CHAPTER 2
PROFILE OF DRUGS
## CHAPTER 2

### Profile of Drugs

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2.1 Drug profile of etoricoxib

2.1.1 Nomenclature and physico-chemical properties

- **Chemical Name**: 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine
- **Empirical formula**: C_{18}H_{15}ClN_{2}O_{2}S
- **Structural formula**:

![Structural formula of etoricoxib](image)

- **Molecular Weight**: 358.84
- **Appearance**: White to off-white powder
- **Solubility**: Practically insoluble in water; freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, chloroform; soluble in isopropyl acetate, ethanol and toluene; sparingly soluble in isopropyl alcohol.
- **Melting point**: 139 to 141° C
- **Dissociation Constant**: pK_a 3.68
- **Storage**: In tightly-closed container

2.1.2 Pharmacological properties

2.1.2.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs. Etoricoxib is an oral, selective COX-2 inhibitor within the clinical dose range.
Across clinical pharmacological studies, it 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.

COX 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 primarily 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.

Approximately 3,100 patients were treated with etoricoxib ≥ 60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of serious thrombotic cardiovascular events between patients receiving etoricoxib ≥ 60 mg, placebo, or non-naproxen NSAIDs. 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 COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic events. 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.

In patients with OA, 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.

In patients with RA, etoricoxib 90 mg once daily provided significant improvements in pain, inflammation, and mobility. These beneficial effects were maintained over the 12-week treatment periods.
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In patients experiencing attacks of acute gouty arthritis, etoricoxib 120 mg once daily over an eight-day treatment period, relieved moderate to extreme joint pain and inflammation comparable to indomethacin 50 mg three times daily. Pain relief was observed as early as four hours after initiation of treatment.

In studies specifically designed to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing. In two 12-week double-blind endoscopy studies, the cumulative 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.

A prespecified, combined analysis of eight clinical trials of approximately 4,000 patients with OA, RA, or chronic low back pain assessed the incidence rate for the following end-points: 1) discontinuation for upper GI symptoms; 2) discontinuation for any GI adverse experiences; 3) new use of gastroprotective medications and 4) new use of any GI medications. There was an approximate 50% risk reduction for these end-points in patients treated with etoricoxib (60, 90 or 120 mg daily) as compared to patients treated with naproxen 500 mg twice daily or diclofenac 50 mg three times daily. There were no statistically significant differences between etoricoxib and placebo.

2.1.2.2 Mechanism of action

Etoricoxib is an NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. Etoricoxib is a potent, orally active, highly selective COX-2 inhibitor within and above the clinical dose range. Two isoforms of cyclooxygenase enzyme have been identified: COX-1 and COX-2. COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and platelet inhibition. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib decreases these clinical signs and symptoms with decreased GI toxicity and without effects on platelet function. Across clinical pharmacology studies, Etoricoxib produced dose-dependent inhibition of COX-2 without
inhibition of COX-1 at doses up to 150 mg daily. The influence on gastroprotective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either etoricoxib 120 mg daily, naproxen 500 mg twice daily, or placebo. Etoricoxib did not inhibit gastric prostaglandin synthesis as compared to placebo. In contrast, naproxen inhibited gastric prostaglandin synthesis by approximately 80% compared with placebo. These data further support the COX-2 selectivity of etoricoxib.

2.1.2.3 Pharmacokinetics

Absorption
Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 96%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean $C_{\text{max}} = 3.6 \mu g/ml$) was observed at approximately 1 hour ($T_{\text{max}}$) after administration to fasted adults. The geometric mean AUC$_{0-24h}$ was 37.8 $\mu g\cdot h/ml$. The pharmacokinetics of etoricoxib is 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 $C_{\text{max}}$ and an increase in $T_{\text{max}}$ 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 0.05-5 $\mu g/ml$. The volume of distribution at steady state ($V_{\text{dss}}$) was approximately 120 litres in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism
Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by 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 catalyse 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**

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 faeces, 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.

**2.1.2.4 Therapeutic indications**

For the symptomatic relief of OA, RA and the pain and signs of inflammation associated with acute gouty arthritis.

**2.1.2.5 Adverse effects**

Gastrointestinal effects: Upper gastrointestinal complications (perforations, ulcers or bleedings (PUBs))

Cardiovascular effects: COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of effect on platelet function. Because etoricoxib does not inhibit platelet aggregation, antiplatelet therapies (e.g. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk of or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, cerebral ischaemia, coronary by-pass graft surgery or peripheral vascular surgery). Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2
selective inhibitors noted above. Appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Renal effects: Reduced renal blood flow, and thereby impair renal function.

Fluid retention, edema and hypertension

Hepatic effects: liver dysfunction and hepatic insufficiency

General effects: Dehydration, Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, hypersensitivity reactions (anaphylaxis, angioedema)

2.1.2.6 Contraindications

Etoricoxib is contraindicated in following conditions:

History of hypersensitivity to the active substance or to any of the excipients, active peptic ulceration or active gastrointestinal bleeding, patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic edema, urticaria, or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-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, children and adolescents under 16 years of age, inflammatory bowel disease and severe congestive heart failure.

2.1.2.7 Dose and administration

Etoricoxib is administered orally and may be taken with or without food. The onset of drug effect may be faster when etoricoxib is administered without food.

Osteoarthritis: The recommended dose is 60 mg once daily.

Rheumatoid arthritis: The recommended dose is 90 mg once daily.

Acute gouty arthritis: The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period.
2.1.2.8 Over dosage

No overdoses of etoricoxib were reported during clinical trials. In clinical studies, 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. 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 dialyzable by haemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.
2.2 Drug profile of cilostazol

2.2.1 Nomenclature and physico-chemical properties\textsuperscript{32-35}

- **Chemical Name:** 6-\{4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy\}-3,4-dihydro-2
  \((1H)\)-quinolinone
- **Empirical formula:** \(C_{20}H_{27}N_{5}O_{2}\)
- **Structural formula:**

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- **Molecular Weight:** 369.47
- **Appearance:** White to off-white crystals or as a crystalline powder
- **Solubility:** Slightly soluble in methanol and ethanol; practically insoluble in water, 0.1 N hydrochloric acid, and 0.1 N sodium hydroxide solution.
- **Melting point:** 160\(^\circ\) C
- **Storage:** In controlled room temperature

2.2.2 Pharmacology\textsuperscript{36-38}

2.2.2.1 Pharmacodynamic properties\textsuperscript{39}

Cilostazol affects both vascular body and cardiovascular function. It produces non-homogeneous dilation of vascular beds, with greater dilation in femoral body than in vertebral, carotid or superior mesenteric arteries. Renal arteries are not responsive to the effect of cilostazol.

In dogs or cynomolgous monkeys, cilostazol increased heart rate, myocardial contractile force, and coronary blood flow as well as ventricular automaticity, as would be expected for a PDE III inhibitor. Left ventricular contractility was increased at doses required to inhibit platelet aggregation. A-V conduction was accelerated. In humans, heart rate
increased in a dose-proportional manner by a mean of 5.1 and 7.4 beats per minute in patients treated with 50 and 100 mg b.i.d., respectively. In 264 patients evaluated with Holter monitors, numerically more cilostazol-treated patients had increases in ventricular premature beats and non-sustained ventricular tachycardia events than did placebo-treated patients; the increases were not dose-related.

2.2.2.2 Mechanism of action
The mechanism of the effects of cilostazol on the symptoms of intermittent claudication is not fully understood. Cilostazol and several of its metabolites are cAMP PDE III inhibitors, inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation. Cilostazol reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, arachidonic acid, epinephrine, and shear stress. Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, as compared to placebo, cilostazol 100 mg b.i.d. produced a reduction in triglycerides of 29.3 mg/dL (15%) and an increase in HDL-cholesterol of 4.0 mg/dL (≈ 10%).

2.2.2.3 Pharmacokinetics

Absorption
Cilostazol is well absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in C_{max} and a 25% increase in AUC. Absolute bioavailability is not known.

Distribution

Plasma Protein and Erythrocyte Binding: Protein binding capacity of cilostazol is 95-98%, predominantly to albumin. The mean percent binding for 3, 4-dehydro-cilostazol is 97.4% and for 4'-trans-hydroxy-cilostazol is 66%.

Mild hepatic impairment did not affect protein binding. The free fraction of cilostazol was 27% higher in subjects with renal impairment than in normal volunteers. The displacement of cilostazol from plasma proteins by erythromycin, quinidine, warfarin, and omeprazole was not clinically significant.
Metabolism and Excretion
Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of cilostazol. Cilostazol and its active metabolites have apparent elimination half-lives of about 11-13 hours. Cilostazol and its active metabolites accumulate about 2-fold with chronic administration and reach steady state blood levels within a few days. The pharmacokinetics of cilostazol and its two major active metabolites were similar in healthy normal subjects and patients with intermittent claudication due to peripheral arterial disease (PAD).

Following oral administration of 100 mg radiolabeled cilostazol, 56% of the total analytes in plasma was cilostazol, 15% was 3, 4-dehydro-cilostazol (4-7 times as active as cilostazol), and 4% was 4'-trans-hydroxy-cilostazol (one fifth as active as cilostazol). The primary route of elimination was the urine (74%), with the remainder excreted in the feces (20%). No measurable amount of unchanged cilostazol was excreted in the urine, and less than 2% of the dose was excreted as 3, 4-dehydro-cilostazol. About 30% of the dose was excreted in the urine as 4'-trans-hydroxy-cilostazol. The remainder was excreted as other metabolites, none of which exceeded 5%. There was no evidence of induction of hepatic microenzymes.

2.2.2.4 Therapeutic indications
Cilostazol is indicated for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance.

2.2.2.5 Adverse effects
More frequent adverse events: Headache, palpitation and diarrhea, hypertension, vomiting, leg cramps, hyperesthesia, paresthesia, dyspnea, rash, hematuria, urinary tract infection, flu syndrome, angina pectoris, arthritis, and bronchitis.

Less frequent adverse events: Chills face edema, fever, generalized edema, malaise, neck rigidity, pelvic pain, retroperitoneal hemorrhage.
Cardiovascular: Atrial fibrillation, atrial flutter, cerebral infarct, cerebral ischemia, congestive heart failure, heart arrest, hemorrhage, hypotension, myocardial infarction, myocardial ischemia, nodal arrhythmia, postural hypotension, supraventricular tachycardia, syncope, varicose vein, vasodilation, ventricular extrasystoles, ventricular tachycardia.

Digestive: Anorexia, cholelithiasis, colitis, duodenal ulcer, duodenitis, esophageal hemorrhage, esophagitis, GOT increased, gastritis, gastroenteritis, gum hemorrhage, hematemesis, melena, peptic ulcer, periodontal abscess, rectal hemorrhage, stomach ulcer, tongue edema.

Endocrine: Diabetes mellitus.

Haemic and Lymphatic: Anemia, ecchymosis, iron deficiency anemia, polycythemia, purpura.

Metabolic and Nutritional: increase creatinine, gout, hyperlipemia, hyperuricemia.

Musculoskeletal: Arthralgia, bone pain, bursitis.

Nervous: Anxiety, insomnia, neuralgia.

Respiratory: Asthma, epistaxis, hemoptysis, pneumonia, sinusitis.

Skin and Appendages: Furunculosis, skin hypertrophy, urticaria.

Special Senses: Amblyopia, blindness, conjunctivitis, diplopia, ear pain, eye hemorrhage.

### 2.2.2.6 Contraindications

Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity. Cilostazol is contraindicated in patients with haemostatic disorders or active pathologic bleeding, such as bleeding peptic ulcer and intracranial bleeding. Cilostazol inhibits platelet aggregation in a reversible manner. Cilostazol is contraindicated in patients with known or suspected hypersensitivity to any of its components.
2.2.2.7 Dose and administration

The recommended dosage of cilostazol is 100 mg b.i.d. taken at least half an hour before or two hours after breakfast and dinner. A dose of 50 mg b.i.d. should be considered during coadministration of such inhibitors of CYP3A4 as ketoconazole, itraconazole, erythromycin and diltiazem, and during coadministration of such inhibitors of CYP2C19 as omeprazole. Patients may respond as early as 2 to 4 weeks after the initiation of therapy, but treatment up to 12 weeks may be needed before a beneficial effect is experienced.

2.2.2.8 Overdose

Information on acute overdosage with cilostazol in humans is limited. The signs and symptoms of an 'acute overdose can be anticipated to be those of excessive pharmacologic effect: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. The patient should be carefully observed and given supportive treatment. Since cilostazol is highly protein-bound, it is unlikely that it can be efficiently removed by hemodialysis or peritoneal dialysis. The oral LD$_{50}$ of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs.
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