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INSTRUCTION
for medical use

FORSANEC®)

Composition:
active substance: etoricoxib;
1 film-coated tablet contains etoricoxib 60 mg, or 90 mg, or 120 mg;
excipients: calcium hydrogen phosphate anhydrous, microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silicon dioxide, magnesium stearate;
film-coating: Opadry II 31G58920 white (hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide (E 171), polyethylene glycols, talc).

Pharmaceutical form. Film-coated tablets.
Main physicochemical properties:
film-coated tablets, 60 mg: white to off white color, oval-shaped biconvex film-coated tablets with a score line on one side and a plain on the other side;
film-coated tablets, 90 mg and 120 mg: white to off white color, round biconvex film-coated tablets plain on both sides.

Pharmacotherapeutic group.
Anti-inflammatory and antirheumatic products, non-steroids. Coxibs.
ATC code: M01A H05.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. There are data that etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.
Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be the main factor responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may

also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

Clinical efficacy and safety

Efficacy

In patients with osteoarthritis, etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12-week treatment period (using similar assessments as the above studies). Etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of hands.

In patients with rheumatoid arthritis, etoricoxib 60 mg and 90 mg once daily both provided significant improvements in pain, inflammation, and mobility. In studies evaluating the 60 mg and 90 mg dose, these beneficial effects were maintained over the 12-week treatment periods. In a comparative study evaluating the 60 mg dose and the 90 mg dose, both regimens were more effective than placebo.

In patients experiencing attacks of acute gouty arthritis, etoricoxib 120 mg once daily over an 8-day treatment period, led to a more pronounced decrease in moderate to extreme joint pain and inflammation comparable to indomethacin 50 mg three times daily. Pain relief was observed as early as 4 hours after initiation of treatment.

In patients with ankylosing spondylitis, etoricoxib 90 mg once daily provided significant reduction in pain, inflammation, as well as improved stiffness and function. The clinical benefit of etoricoxib was observed as early as the second day of therapy after initiation of treatment and was maintained throughout the 52-week treatment period. Etoricoxib therapy at a dose of 60 mg or 90 mg daily demonstrated similar efficacy compared to naproxen 1000 mg daily. Among inadequate responders to 60 mg daily for 6 weeks, dose escalation to 90 mg daily improved spinal pain intensity score compared to continuing on 60 mg daily.

In a clinical study evaluating postoperative dental pain, etoricoxib 90 mg administered once daily for up to three days had a more pronounced analgesic effect than placebo. In the subgroup of patients with moderate pain, etoricoxib 90 mg demonstrated a similar analgesic effect to that of ibuprofen 600 mg, and greater than that of combination of paracetamol/codeine 600 mg/60 mg). The proportion of patients using rescue medication within the first 24 hours of dosing was 40.8% for etoricoxib 90 mg, 25.5% for ibuprofen 600 mg every 6 hours, and 46.7% for paracetamol/codeine 600 mg/60 mg every 6 hours compared to 76.2% for placebo. The onset of analgesic action (perceptible pain relief) of 90 mg etoricoxib was 28 minutes after dosing.

Safety

There was no significant difference between etoricoxib and diclofenac in the rate of cardiovascular thrombotic events. Cardiorenal adverse events were observed more frequently with etoricoxib than with diclofenac, and this effect was dose-dependent. Gastrointestinal (GI) and hepatic adverse events were observed significantly more frequently with diclofenac than etoricoxib. The incidence of adverse experiences considered serious or resulting in drug discontinuation was higher with etoricoxib than diclofenac.

Cardiovascular safety results.

The rate of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) was comparable between etoricoxib and diclofenac. There were no statistically significant differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analyzed including patient categories across a range of baseline cardiovascular risk. When considered separately, the relative risks for confirmed thrombotic cardiovascular serious adverse events with etoricoxib 60 mg or 90 mg compared with diclofenac 150 mg were similar.

Cardiovascular mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Cardiorenal events.

The incidence of discontinuations due to hypertension-related adverse events was statistically significantly higher for etoricoxib than for diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg. The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalization or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to edema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).

Gastrointestinal tolerability results.

A significantly lower rate of discontinuations of treatment for any clinical GI adverse event (e.g., dyspepsia, abdominal pain, ulcer) was observed with etoricoxib compared with diclofenac.

Gastrointestinal safety results.

Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. A significantly lower rate of overall upper GI events was observed with etoricoxib compared to diclofenac. There was no significant difference between etoricoxib and diclofenac in the rate of complicated events. For the subset of upper GI hemorrhage events (complicated and uncomplicated combined), there was no significant difference between etoricoxib and diclofenac. The upper GI benefit for etoricoxib compared with diclofenac was not statistically significant in patients taking concomitant low-dose acetylsalicylic acid (ASA) (approximately 33% of patients).

The rates of confirmed lower GI clinical events (small or large bowel perforation, obstruction, or hemorrhage) were not significantly different between etoricoxib and diclofenac.

Hepatic safety results.

Etoricoxib was associated with a statistically significantly lower rate of discontinuations due to hepatic-related adverse experiences than diclofenac. Most hepatic adverse experiences in the were non-serious.

<u>Additional thrombotic cardiovascular safety data.</u>

There was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥60 mg, placebo, or other nonsteroidal anti-inflammatory drugs (NSAID) (non-naproxen). However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of thromboembolic events. Selective COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

<u>Additional gastrointestinal safety data.</u>

The incidence of gastroduodenal ulceration was significantly lower in patients treated with etoricoxib 120 mg once daily than in patients treated with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. Etoricoxib had a higher incidence of ulceration as compared to placebo.

<u>Renal function study in the elderly.</u>

Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at day 14 when compared to celecoxib and naproxen.

Pharmacokinetics.

Absorption.

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 µg/ml) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve ($AUC_{0–24}$) was 37.8 µg×hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in C_{max} and an increase in T_{max} by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution.

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (V_{dss}) was approximately 120 l in humans. There is evidence that etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism.

Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by cytochrome enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyze the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination.

There is evidence that following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in feces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

Characteristics in patients

Elderly patients.

Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Gender.

The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic impairment.

Patients with mild hepatic dysfunction (Child-Pugh score 5–6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7–9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are

no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10).

Renal impairment.

The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on hemodialysis were not significantly different from those in healthy subjects. Hemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min).

Pediatric patients.

The pharmacokinetics of etoricoxib in pediatric patients (<12 years old) have not been studied.

It is known that the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in pediatric patients have not been established.

Clinical characteristics.

Indications.

Symptomatic therapy of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.

Short-term treatment of moderate pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

Contraindications.

Hypersensitivity to the active substance or to any of the excipients.

Active peptic ulceration or active gastro-intestinal bleeding.

Bronchospasm, acute rhinitis, nasal polyps, angioneurotic edema, urticaria, or allergic-type reactions, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

Pregnancy and lactation.

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

Estimated renal creatinine clearance <30 ml/min.

Patient's age under 16 years.

Inflammatory bowel disease.

Congestive heart failure (NYHA II–IV).

Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.

Established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

Interaction with other medicinal products and other forms of interaction.

Pharmacodynamic interactions.

Oral anticoagulants.

In subjects stabilized on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalized Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists. NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or angiotensin II antagonists and agents that

inhibit COX may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic acid.

In a study in healthy subjects, at steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

Cyclosporin and tacrolimus.

Although interaction of etoricoxib with these drugs has not been studied, coadministration of NSAID with cyclosporin or tacrolimus may increase the nephrotoxic effect of the latter. Renal function should be monitored when etoricoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

The effect of etoricoxib on the pharmacokinetics of other drugs.

Lithium.

NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate.

Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. Data on the effect of etoricoxib 120 mg on the pharmacokinetics of methotrexate are conflicting. Thus, in one study, etoricoxib 120 mg had no effect on plasma concentrations and renal clearance of methotrexate, but in the other study with the same dose of etoricoxib, plasma concentrations of methotrexate increased by 28% and renal clearance with methotrexate decreased by 13%. Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

Oral contraceptives.

Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC_{0-24} of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC_{0-24} of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thromboembolic events in women at risk).

Hormone replacement therapy (HRT).

Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg conjugated estrogens) for 28 days, increased the mean steady state AUC_{0-24} of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of etoricoxib (30, 60, and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24}) to these estrogenic components were less than half of those observed when conjugated estrogens were administered alone and the dose was increased from 0.625 to 1.25 mg. Higher doses of conjugated estrogens were not studied in combination with

etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in estrogen exposure might increase the risk of adverse events associated with HRT.

Prednisone/prednisolone.

Etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

Digoxin.

Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma AUC_{0-24} or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33%). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolized by sulfotransferases.

Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolized by human sulfotransferases (e.g., oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolized by CYP isoenzymes.

Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

Effects of other drugs on the pharmacokinetics of etoricoxib.

The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyze the main metabolic pathway, but their quantitative roles have not been studied *in vivo*.

Ketoconazole.

Ketoconazole is a potent inhibitor of CYP3A4. Dosed at 400 mg once a day for 11 days to healthy volunteers, ketoconazole did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC).

Voriconazole and miconazole.

Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib, but is not considered to be clinically meaningful based on published data.

Rifampicin.

Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. This interaction may result in recurrence of symptoms. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin.

Antacids.

Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

Special warnings and precautions for use.

Gastrointestinal (GI) effects

Upper GI complications (perforations, ulcers or bleedings), some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib. Caution is advised with treatment of patients most at risk of developing a GI complication with NSAIDs; the elderly, patients using any

other NSAID or acetylsalicylic acid (ASA) concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.
There is a further increase in the risk of GI adverse effects (gastrointestinal ulceration or other GI complications) when etoricoxib is taken concomitantly with ASA, even at low doses (see "Interaction with other medicinal products and other forms of interaction" section). A significant difference in GI safety between selective COX-2 inhibitors combined with ASA and NSAIDs with ASA has not been demonstrated in long-term clinical trials (see "Pharmacological properties" section).
Cardiovascular effects
Clinical trials suggest that the selective COX-2 inhibitors may be associated with a risk of thrombotic events (especially myocardial infarction and stroke). As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see "Pharmacological properties", "Contraindications", "Administration and dosage" and "Adverse reactions" sections).
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration (see "Pharmacological properties" section).
COX-2 selective inhibitors are not a substitute for ASA for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore, antiplatelet therapies should not be discontinued (see "Pharmacological properties" and "Interaction with other medicinal products and other forms of interaction" sections).
Renal effects.
Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.
Fluid retention, edema and hypertension.
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in patients taking etoricoxib. All NSAIDs, including etoricoxib, can be associated with new onset or recurrent congestive heart failure (for information regarding a dose related response see "Pharmacological properties" section). Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing edema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.
Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib (see "Contraindications" section), and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.
Hepatic effects.
Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with etoricoxib 30, 60 and 90 mg daily.

Any patients with symptoms suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

General recommendations.

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered. Medically appropriate supervision should be maintained when using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Caution should be used when initiating treatment with etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see "Contraindications" section). Patients appear to be at highest risk for these reactions early in the course of therapy with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see "Adverse reactions" section). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants (see "Interaction with other medicinal products and other forms of interaction" section).

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase and prostaglandin synthesis, is not recommended in women attempting to conceive (see "Pharmacological properties" and "Use during pregnancy and lactation" sections).

Forsanec®, film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Excipients.

The drug contains lactose. If a patient has an intolerance to some sugars, it is necessary to consult a doctor before taking this drug.

Use during pregnancy and lactation.

Pregnancy

No clinical data on using etoricoxib during pregnancy are available. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

Breastfeeding

It is not known whether etoricoxib is excreted in human milk. In animals, etoricoxib is known to be excreted in milk. Women who use etoricoxib must not breastfeed.

Fertility.

The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive.

Effects on ability to drive and use machines.

Patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery.

Administration and dosage.

Etoricoxib is administered orally and may be taken with or without food. The onset of the effect of the medicinal product may be faster when etoricoxib is administered without food. This should be considered when rapid symptomatic relief is needed.

The 60 mg tablet can be divided in half. 90 mg and 120 mg tablets should not be divided.

As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

Osteoarthritis

The recommended dose is 30 mg once daily (use in the form of 60 mg tablet which can be divided into equal parts). In some patients with insufficient relief from symptoms, an increased dose of 60 mg once daily may increase efficacy. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Rheumatoid arthritis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilized, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Ankylosing spondylitis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilized, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Acute pain conditions

For acute pain conditions, etoricoxib should be used only for the acute symptomatic period.

Acute gouty arthritis

The recommended dose is 120 mg once daily. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days.

Postoperative dental surgery pain

The recommended dose is 90 mg once daily, limited to a maximum of 3 days. Some patients may require other postoperative analgesia in addition to etoricoxib during the three-day treatment period.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

- the dose for osteoarthritis should not exceed 60 mg daily;
- the dose for rheumatoid arthritis and ankylosing spondylitis should not exceed 90 mg daily;
- the dose for acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment;
- the dose for postoperative acute dental surgery pain should not exceed 90 mg daily, limited to a maximum of 3 days.

Special populations

Elderly patients

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Patients with hepatic impairment

Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5–6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7–9), regardless of indication, the dose of 30 mg once daily should not be exceeded (use in the form of 60 mg tablet which can be divided into equal parts).
Clinical experience is limited particularly in patients with moderate hepatic dysfunction; therefore, caution is advised when prescribing the drug. There is no clinical etoricoxib experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contraindicated in these patients.
Patients with renal impairment
No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contraindicated.

Pediatric population.
Etoricoxib is contraindicated in children and adolescents under 16 years of age.

Overdose.
Administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).
In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.
Etoricoxib is not dialysable by hemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

Adverse reactions.
Adverse reactions are defined by frequency: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1000), rare (<1/10000).
Infections and infestations: common – alveolar osteitis; uncommon – gastroenteritis, upper respiratory infection, urinary tract infection.
Blood and lymphatic system disorders: uncommon – anemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia.
Immune system disorders: uncommon – hypersensitivity[ß]; rare – angioedema / anaphylactic/anaphylactoid reactions including shock.
Metabolism and nutrition disorders: common – edema / fluid retention; uncommon – appetite increase or decrease, weight gain.
Psychiatric disorders: uncommon – anxiety, depression, mental acuity decreased, hallucinations; rare – confusion, restlessness.
Nervous system disorders: common – dizziness, headache; uncommon – dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence.
Eye disorders: uncommon – blurred vision, conjunctivitis.
Ear and labyrinth disorders: uncommon – tinnitus, vertigo.
Cardiac disorders: common – palpitations, arrhythmia; uncommon – atrial fibrillation, tachycardia, congestive heart failure, non-specific ECG changes, angina pectoris, myocardial infarction[§].
Vascular disorders: common – hypertension; uncommon – flushing, cerebrovascular accident[§], transient ischemic attack, hypertensive crisis, vasculitis.

Respiratory, thoracic and mediastinal disorders: common – bronchospasm; uncommon – cough, dyspnea, epistaxis.
Gastrointestinal disorders: very common – abdominal pain; common – constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, esophagitis, oral ulcer; uncommon – abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including GI perforation and bleeding, irritable bowel syndrome, pancreatitis.
Hepatobiliary disorders: common – ALT increased, AST increased; rare – hepatitis, hepatic failure, jaundice.
Skin and subcutaneous tissue disorders: common – ecchymosis; uncommon – facial edema, pruritus, rash, erythema, urticaria; rare – Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption.
Musculoskeletal and connective tissue disorders: uncommon – muscular cramp/spasm, musculoskeletal pain/stiffness.
Renal and urinary disorders: uncommon – proteinuria, serum creatinine increased, renal failure / renal insufficiency (see "Special warnings and precautions for use" section).
General disorders and administration site conditions: common – asthenia/fatigue, flu-like symptoms; uncommon – chest pain.
Investigations: uncommon – blood urea nitrogen increased, creatine phosphokinase increased, hyperkaliemia, uric acid increased; rare – blood sodium decreased.
ß Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy".
§ Selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).
The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is an important procedure. It allows continued monitoring of the benefit/risk ratio of the medicinal product use. Qualified healthcare professionals should report all suspected adverse reactions.

Shelf life.
2 years.

Storage conditions.
Store in the original package at temperature below 25°C.
Keep out of the reach of children.

Package.
7 tablets in blister; 1 or 4 blisters in carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of its business activity.

Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

Date of last revision.