Brocks et al. found that the stereoselectivity of the pharmacokinetic profile of etodolac found in plasma was not similarly present in the synovial fluid. After a single dose of etodolac 200mg, the S to R concentration ratio in 6 patients with rheumatoid arthritis was 0.074 in plasma, and 0.17 in synovial fluid. The concentrations of the R-enantiomer did not differ between synovial fluid and plasma. On the other hand, there was a 1.7 -fold higher concentration of S-etodolac in the synovial fluid than in the plasma. This observation was important, because it showed that the S-enantiomer, which possesses most of the pharmacological effect of etodolac, concentrates more than its antipode in the proposed site of action of NSAIDs. This is consistent with the observed stereoselectivity in the extravascular tissue distribution of etodolac in the rat.

Interestingly, Brocks et al. noted the presence of considerable quantities of acylglucuronidated etodolac in the synovial fluid. This finding had not been reported previously for other NSAIDs. The presence of acyl-glucuronides in the synovial fluid may have been secondary to the disease process, in which inflammatory changes in the synovial membrane led to altered synovial permeability. Indeed, etodolac is also interesting in that compared with most of the NSAIDs, high concentrations of glucuronidated drug are found in plasma, which in tum enhances the penetration of the acyl-glucuronides into synovial fluid. The possibility of trans-synovial diffusion of conjugates was supported by the significant correlation between plasma and synovial fluid concentrations of S-etodolac conjugates.

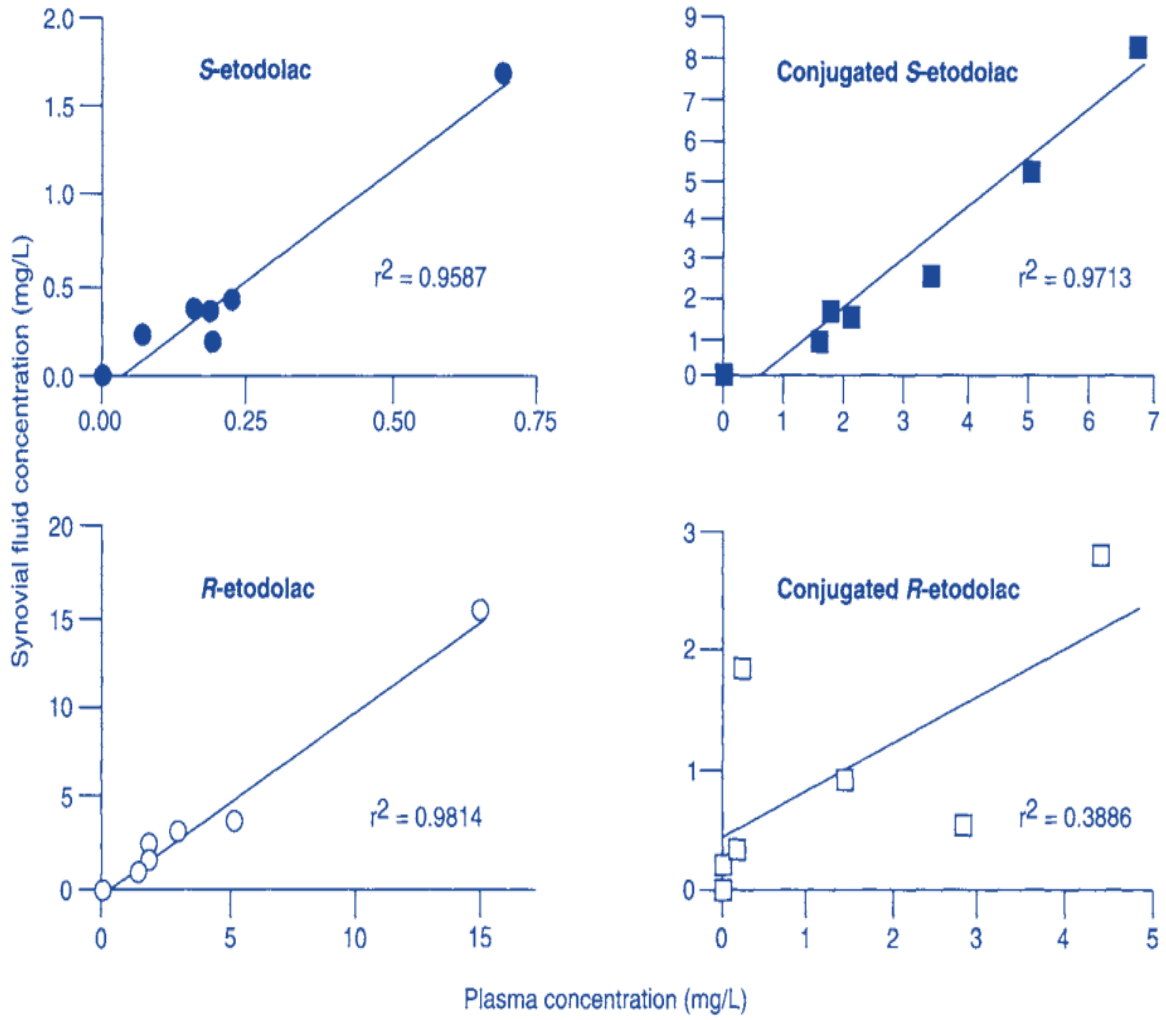


Fig. 1. Relationships between the plasma and synovial fluid concentrations of unchanged and acyl-glucuronidated etodolac enantiomers in patients with arthritis who received a single dose of racemic etodolac 200mg

The possibility that etodolac was glucuronidated by the synovial membrane itself was unlikely, because microsomal protein isolated from the synovial membrane of a patient with rheumatoid arthritis was devoid of glucuronidation activity in vitro. The levels of β-glucuronidase are increased in inflamed joints, and this could have caused the 2-fold higher concentrations of the S-enantiomer in synovial fluid.

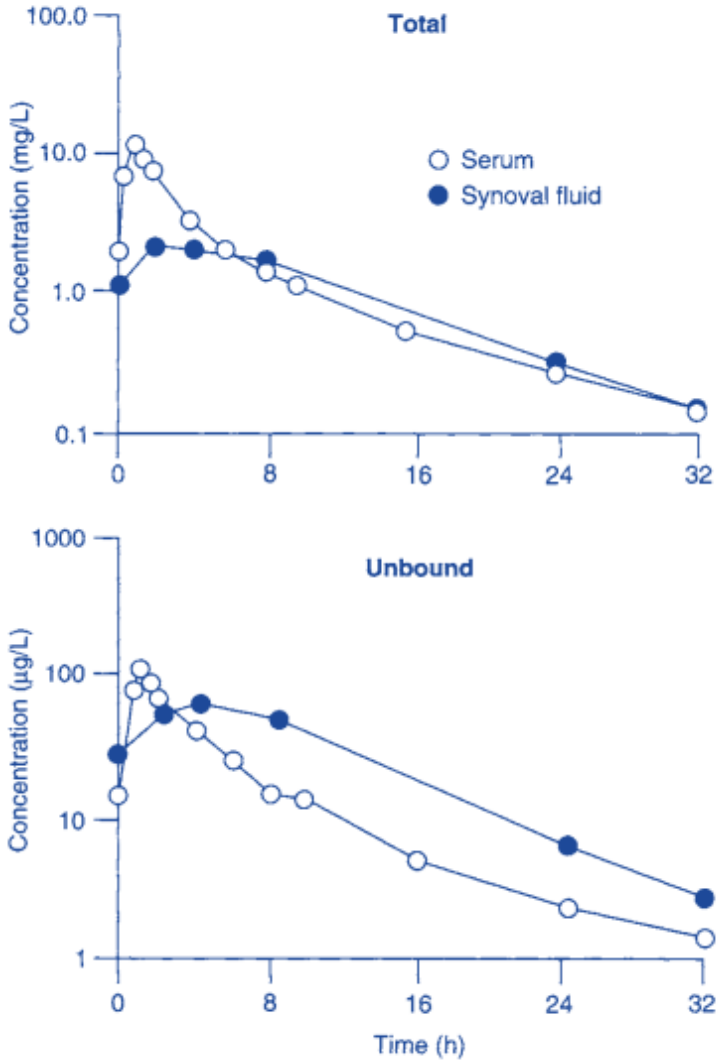


Fig. 2. Nonstereospecific mean concentration versus time profiles of total and unbound etodolac in the serum and synovial fluid of 5 patients with arthritis who had received racemic etodolac 200mg twice daily for 7 days (from Kraml et al. 1988, with permission)

Elimination[3]

The t1/2β of racemic etodolac is of moderate duration, with mean values between 7 and 8 hours. There is no statistically significant difference between the t1/2β of etodolac enantiomers in healthy volunteers or elderly patients. Racemic etodolac displays linear pharmacokinetics between single doses of 200 to 1600mg, or multiple doses of 200 to 600 mg/day in a sustained release formulation. Therefore, over the range of doses used clinically, the elimination processes do not appear to become saturated. However, linearity has not been verified for individual enantiomers of etodolac.

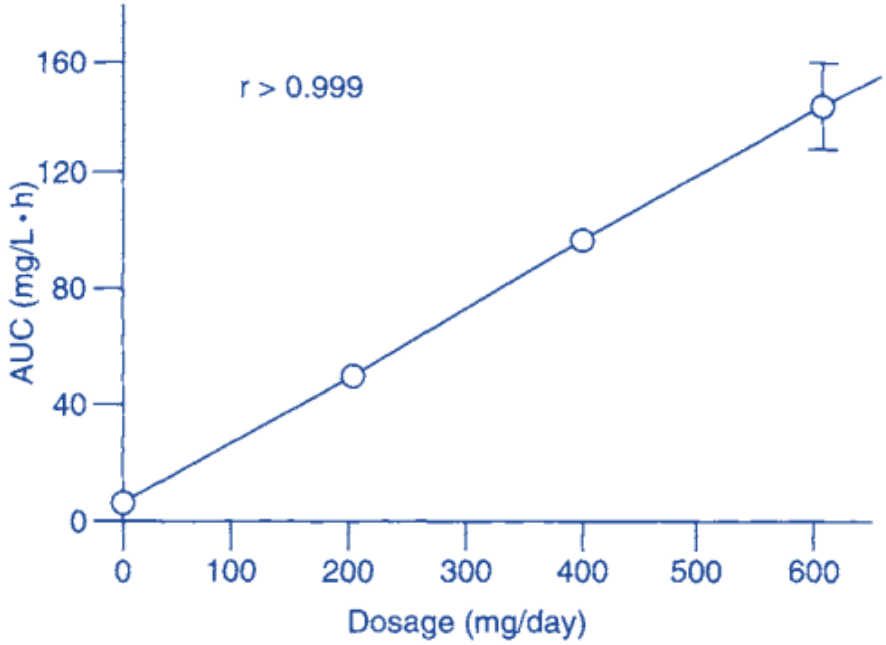


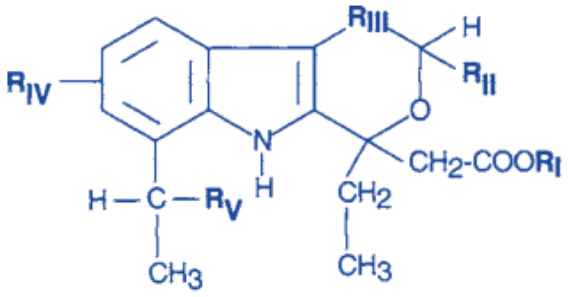
Fig. 3. Relationship between dose and mean area under the serum concentration-time curve (AUC) of racemic etodolac in healthy individuals

Metabolism[3]

Most (61%) of the dose of [^{14}C]etodolac is found in the urine within 24 hours. Thin layer chromatography for isolation and mass spectroscopy and nuclear magnetic resonance for identification were used to characterise the metabolites of etodolac. The acyl-glucuronide of etodolac accounted for 20% of the drug recovered in the urine. Hydroxylated etodolac was also found and accounted for 46% of the drug recovered in the urine. Hydroxylated metabolites included 6- and 7-hdroxy-etodolac, and 8-(l'-hydroxyethyl)- etodolac. These metabolites were predominantly found in the urine as their respective glucuronide conjugates. In serum, Ferdinandi et al. found 90% of radiolabelled drug as unconjugated material. Of this, 70 to 80% was present as unchanged etodolac, 10% was 7-hydroxyetodolac, and 1 to 2% was 6-hydroxy-etodolac.

An unusual metabolite of etodolac, 4-ureidoetodola, has been found in the urine of humans, rats, dogs and mice. In humans, this metabolite accounted for 8.1 % of the radioactively labelled dose recovered in the urine. HPLC analysis of urine extracts showed equal concentrations of both 4-ureido- etodolac diastereomers. The formation of the ureide

metabolite did not seem to require the initiaI metabolism of etodolac to 4-hydroxy-etodolac, because the hydroxyl group of 4-hydroxy-etodolac was only spontaneously converted to the ureide under nonphysiological, acidic conditions. Therefore, another intermediate was postulated to be involved in the formation of 4-ureido-etodolac.



Metabolite	R_I	R_{II}	R_{III}	R_{IV}	R_V
6- *or* 7-hydroxy-etodolac	H	H	CH_2	OH	H
Acyl-glucuronide	Glucuronic acid	H	CH_2	H	H
8-(1′-hydroxyethyl) etodolac	H	H	CH_2	H	OH
4-ureido-etodolac	H	H	$CHNHCONH_2$	H	H

Fig. 4. The major metabolites of etodolac in humans

The rate of metabolism of the S-enantiomer appears to be higher than that of the R -enantiomer, as indicated by its higher oral clearance (CLIP). However, this does not necessarily indicate a difference between the enantiomers in the proportion metabolised to oxidised and acyl-glucuronidated drug. In individuals given racemic etodolac 200mg, the proportion of the dose recovered as acylglucuronidated enantiomer in the urine was the same for the enantiomers (approximately 71%). Because etodolac is nearly completely metabolised, the remainder of the dose of each enantiomer is probably metabolised to the oxidised metabolites previously characterised. The exact proportion of each enantiomer metabolised to the different oxidised metabolites, however, is unknown.

The hydroxylated metabolites of etodolac, and ureido-etodolac, possess very little if any pharmacological activity, as determined using rat adjuvant arthritis, and prostaglandin production by chondrocytes. The acyl-glucuronides of etodolac are capable of forming irreversible complexes with solutions of purified human serum albumin in vitro. The binding of this metabolite to albumin in vivo, and its possible enantioselectivity and therapeutic relevance, remain to be established. Smith et al. noted that the β1-acyl-glucuronides of etodolac are much more stable than those of some other NSAIDs, which may explain in part their relatively high concentrations present in vivo.

Excretion[3]

In humans the metabolites of etodolac are primarily excreted in the urine, although only negligible quantities of etodolac are excreted unchanged in the urine and bile. After giving [^{14}C]etodolac to 4 healthy Black male volunteers, Ferdinandi et al. found that 61 % of the administered dose was recovered in urine over 24 hours. Over 7 days, 69 to 76% of the radioactivity was recovered. During a 7-day collection of both urine and faeces, 80 to 92% of the administered radioactivity was recovered.

Biliary excretion of NSAIDs or their unstable metabolites (e.g. glucuronides) may contribute to the gastrointestinal adverse effects of this class of drugs. For etodolac, in 2 patients in whom biliary T-tubes were inserted, the post-surgical cumulative excretion of both acyl-glucuronidated etodolac enantiomers into the bile was less than 1% of the dose. In another patient, less than 4% of the cumulative dose was excreted in the bile. Therefore, it would appear that most of acylβ1- glucuronidated etodolac is excreted in the urine. Some caution is necessary in interpreting the data, however, because there may be a surgically related reduction in bile flow, which might diminish the excretion of conjugates into the bile. Nevertheless, gastrointestinal toxicity due to the substantial presence of etodo1ac in the site secondary to biliary excretion is unlikely.

Pharmacokinetic Profile in Special Populations[3]

Effects of Aging

The pharmacokinetics of etodolac in elderly individuals were compared with those in young individuals. In each group after repeated administration of etodo1ac (every 12 hours) for 7 days, the pharmacokinetic

parameters did not differ significantly between young and elderly individuals. In the elderly there was a significant increase of 13% in the AUCO-12 between the first and the seventh days of administration; however, the investigators considered that this would be of little importance clinically. It was concluded that dosage adjustments were probably not required in elderly patients.

Aging also had no discernible effect on the plasma concentration of etodolac enantiomers in nonarthritic elderly volunteers with normal renal and hepatic function. Furthermore, there was no difference between young and elderly individuals in the cumulative renal excretion and renal clearance of the acylglucuronidated enantiomers.

There are no data available describing the pharmacokinetics in children or infants.

Pharmacokinetics in Osteoarthritis

In their study involving the elderly, Scatina et al. also included a group of 20 elderly patients with osteoarthritis. The pharmacokinetics and serum protein binding of etodolac in this group of individuals were similar to those of the young individuals. However, after multiple doses there was no detectable accumulation of drug in the osteoarthritic patients, unlike the healthy elderly individuals. The influence of osteoarthritis on the pharmacokinetics of the pharmacologically active enantiomer of etodolac has not been reported.

Pharmacokinetics in Patients with Hepatic Cirrhosis

In a published abstract, the pharmacokinetics of etodolac in patients with hepatic cirrhosis were reported. There were no differences in AUC, Cmax, tmax, or protein binding in serum between patients with hepatic cirrhosis and a control group of young healthy volunteers. It was concluded that dosage adjustments in such patients are not necessary. However, this conclusion must be viewed with some prudence because stereochemical concerns were not addressed. Specifically, a change in plasma concentrations of the Senantiomer might be obscured by the much higher concentrations of the R-enantiomer in plasma and serum.

Pharmacokinetics in Renal Disease

To date there is no published report describing the pharmacokinetics of etodolac in patients with renal failure. Nevertheless, it is of interest that the concentrations of acyl-glucuronidated etodolac enantiomer in the plasma of patients with rheumatoid arthritis were somewhat higher than those in young and elderly individuals. Unfortunately, the renal function of these patients was not known. Due to the

severity of their disease, which probably resulted from years of therapy with other NSAIDs, it is possible that some degree of diminished renal function was present that could explain the relatively high plasma concentrations of acylglucuronides in patients with rheumatoid arthritis. It is notable that after administration of ketoprofen, concentrations of acyl-glucuronidated ketoprofen were elevated in elderly patients with osteoarthritis or rheumatoid arthritis, but not healthy individual or young patients with osteoarthritis or rheumatoid arthritis. Excretion of the glucuronidated metabolic products of NSAIDs appears to be highly dependent upon kidney function. Although these metabolites are inactive, they may result in elevation of the parent drug concentration because of they are unstable. The validity of this suggestion and its clinical significance is yet to be tested.

Post-Surgical Patients

In 3 patients given etodolac after cholecystectomy, there appeared to be a delay in absorption. The tmax for each patient was greater than 4 hours compared with a tmax of 2 hours or less in 11 of 12 healthy individuals. Decreases in gastrointestinal transit time post-surgery, opiate analgesics and lack of ambulation might have caused the apparent delay in absorption.

Tolerability[2]

Drug tolerability is a function of a number of factors (e.g. individual risk factors, dose and duration of treatment). Elderly individuals, receiving chronic NSAID therapy, are, as a group, usually at the greatest risk (notwithstanding the fact that risk is ultimately an individual and not a group phenomenon). Analyses of large numbers of patients treated for painful conditions over periods of several weeks give reasonable estimates of more common adverse events. It is generally accepted that rare side-effects are not detected by such studies and are either reported in individual case reports or are detected in the analysis of large pharmacoepidemiology data bases.

A comparison of adverse events rates for etodolac based on placebocontrolled trials has been reviewed by Bacon. The analysis was based on trials involving patients with either RA or OA, and was subdivided by age above and below 65 years. These data suggest that etodolac is as well tolerated by the elderly as by younger individuals. A subanalysis did not find any rising trend which related withdrawal rates from etodolac to advancing age. It is of note that the majority of adverse events occurred with similar frequency in placebo and etodolac recipients. Dyspepsia and nervous system events were significantly more common in etodolac recipients

(cf. placebo recipients) under age 65 years, but no difference was detected between etodolac and placebo in those > 65 years. This is somewhat surprising since the latter, generally, are considered to be at higher risk of such events.

In another study of 315 subjects of 60 years or older treated for four weeks with etodolac 600 mg per day, discontinuation rates due to adverse events were infrequent: epigastric pain (2%), nausea (1%), dyspepsia, haematomas, weakness (0.3%). Overall, withdrawal rates from etodolac were approximately 8%, which was similar to those from diclofenac and piroxicam. The incidence of ulcers and gastrointestinal bleeding associated with etodolac was < 1% and was not dose related. Since studies of less than several thousand patients are unlikely to detect rare adverse events or low frequency idiosyncratic reactions, it is important to also consider safety data from larger data bases. Schattenkirchner has reviewed data from 3302 patients enrolled in double-blind and open-label clinical trials, and from 8334 patients taking etodolac in post-marketing surveillance studies. Gastrointestinal ulceration rates were less than 0.3% and drug-related hepatic, renal and haematological dysfunction were rarely observed. It can be concluded that etodolac is safe and generally well tolerated irrespective of adult age.

Table III. Incidence of adverse events by age-group in placebo-controlled etodolac trials

Adverse body system event*	<65 years		≥65 years	
	Etodolac (%)† (n = 230)	Placebo (%) (n = 182)	Etodolac (%)† (n = 135)	Placebo (%) (n = 88)
Body as a whole				
Any event	28	22	23	19
Asthenia	7	5	3	1
Headache	10	8	6	11
Infection	5	4	4	1
Malaise	3	1	<1	0
Abdominal pain	12 ‡	5	14	7
Back pain	<1	3	0	2
Digestive system				
Any event	31	24	29	25
Constipation	2	4	2	1
Diarrhoea	11	7	10	10
Dyspepsia	17 ‡	9	17	13
Flatulence	6	4	9	4
Nausea	9	6	9	5
Vomiting	4	2	1	1
Abnormal stools	3	2	5	5
Nervous system				
Any event	14 ‡	7	10	8
Dizziness	6	2	6	1
Insomnia	2	2	2	3
Respiratory system				
Any event	7	8	7	3
Increased cough	3	3	<1	2
Pharyngitis	4	4	4	2
Rhinitis	3	3	3	0
Skin and appendages				
Any event	11	6	6	7
Pruritus	4	2	2	2
Rash	5	3	3	4

*All causalities; †Daily dose ≥600 mg; ‡Significantly different from placebo ($p \leq 0.05$)

Table IV. Incidence of adverse events in 315 elderly patients (>60 years) treated for 4 weeks with etodolac, 600 mg/day

Adverse event (*n*)	Mild or moderate severity	Study-drug related*	Etodolac discontinued
Epigastric pain (19)	19 (6%)	14 (4%)	7 (2%)
Burning sensation (5)	5 (1.6%)	3 (1%)	0 (0%)
Nausea (5)	4 (1.3%)	4 (1.3%)	3 (1%)
Dyspepsia (2)	2 (0.6%)	1 (0.3%)	1 (0.3%)
Itching (2)	1 (0.3%)	1 (0.3%)	0 (0%)
Haematemesis (1)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Weakness (1)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Malaise (1)	1 (0.3%)	1 (0.3%)	0 (0%)
Muscle pain (1)	1 (0.3%)	1 (0.3%)	0 (0%)
Dizziness (1)	1 (0.3%)	1 (0.3%)	0 (0%)
Loss of appetite (1)	1 (0.3%)	1 (0.3%)	0 (0%)

*Possibly, probably, or definitely related to etodolac treatment

Drug-drug interactions[2]

Although no studies of drug-drug interactions with etodolac have been published, unpublished data are summarized in the Compendium of Pharmaceuticals and Specialties (CPS). As is the case for all NSAIDs, discretion is advised when prescribing etodolac with the following drugs: cyclosporin, digoxin, lithium, methotrexate, and warfarin. In each instance etodolac may increase the plasma concentration of the co-therapy and result in an increase in its toxicity.

Studies on Etodolac[1]

Osteoarthritis

Four reports have been published on the efficacy and safety of etodolac in the treatment of OA of the hip or knee. In two 12-week double-blind, parallel-group studies, the efficacy of etodolac was compared with that of aspirin and placebo. A total of 88 OA patients participated in the double-blind trials, 32 of whom received etodolac. Daily dosages were titrated from a minimum of 100 to 400 mg of etodolac and from 2400 to 4800 mg of aspirin. In the year-long open-label study, dosages of etodolac were also titrated to 400 rag/day. In all studies, the drugs were

administered after a disease flare occurred upon withdrawal of the patient's currently used NSA!D; the flare had to occur within 2 weeks.

Efficacy was evaluated with the following assessments: range of motion of hip or knee; 50-foot (approximately 15 m) walking time; duration of morning stiffness; joint tenderness; weight-bearing pain while standing, walking, getting into and out of bed, getting up from a chair, and climbing stairs; average of these scores; pain at night; investigator's global evaluation; and patient's global evaluation. Results of efficacy evaluations were compared by a two-way analysis of variance. Statistical significance was attained when $p < 0.05$. Safety evaluations were based on physical examinations, patient complaints, and laboratory tests. The latter included blood chemistry determinations, urinalysis, hematologic tests, and tests for fecal occult blood. In the 12-week studies, etodolac was as effective as aspirin in the treatment of OA. In one study. etodolac was significantly ($p < 0.05$) more effective than placebo according to 11 of 15 clinical assessments, whereas aspirin was more effective than placebo in only three assessments. One of the 12 patients receiving etodolac and three of the ten patients receiving aspirin withdrew from the study because of lack of efficacy of the medication. In the other study, etodolac was significantly more effective than placebo according to 13 of 16 clinical assessments, whereas aspirin was more effective in three assessments. Only one of 20 patients receiving etodolac withdrew because of lack of efficacy. Eight patients of the 22 receiving aspirin withdrew for this reason. Overall, there were no statistically significant differences in effectiveness between aspirin and etodolac in either study. In the 52-week multicenter trials, improvement from baseline occurred in all 16 efficacy variables in patients with OA of the knee and in 13 of 18 variables in patients with OA of the hip.

In the 12-week studies, two (6.7%) patients receiving etodolac and nine (28.1%) receiving aspirin withdrew because of adverse effects. More adverse effects were reported by patients receiving aspirin than by those receiving etodolac or placebo. These effects were predominantly associated with the gastrointestinal system, the central nervous system, and special sensory organs. Overall, the frequency of new complaints from patients receiving etodolac was similar to that from patients receiving placebo. No clinically significant abnormalities were found in laboratory test results.

Rheumatoid arthritis

Published reports on the efficacy and safety of etodolac in the treatment of RA include eight reports on parallel-group studies and one preliminary report on a crossover study against naproxen. The study duration ranged from 2 to 51 weeks and sample sizes ranged from 18 to 475 patients. A total of 638 patients received etodolac.

Double-blind parallel-group and crossover studies

Treatment with etodolac was compared with treatment with placebo alone, with aspirin or placebo, with aspirin alone, with sulindac or placebo, and with naproxen. Daily dosages ranged from 50 to 600 mg for etodolac and from 3600 to 4800 mg for aspirin; sulindac dosage was 400 mg/day and naproxen was given in a dosage of 1000 mg/day. If patients were receiving NSAIDs at the screening visit, study drugs were administered only if a flare occurred within a washout period not exceeding 2 weeks.

The effectiveness of etodolac in relieving the signs and symptoms of rheumatoid arthritis was evaluated with ten assessments: number of painful joints, number of swollen joints, duration of morning stiffness, grip strength, 50-foot (approximately 15 m) walking time, pain intensity, articular index (calculated from the number of painful and swollen joints), erythrocyte sedimentation rate, investigator's global evaluation, and patient's global evaluation. A two-way analysis of variance was used to analyze the efficacy data. In all studies, results were considered statistically significant if $p < 0.05$.

Safety evaluations were based on physical examination, patient complaints, and laboratory tests, including blood chemistry and hematologic assessments, urinalysis, and test for fecal occult blood. The 51-week study included ophthalmologic and audiometric examinations.

The results of all the studies showed that etodolac was effective in the treatment of RA. Etodolac was consistently and significantly ($p < 0.05$) superior to placebo in most assessments. In the studies that compared etodolac with aspirin or sulindac, etodolac was found to be as effective as the reference compounds.

The number of patients withdrawing because of lack of efficacy was similar in the groups receiving etodolac and the groups receiving other active drugs. In the 51-week trial, significantly more etodolac-treated patients than aspirin-treated patients withdrew because of

lack of efficacy. However, one third of the etodolactreated patients withdrew the first month, during or shortly after the titration period, before an adequate therapeutic trial. Moreover, the titration period in this study was initiated with a dose below the therapeutic range.

In all studies, etodolac was well tolerated. In three placebo-controlled studies involving 657 patients, the frequency of patient complaints in the etodolac groups and the placebo groups was remarkably similar: There were no statistically significant differences between the two groups. Compared with aspirin, etodolac had a superior safety profile. In three large studies, involving 933 patients, the frequency of gastrointestinal complaints and tinnitus was statistically significantly greater in the aspirin groups than in the etodolac groups. In addition, the number of patients withdrawing from trials because of adverse effects was greater in the aspirin group than in the etodolac group. In three of the studies, the difference was statistically significant. Abnormalities in laboratory tests were few and generally not clinically significant in patients receiving etodolac. One patient of 224 receiving etodolac developed leukopenia that the investigator attributed to etodolac therapy. Ophthalmologic and audiometric tests revealed no clinically significant new abnormalities in either treatment group.

In a randomized, double-blind study, treatment with etodolac was compared with treatment with naproxen. After a 2- week washout period, patients received etodolac 400 mg/day or naproxen 1000 mg/day for 6 weeks. Following a second 2-week washout period, patients received the alternative drug for 6 weeks. Etodolac-treated patients had a statistically significantly greater improvement in their global evaluations and erythrocyte sedimentation rate from baseline levels compared with naproxen-treated patients. Articular index, investigator's global evaluation, pain intensity, and grip strength all showed improvement over baseline greater with etodolac than with naproxen, although the improvement did not attain significance. Patient complaints were similar in the two treatment groups ; gastrointestinal side effects were the most common. There were no clinically significant changes in laboratory variables during treatment with either drug.

Clinical Applications[2]

Oral postsurgical pain

The most common method of evaluating the efficacy of an analgesic agent is the dental pain model which utilizes the extraction of the third molar(s). The dental pain model has become

popular because the surgical procedures can be easily categorized, and each subpopulation is relatively homogeneous. There are also data that substantiate the assay sensitivity of the dental pain model, and its usefulness in predicting the general analgesic efficacy of non-steroidal anti-inflammatory drugs.

The role of etodolac in the management of postsurgical pain, following third molar extraction, has been reported in nine separate studies from the USA, one of which contains three separate trials, and which partially reports some of the data from one of the other studies. Results of two other studies have been reported only in reviews. All eleven studies were conducted as double-blind randomized placebo-controlled, parallel studies, in which patients received a single dose of medication, and self-rated pain at several subsequent time points up to 12 h following initial dosing. In all nine studies reported in full, a local anaesthetic, with or without a sedative was used for the extraction (surgical or non-surgical) of one or more impacted or erupted third molars. Patients were required to experience moderate to severe pain before receiving a single dose of study medication. In addition to a placebo control group, all studies included an active control group, either aspirin or zomepirac. All studies included two or more etodolac groups dosed at defined levels between 50 mg and 400 mg. Treatment response was measured using several techniques: pain intensity (PI), pain relief (PR), global evaluation of drug efficacy, time to onset of analgesia, time of peak analgesia and duration of analgesia. In addition to these direct measures, two summary variables were derived - sum of pain intensity differences (SPID) and total pain relief (TOTPAR), the former being derived from PI scores and the latter from PR scores over serial time intervals. The same efficacy measures were employed in all studies. In all studies, randomization was successful and treatment groups were comparable at baseline.

All nine study reports provided details of multiple analyses comparing different drugs, different doses, different variables, and different time intervals. No correction was made for multiple statistical comparisons. However, the results of these separate studies were remarkably similar. The principal observations were as follows: etodolac was superior to placebo in all studies, and, at higher doses, was comparable or superior to aspirin. Although zomepirac was withdrawn from the market by its manufacturer during the conduct of two of the studies etodolac was comparable to zomepirac in analgesic potency.

The onset of analgesia with etodolac occurred within 30-60 min, peak analgesia occurring between 30 and 120 min depending on dose. The duration of analgesia was a function of dose,

being approximately 2 h for the 200 mg dose and 4-6 h for the 400 mg dose. Several studies suggested that etodolac might be a superior analgesic to aspirin having an earlier onset of action and longer duration of analgesia at certain dose levels. Because of the generally low level of adverse events, formal statistical comparisons of event rates were not performed in any of the nine studies. However, all test compounds appeared to be well tolerated. Collectively it can be concluded from these studies that etodolac is an effective and well-tolerated analgesic in the treatment of pain following third molar extraction. Furthermore, its analgesic effects are comparable to zomepirac and comparable, or possibly superior, to aspirin for this purpose. In two studies by Mehlisch et al. and Gaston et al. published only in review format, etodolac (200 mg, 400 mg) was compared against a codeine (60 mg)/ acetaminophen (600 mg) combination analgesic in placebo-controlled trials of patients undergoing oral surgery. Sample sizes were 179 and 177 patients, respectively. Etodolac was superior to placebo, and produced analgesia within 30 min which lasted 5-6 h. In Mehlisch's study, etodolac 200 mg, provided comparable analgesia to the codeine/ acetaminophen combination. However, etodolac 400 mg provided significantly greater ($p \leq 0.05$) analgesia (over 3-12 h) than the opioid-based combination. Although complete manuscripts were not available for review, it is of note in both studies that the area under the pain relief curves was greater for etodolac 400 mg than for the codeine/acetaminophen combination. This suggests that etodolac, at higher doses, may outperform a complex opioid-based analgesic with respect to pain relief in this disease setting.

Postsurgical (orthopaedic or urological) pain

The analgesic activity of various (25, 50, 100, 200, and 400 mg) doses of etodolac was compared against 650 mg of aspirin by Versichelen et al. in a double-blind placebo-controlled trial. A total of 146 patients, with moderate or severe pain following orthopaedic or urological surgical interventions, were followed for 8 h after a single dose of test medication given 13-25 h after the start of surgery. The following outcomes were assessed: PI, PR, SPID, TOTPAR, and duration of analgesia. The exact surgical procedures performed were not specified in the report. A significant ($p = 0.0001$) dose-response relationship was observed for etodolac, with statistically superior efficacy (cf. placebo) detected at doses > 100 mg. At .400 mg etodolac, significantly greater pain relief was observed than with aspirin 650 mg and the duration of analgesia was longer (7.6 h vs. 5.2). Adverse events were reported to be too few to be analysed (etodolac = 4, placebo = 1 patient). These data indicate that a single dose of etodolac at /> 100

mg is effective in the relief of pain of moderate or severe intensity following orthopaedic or urological surgery. It would have been useful, in this report, to know exactly which types of surgery were undertaken and whether the effects differed between the clinical situations. However, this was a randomized trial and the overall effects are likely to be unbiased.

Postepisiotomy pain

The efficacy of etodolac in the treatment of postepisiotomy pain has been evaluated in a double-blind, randomized, placebo-controlled, parallel trial. One hundred and fifty-nine women, with moderate or severe pain following episiotomy, were randomized to either etodolac 25 mg or 100 rag, aspirin 650 mg, or placebo. A single dose of study medication was provided and patients self-assessed pain at several points over the next 8 h. Pain measures included the following: PI, PR, SPID, TOTPAR, onset of analgesia, duration of analgesia, and patient global assessment of drug efficacy.

The 25 mg dose provided no analgesia. However, etodolac 100 mg was superior to placebo and comparable in analgesia to aspirin 650 mg. Most patients experienced some analgesia 1 h after dosing with etodolac 100 rag, with peak effects lasting from the second to fourth hour and providing a duration of analgesia of nearly 6 h. In this study, etodolac 100 mg was efficacious and well tolerated, indicating a role for etodolac in the treatment of postepisiotomy pain.

Acute sports injuries

Etodolac (300 mg po tid) has been compared against naproxen (500 mg po bid) using a double-blind, randomized, controlled, parallel trial design in 99 patients with acute sports injuries (excluding fractures). Patients, who were experiencing moderate or severe pain, were followed over seven days and evaluated using the following measures: spontaneous pain intensity, induced pain intensity, range of motion, tenderness, heat, swelling, erythema and both patient and physician global evaluations. Concomitant physiotherapy was permitted but not co-therapy with either analgesic or NSAID class agents.

Patients in both treatment groups showed significant improvement by day 2 on all variables, this effect being sustained throughout the remainder of the study. In general, the two drugs were comparable in their efficacy. No statistical analysis was performed on adverse events

because of their low frequency. However, there were similar numbers of events in both treatment groups.

The data indicate that etodolac is efficacious in relieving pain, stiffness and swelling associated with acute sports injuries, has a prompt onset of action, is well tolerated and comparable to naproxen for this purpose. Two other studies of acute sport injuries (Ferreira and Espirandelli, Simon and Mesquida) reported only in review format, etodolac 600 mg daily was comparable with diclofenac 150 mg daily.

Soft-tissue rheumatism

Etodolac has been evaluated in the treatment of the following forms of soft-tissue rheumatism: tendonitis and bursitis, periarthritis, radiculalgia, and low back pain.

Tendonitis and bursitis

Three studies have been conducted comparing etodolac 600 mg daily and either naproxen 1000 mg daily (Cisneros, Innarritu and Cervantes quoted in) or diclofenac 100 mg daily. These studies have only been reported in review format. The three separate studies were conducted over 7-14 days, each evaluating approximately 60 patients. Etodolac was comparable in efficacy to diclofenac and either equivalent or superior to naproxen.

Periarthritis

Etodolac 600 mg daily has been compared with piroxicam (40 mg daily for 48 h, then 20 mg daily) in a double-blind, randomized, controlled parallel, trial of two weeks duration in 110 patients with scapulo-humeral periarthritis. All efficacy measures significantly improved in both treatment groups, no significant between-drug differences being noted.

Radiculalgia

Etodolac 600 mg daily has been compared with diclofenac 150 mg daily in a doubleblind, randomized, placebo-controlled, parallel trial of five days duration in 204 patients with acute lumbo-radiculalgia. Lumbo-radiculalgia was defined as pain associated with nerve root

compression at L4, L5 or S 1. Both active treatments were superior to placebo on all efficacy measures but no significant differences were noted between etodolac and diclofenac.

Low back pain

Etodolac 400 mg daily has been compared with piroxicam-[3-cyclodextrin (PBC) 20 mg daily in a randomized, controlled, parallel trial of seven days duration. Reductions in pain scores were noted in both treatment groups, and statistically significant between-treatment differences were observed in favour of PBC. It does not appear from the publication that this study was conducted in a double-blind fashion, and an expectation bias might account for the observed differences in efficacy. In addition, the dose of etodolac was submaximal (i.e. 400 mg daily), and, therefore, drug dosages may not have been comparable. Overall, the aforementioned studies suggest that etodolac is comparable to other NSAIDs, and superior to placebo, in the treatment of various forms of soft-tissue rheumatism.

Primary dysmenorrhoea

Primary dysmenorrhoea (cf. secondary dysmenorrhoea) occurs in the absence of any discernable pelvic pathology. It is a common condition usually of nulliparous women occurring for several months or years after the menarche. The mechanism of pain generation has not been completely elucidated. However, the PGF2 /PGE2 ratio is higher in patients with primary dysmenorrhoea, these PGs affecting not only the musculature of the myometrium but also the uterine vessels. Myometrial enlargement is closely associated with primary dysmenorrhoea as are higher endometrial concentrations of PGs. An alternative approach to the management of primary dysmenorrhoea with oral contraceptives is the use of PG inhibitors, i.e. NSAIDs. The latter approach has resulted in a response rate (reduced pain and associated symptoms) of approximately 90%. In a study reported by Zecchi de Souza et al., 40 patients with primary dysmenorrhoea were evaluated over two menstrual cycles in a double-blind, randomized, placebo-controlled, cross-over study of etodolac. The medication (200 mg) was taken at the onset of symptoms and every 12 h thereafter while symptoms persisted (maximum = 5 days). Acetaminophen was provided as a rescue analgesic to be taken if absolutely necessary. Treatment groups were comparable at baseline. Significant differences, favouring etodolac, were observed for reductions in pelvic pain (both pain severity and percentage of patients

reporting relief), fatigue (both fatigue severity and percentage of patients reporting relief), depression and lower limb pain. There were no differences in the use of rescue analgesia. Both patient and physician global assessments favoured better symptom relief during the etodolactreated cycle ($p < 0.05$). No differences in tolerability were noted (etodolac vs. placebo), and there were no discontinuations from either treatment due to adverse events. Despite using a relatively small sample size, the investigators were able to detect statistically significant improvements in key symptom variables. There is precedent for the successful application of non-hormonal anti-inflammatory medications in the treatment of primary dysmenorrhoea. This study indicates that etodolac is efficacious and well tolerated, and suggests its inclusion as an option in the treatment of this common painful problem.

Abstracts on S-etodolac

A multicentric, randomized, comparative clinical trial to evaluate the efficacy and safety of S-etodolac in the treatment of osteoarthritis in Indian patients[5]

Abstract

Objective: To compare the efficacy and safety of S-etodolac with etodolac in the treatment of osteoarthritis in Indian patients.

Materials and methods: This was a double-blind, multicentric, comparative clinical trial conducted in 108 Indian patients with osteoarthritis. All patients received either S-etodolac ER 300 mg or etodolac ER 600 mg tablets once daily. Assessment was done on the basis of WOMAC score and VAS pain score, patient's and physician's global assessment of the arthritic condition. All patients were evaluated after every 2 weeks for 4 weeks for efficacy and safety variables.

Results and discussion: Total 49 patients in the test group and 52 patients in the reference group completed the study. There was significant improvement ($p < 0.0001$) in all WOMAC subscales (pain, stiffness and physical function), WOMAC total score and VAS pain score in both the groups. Patient's and physician's global assessment of the arthritic condition also improved significantly ($p < 0.0001$). All patients showed improvement in WOMAC and VAS pain score by (3) 20%. There was no significant difference between the groups for the efficacy parameters. The adverse events reported were few and no serious adverse events were reported. Total 5 patients in S-etodolac group and 2 patients in etodolac group dropped out of the study.

Only 1 patient dropped out because of the side effects of burning sensation, palpitations and anxiety in the test group.

Conclusion: The present study has established the efficacy, tolerability and safety of S-etodolac extended release tablets in the treatment of osteoarthritis in Indian patients.

Recent clinical experience with etodolac in the treatment of osteoarthritis of the knee[6]

Abstract

Interim results are reported for three double-blind clinical trials comparing etodolac, a new nonsteroidal anti-inflammatory drug (NSAID), with piroxicam, diclofenac, or naproxen in patients with osteoarthritis (OA) of the knee. Patients assigned to receive etodolac were given 200 mg three times a day in the diclofenac comparison and 300 mg twice a day in the other two studies. The comparator groups in the three studies received piroxicam 20 mg once a day, diclofenac 50 mg three times a day, or naproxen 500 mg twice a day. The length of the studies ranged from 6 to 12 weeks, and patients were seen at baseline and every 2 weeks thereafter. Etodolac, piroxicam, and diclofenac treatment consistently resulted in similar and statistically significant changes from baseline, indicative of improvement, in all primary efficacy variables (physicians' and patients' global assessments of improvement, pain intensity, and night pain) at every evaluation. In the comparison with naproxen, patients who received etodolac showed statistically significant improvement at most evaluations, whereas significant changes were less frequent in the naproxen group. Response rates in the three studies (response was defined as a decrease of 1 or more units in the patient's overall global evaluation, which is based on a 5-point scale ranging from 1 = very good to 5 = very poor) were as follows: etodolac 72%, piroxicam 75%; etodolac 66%, diclofenac 56%; and etodolac 40%, naproxen 16%. These interim results suggest that the efficacy of etodolac compares favorably with that of other NSAIDs in the treatment of OA of the knee.

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Survey Form

1) In your clinical practice how many patients of osteoarthritis do you see per day?

A. < 5
B. 5- 10
C. > 10

2) Osteoarthritis is more common in

A. Males
B. Females
C. There is no gender difference

3) Which age group is more prone to osteoarthritis

A. 40- 50 years
B. 50 – 60 years
C. > 60 years

4) Patients of Osteoarthritis generally present with a history of some comorbid condition

A. Agree
B. Disagree

5) In your clinical practice which comorbidity is more common in patients with osteoarthritis?

A. Diabetes
B. Hypertension
C. Thyroid disorders
D. Renal disease

6) What attributes do you keep in mind during selection of NSAIDs in patients with OA?

A. Efficacy
B. Safety
C. Selective pharmacological profile and simpler pharmacokinetic profile
D. Reduced drug–drug interactions
E. All of the above

7) In your clinical practice do you prefer unichiral NSAIDS over NSAIDS for pain management?

A. Yes
B. No

8) How much reduction in pain intensity do you see with S-Etodolac tablets in patients with OA?

A. Up to 60%
B. Up to 70%
C. Up to 80%

9) In your clinical practice, what is the usual duration required for OA/RA treatment with S-Etodolac?

A. 4- 6 weeks
B. 6- 8 weeks
C. 8- 10 weeks
D. More than 10 weeks

10) How would you rate the efficacy of S-Etodolac in treatment of osteoarthritis on basis of various parameters for assessment of pain?

A. Effective
B. Highly effective
C. Excellent

11) S-Etodolac is a safe option for pain management in patients with osteoarthritis with or without comorbidities?

A. Agree

B. Disagree

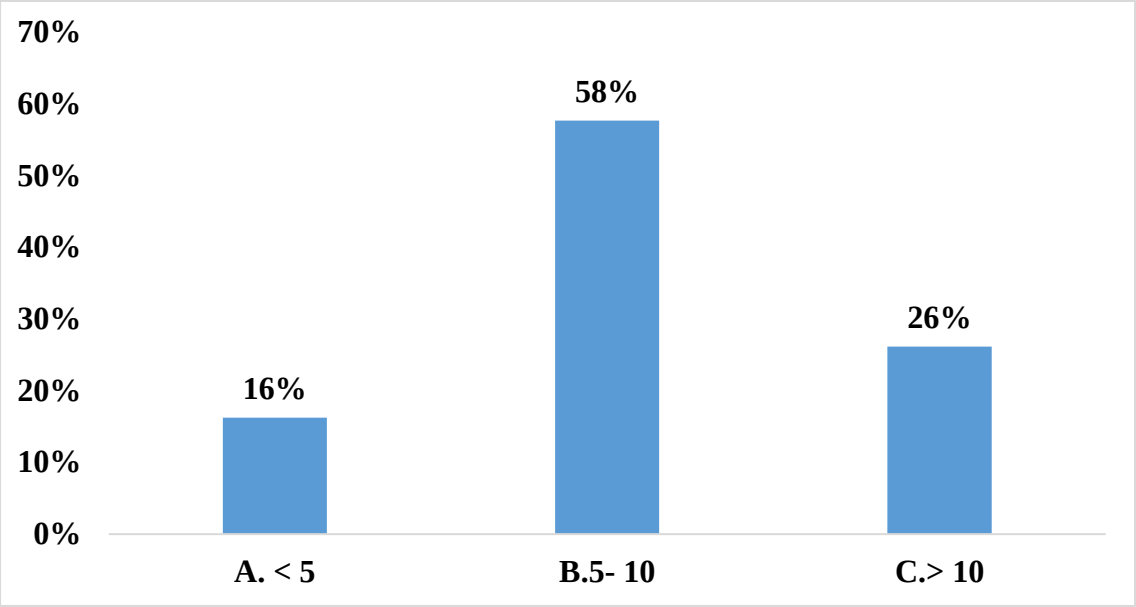
Survey Findings

1) In your clinical practice how many patients of osteoarthritis do you see per day?

A. < 5

B. 5- 10

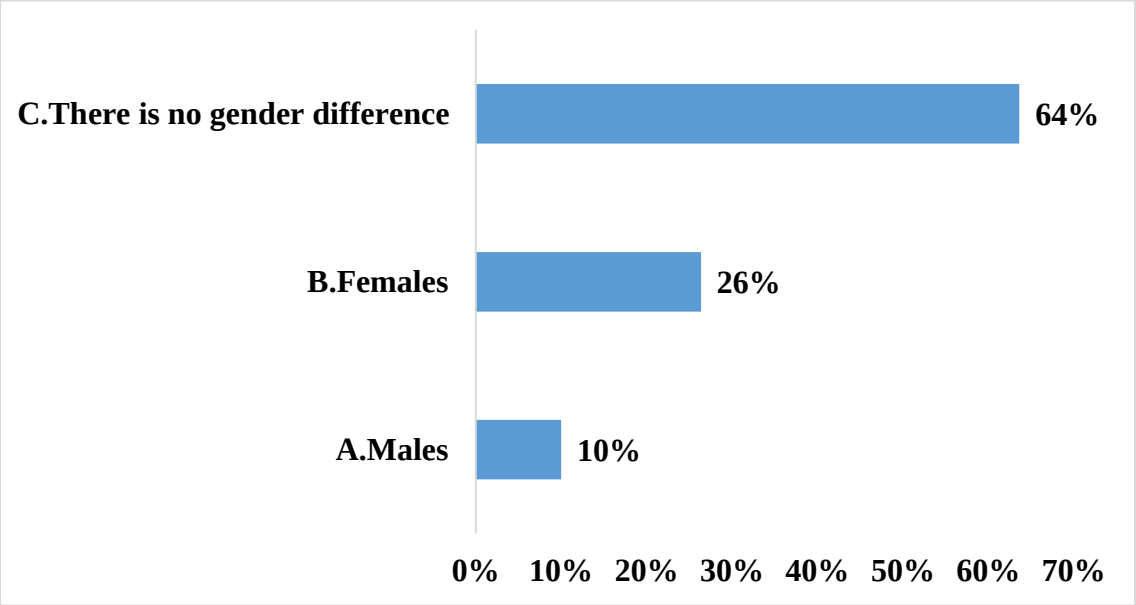
C. > 10



As per 58% of doctors, they per day see 5-10 patients of osteoarthritis in their clinical practices.

2) Osteoarthritis is more common in

A. Males
B. Females
C. There is no gender difference



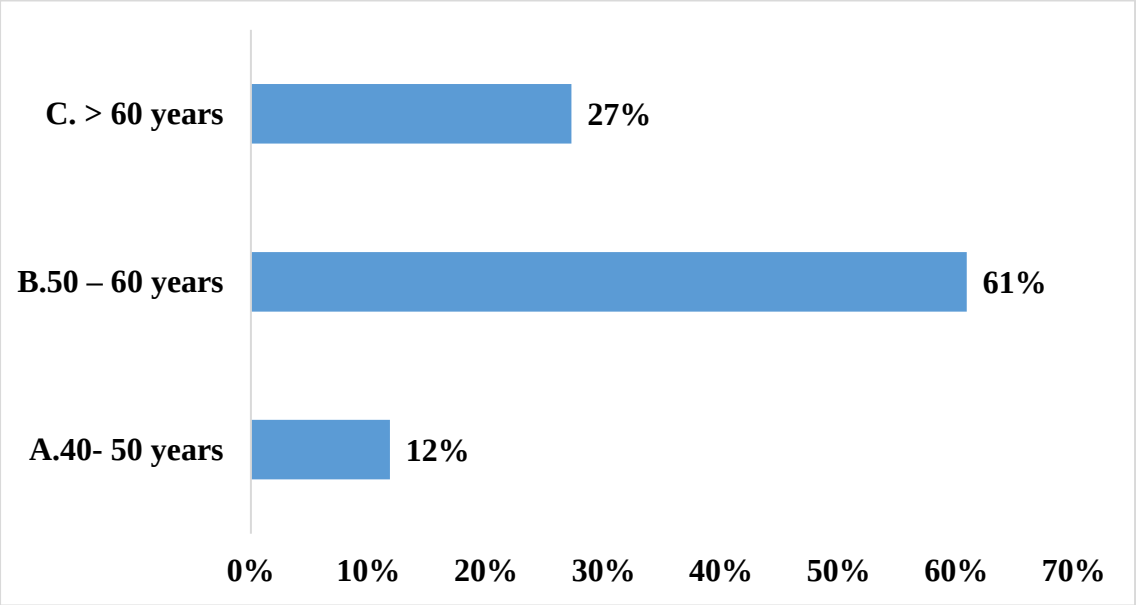
As per 64% of doctors, there is no gender difference in osteoarthritis.

3) Which age group is more prone to osteoarthritis

A. 40- 50 years

B. 50 – 60 years

C. > 60 years

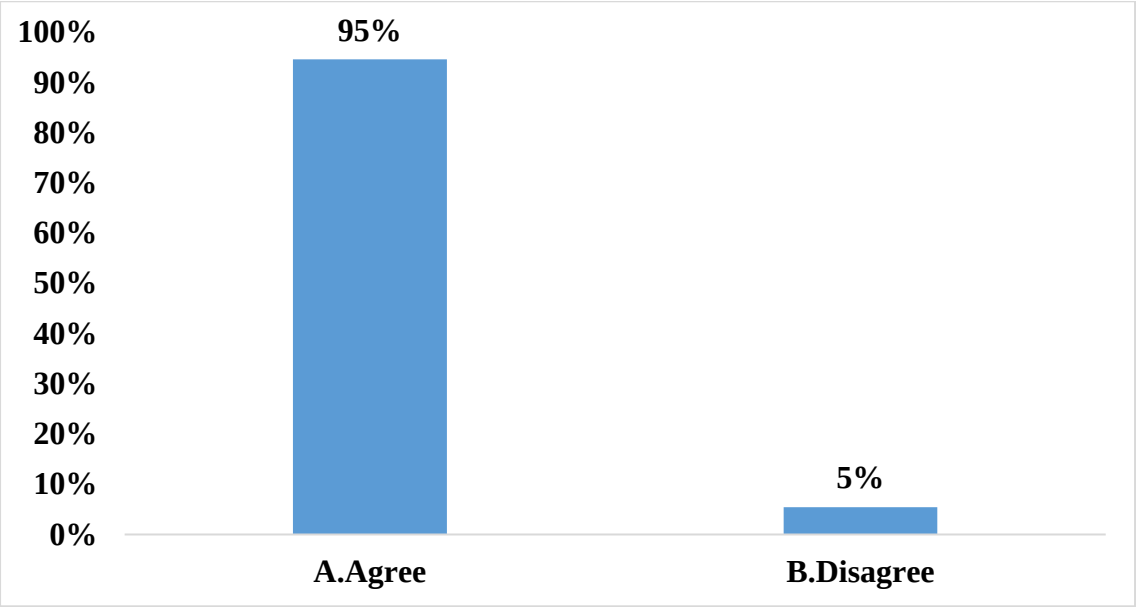


As per 61% of doctors, 50 – 60 years age group is more prone to osteoarthritis.

4) Patients of Osteoarthritis generally present with a history of some comorbid condition

A. Agree

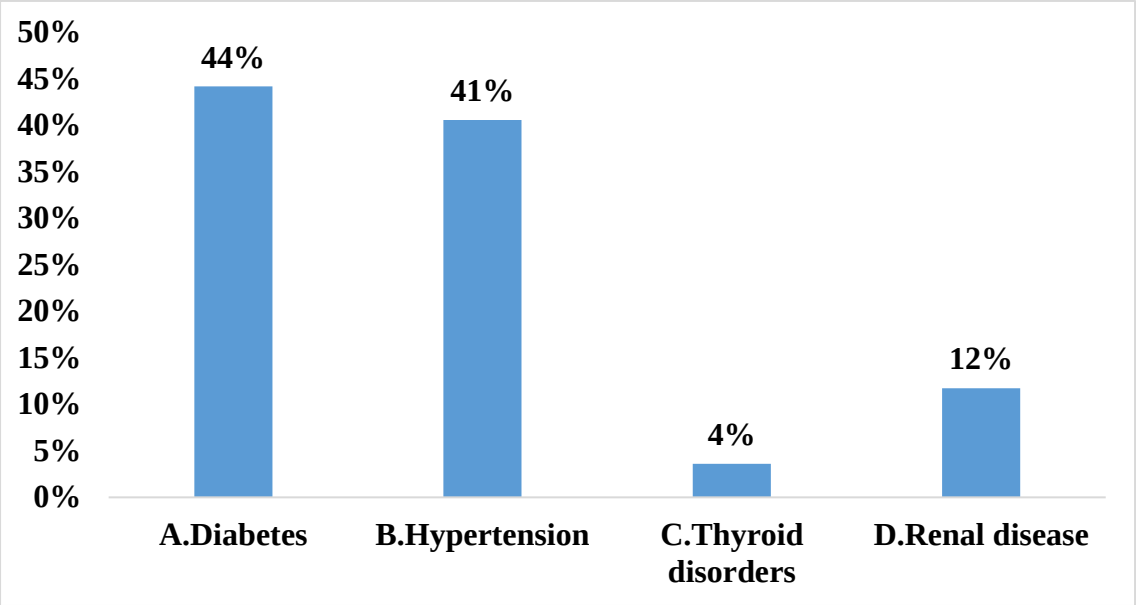
B. Disagree



According to majority of doctors, 95%, they agree that patients of osteoarthritis generally present with a history of some comorbid condition.

5) In your clinical practice which comorbidity is more common in patients with osteoarthritis?

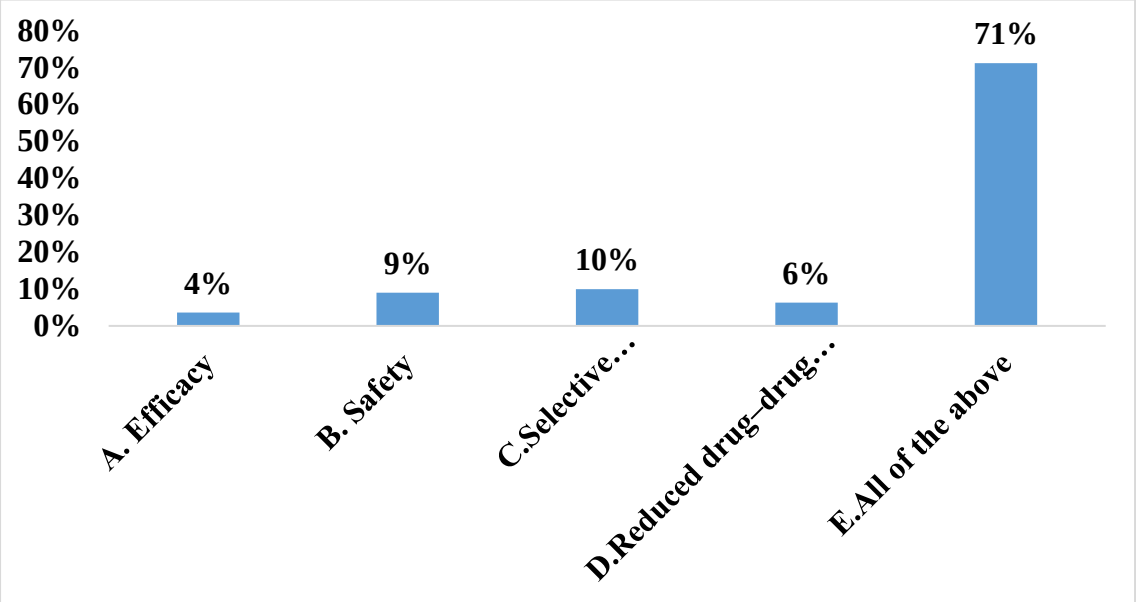
A. Diabetes
B. Hypertension
C. Thyroid disorders
D. Renal disease



According to 44% of doctors, diabetes is more common in patients with osteoarthritis in their clinical practices.

6) What attributes do you keep in mind during selection of NSAIDs in patients with OA?

A. Efficacy
B. Safety
C. Selective pharmacological profile and simpler pharmacokinetic profile
D. Reduced drug–drug interactions
E. All of the above

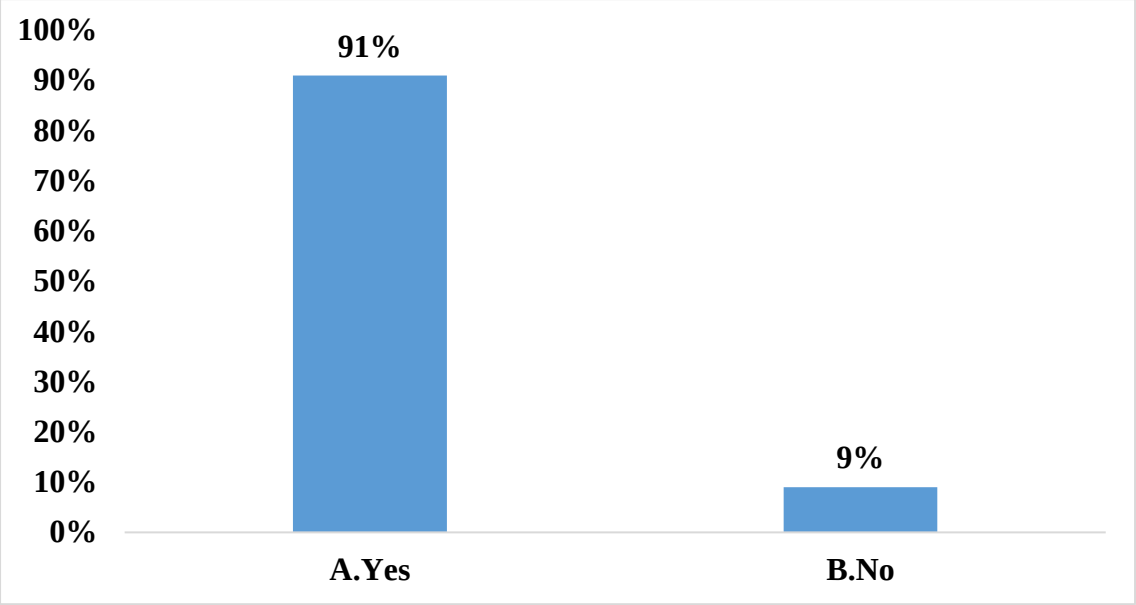


As per majority of doctors, 71%, the attributes kept in mind during selection of NSAIDs in patients with oa are efficacy, safety, selective pharmacological profile and simpler pharmacokinetic profile and reduced drug–drug interactions.

7) In your clinical practice do you prefer unichiral NSAIDS over NSAIDS for pain management?

A. Yes

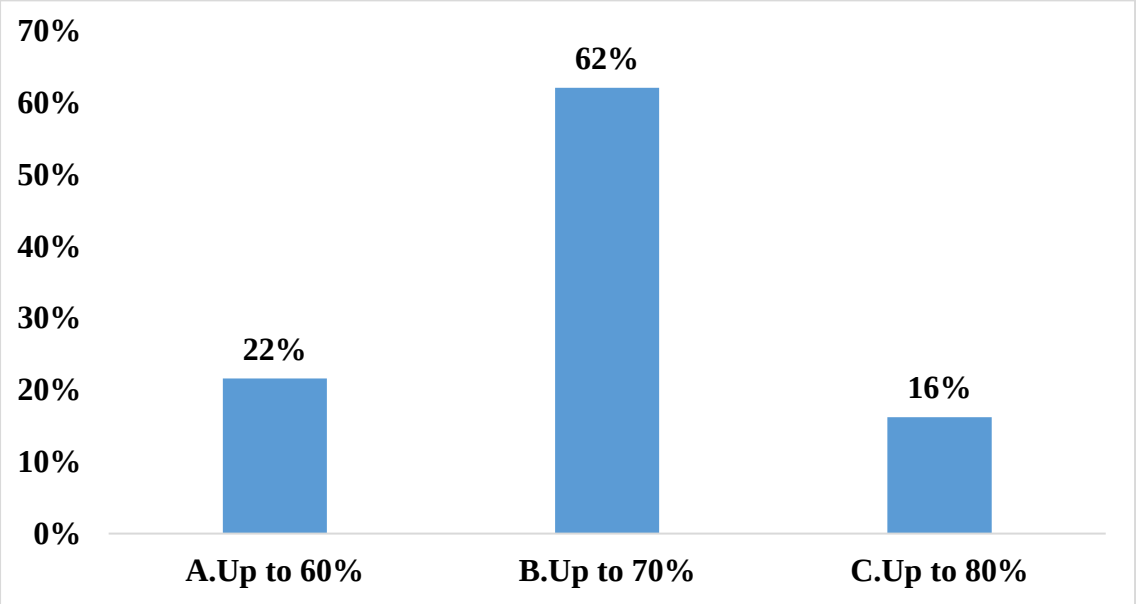
B. No



As per majority of doctors, 91%, they prefer unichiral NSAIDS over NSAIDS for pain management in their clinical practices.

8) How much reduction in pain intensity do you see with S-Etodolac tablets in patients with OA?

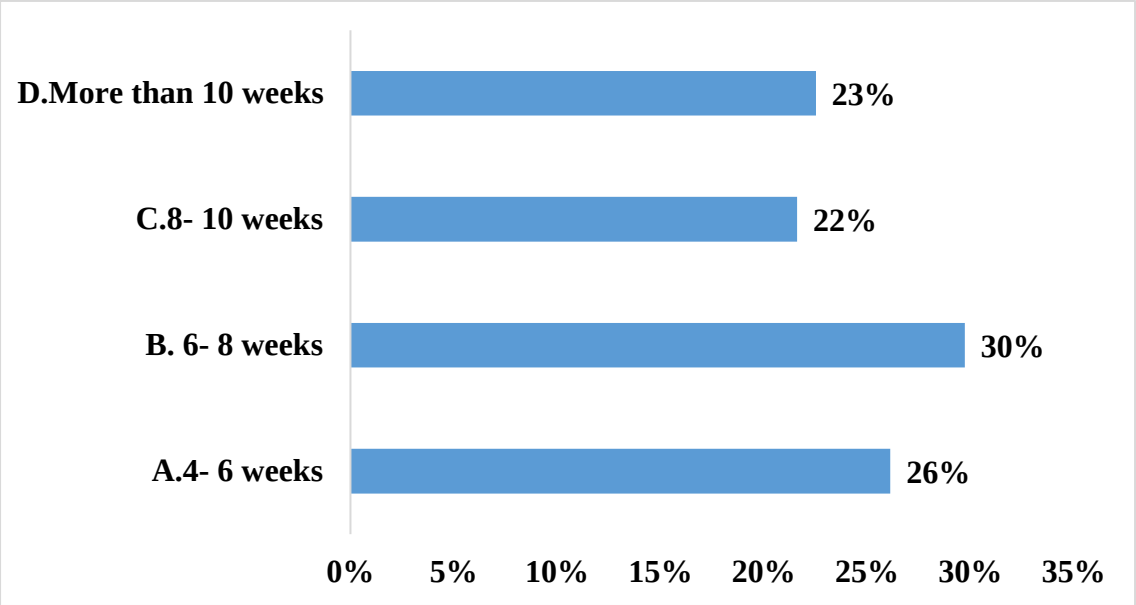
A. Up to 60%
B. Up to 70%
C. Up to 80%



As per 62% of doctors, they see up to 70% reduction in pain intensity with s-etodolac tablets in patients with oa.

9) In your clinical practice, what is the usual duration required for OA/RA treatment with S-Etodolac?

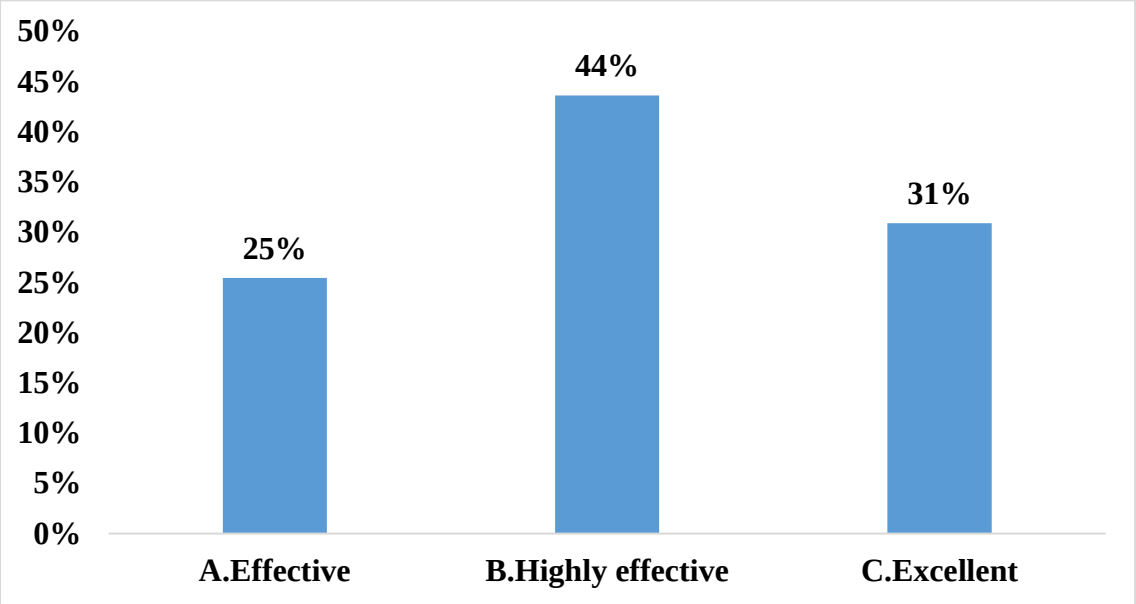
A. 4- 6 weeks
B. 6- 8 weeks
C. 8- 10 weeks
D. More than 10 weeks



According to 30% of doctors, 6- 8 weeks is the usual duration required for oa/ra treatment with s-etodolac in their clinical practices.

10) How would you rate the efficacy of S-Etodolac in treatment of osteoarthritis on basis of various parameters for assessment of pain?

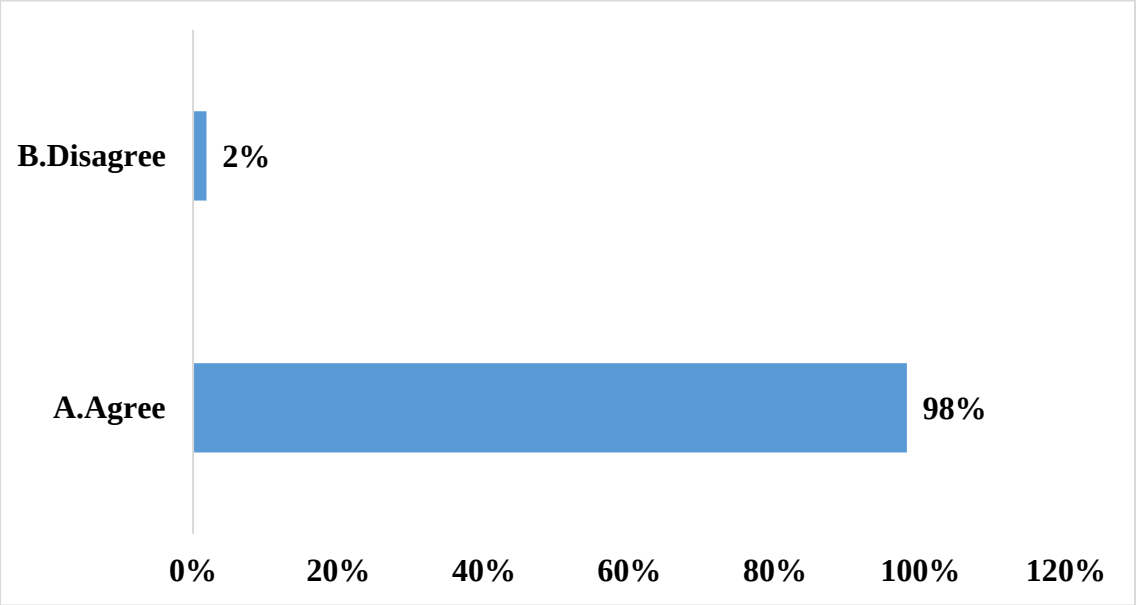
A. Effective
B. Highly effective
C. Excellent



According to 44% of doctors, they rate the efficacy of s-etodolac in treatment of osteoarthritis on basis of various parameters for assessment of pain as highly effective.

11) S-Etodolac is a safe option for pain management in patients with osteoarthritis with or without comorbidities?

A. Agree
B. Disagree



As per majority of doctors, 98%, they agree that s-etodolac is a safe option for pain management in patients with osteoarthritis with or without comorbidities.

Summary

- As per 58% of doctors, they per day see 5-10 patients of osteoarthritis in their clinical practices.
- As per 64% of doctors, there is no gender difference in osteoarthritis.
- As per 61% of doctors, 50 – 60 years age group is more prone to osteoarthritis.
- According to majority of doctors, 95%, they agree that patients of osteoarthritis generally present with a history of some comorbid condition.According to 44% of doctors, diabetes is more common in patients with osteoarthritis in their clinical practices.
- As per majority of doctors, 71%, the attributes kept in mind during selection of NSAIDs in patients with oa are efficacy, safety, selective pharmacological profile and simpler pharmacokinetic profile and reduced drug–drug interactions.
- As per majority of doctors, 91%, they prefer unichiral NSAIDS over NSAIDS for pain management in their clinical practices.
- As per 62% of doctors, they see up to 70% reduction in pain intensity with s-etodolac tablets in patients with oa.
- According to 30% of doctors, 6- 8 weeks is the usual duration required for oa/ra treatment with s-etodolac in their clinical practices.
- According to 44% of doctors, they rate the efficacy of s-etodolac in treatment of osteoarthritis on basis of various parameters for assessment of pain as highly effective.
- As per majority of doctors, 98%, they agree that s-etodolac is a safe option for pain management in patients with osteoarthritis with or without comorbidities.

Consultant Opinion

Market Opportunities:

- There is a substantial patient population affected by OA, with doctors reporting seeing 5-10 OA patients per day. This presents an opportunity for pharmaceutical companies to develop and market effective treatments for OA.

Value for Healthcare Professionals:

- Healthcare professionals can benefit from continued education and training on the management of OA, including the selection of appropriate NSAIDs and pain management strategies.

Adverse Effect Management:

- Healthcare professionals should be vigilant in monitoring patients for potential adverse effects associated with NSAID therapy for OA. Providing guidance on adverse effect management and patient education can enhance treatment safety and adherence.

Withdrawal Management:

- In cases where discontinuation of NSAID therapy is necessary, healthcare professionals should implement appropriate withdrawal management strategies to minimize potential risks and adverse effects for patients.

Market Positioning:

- Pharmaceutical companies can position their NSAID products, such as S-etodolac, as effective and safe options for pain management in patients with OA. Emphasizing the efficacy, safety, and tolerability of these medications can differentiate them in the market and increase their adoption by healthcare professionals.

Personalized Treatment Decisions:

- Healthcare professionals should adopt a personalized approach to treatment decisions for patients with OA, considering individual patient characteristics, preferences, and treatment goals. This may involve tailoring NSAID therapy regimens based on patient-specific factors and comorbidities.

Improving Patient Outcomes:

- Pharmaceutical companies and healthcare professionals should collaborate to develop and implement strategies aimed at improving patient outcomes in OA. This may include conducting clinical trials to evaluate the efficacy and safety of novel treatment approaches, as well as providing comprehensive patient education and support resources.

In conclusion, there are significant opportunities for healthcare professionals and pharmaceutical companies to enhance patient care and outcomes in OA through targeted interventions, personalized treatment approaches, and collaborative efforts to advance research and innovation in this field.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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