III. DRUG PROFILE

1) ETORICOXIB\textsuperscript{98, 99, 100, 101}

Etoricoxib is a selective cyclooxygenase-2 enzyme (COX-2) inhibitor. Like any other COX-2 selective inhibitor, Etoricoxib selectively inhibits isoform 2 of cyclooxygenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid. Therapeutic indications for Etoricoxib are treatment of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, chronic low back pain, acute pain and gout.

**Chemical Structure of Etoricoxib**

![Chemical Structure of Etoricoxib](image)

- **IUPAC name**: 5-chloro-3-(4-methanesulfonylphenyl)-2-(6-methylpyridin-3-yl) pyridine
- **Molecular formula**: $\text{C}_{18}\text{H}_{15}\text{ClN}_{2}\text{O}_{2}\text{S}$
- **Molecular weight**: 358.842
- **Melting point**: 134-135\textdegree C
- **Solubility**: soluble in methanol and ethanol
Standards

1. UV - The absorbance at the maximum is 234 nm
2. Melts at 134- 135°C
3. I.R.- The spectrum obtained with Etoricoxib
4. Loss on drying - Not more than 0.5% w/w
5. Heavy metals - Maximum 20 ppm
6. Sulphated ash - Maximum 0.10% w/w
7. Purity by HPLC – Minimum 99.0%

Clinical Pharmacology

Absorption
After oral administration, Etoricoxib is rapidly absorbed and bioavailability is almost 100%.

Distribution
Etoricoxib is highly protein-bound (92%).

Metabolism
Etoricoxib is metabolized in liver by CYP3A4 to metabolites Etoricoxib 1'-N'-oxide and 6-hydroxymethyletoricoxib.

Elimination
About 70% of administered dose is excreted through urine and 20% is excreted in faeces. Plasma half-life is 22 hours.

Adverse drug reactions
Gastrointestinal tract disorders; ischaemic cardiac events; hypersensitivity reactions, headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, tinnitus, photosensitivity; blood disorders, fluid retention, hypertension; dry mouth, taste disturbance, mouth ulcers; appetite and weight changes; chest pain, fatigue, paraesthesia, influenza-like syndrome, myalgia and renal toxicity.
Drug interactions
CYP3A4 inhibitors or inducers; rifampicin, ethinyl oestradiol; oral salbutamol and minoxidil. Antidepressant SSRIs and venlafaxine may increase risk of bleeding. Risk of side effects are increased with concomitant use of aspirin, cyclosporine, ketorolac or other NSAIDs, lithium, methotrexate, coumarins, phenindione, phenytoin and sulphonylureas.

Dose
1. Osteoarthritis - Adult 60 mg once a daily
2. Rheumatoid arthritis – Adult 90 mg once a daily
3. Acute gout – Adult 120 mg once a daily, maximum duration- 8 days.

Mechanism of drug action
Etoricoxib selectively inhibits isoform 2 of cyclooxygenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid.

![Figure 3.1: Mechanism of action of Etoricoxib](image-url)
Prostaglandin is widely distributed throughout the body and exerts effect on most organs and tissues. Prostaglandin mainly responsible for inducing pain in body. They are synthesized from Arachidonic acid by the action of prostaglandin synthetase (Cyclooxygenase), an enzyme which is almost universally distributed in the body. This steps forms the endoperoxidase and can be blocked by Non-steroidal anti-inflammatory drug like Etoricoxib which selectively inhibit Cyclooxygenase 2 (COX 2) enzyme. So Prostaglandin synthesis is blocked.


2) CELECOXIB

Celecoxib is NSAIDs belonging to selective COX 2 inhibitor. Chemically is a diaryl-substituted pyrazole.

![Chemical structure of Celecoxib](image)

4-[5-(4-methylphenyl)-3-(trifluoromethyl) pyrazol-1-yl] benzene Sulfonamide

Table 3.1: Physical & biopharmaceutical property of drug.

<table>
<thead>
<tr>
<th>Particular</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
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<td>Molecular weight</td>
<td>381.38;</td>
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<tr>
<td>Molecular mass</td>
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</tr>
<tr>
<td>Melting point</td>
<td>157-158&lt;sup&gt;0&lt;/sup&gt;c</td>
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<td>Route of administration</td>
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<tr>
<td>Bioavailability</td>
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<tr>
<td>Protein binding</td>
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<tr>
<td>Metabolism</td>
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<tr>
<td>Half life</td>
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<tr>
<td>Excretion</td>
<td>Renal 27%, faecal 57%</td>
</tr>
<tr>
<td>Legal status</td>
<td>Prescription only</td>
</tr>
</tbody>
</table>

Dose

The usual adult dose of celecoxib is 100 to 200 mg once or twice a day.
3.2 PHARMACOKINETICS

3.2.1 Absorption:

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose-proportional up to 200 mg BID in conventional tablet.

3.2.2 Food Effects:

When CELECOXIB were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

3.2.3 Distribution:

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

3.2.4 Metabolism:

Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

3.2.5 Excretion:

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radio labeled drug, approximately 57% of the dose was excreted in the feces and 27%
was excreted into the urine. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 ml/min.

3.3 PHARMACODYNAMICS

3.3.1 Mechanism of Action

Celecoxib is a non steroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, Celecoxib reduced the incidence and multiplicity of tumors.

3.4 CLINICAL STUDIES

3.4.1 Celecoxib in Osteoarthritis

Celecoxib has demonstrated significant reduction in joint pain. Celecoxib was evaluated for treatment of the signs and the symptoms of OA of the knee and hip.

3.4.2 Rheumatoid Arthritis

CELECOXIB has demonstrated significant reduction in joint tenderness/pain and joint swelling.

3.4.3 Juvenile Rheumatoid Arthritis

Celecoxib significantly reduced relative to baseline joint inflammation, pain intensity and the duration of morning stiffness and improved handgrip strength.

3.4.4 Ankylosing Spondylitis

The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by Celecoxib in patients ankylosing spondylitis.

3.4.5 Analgesia, including Primary Dysmenorrhea

In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, Celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of Celecoxib provided pain relief within 60 minutes.
3.5. ADVERSE EFFECTS

3.5.1. Gastrointestinal (GI) Effects

Celecoxib can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal.

3.5.2. Hepatic Effects

Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including Celecoxib.

3.5.3. Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decomposition. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

3.5.4. Anaphylactic Reactions

As with NSAIDs in general, anaphylactic reactions have occurred in patients without known prior exposure to CELECOXIB. In post-marketing experience, rare cases of anaphylactic reactions and angio edema have been reported in patients receiving. Celecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without
nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

3.5.5. Skin Reactions

Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal.

3.5.6. Pregnancy

In late pregnancy, starting at 30 weeks gestation, Celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

3.5.7. Corticosteroid Treatment

Celecoxib cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

3.5.8. Hematological Effects

Anemia is sometimes seen in patients receiving Celecoxib. In controlled clinical trials the incidence of anemia was 0.6%.

3.5.9. Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Celecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.
3.5.10. Concomitant NSAID Use

The concomitant use of Celecoxib with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

3.6. DRUG INTERACTIONS:

In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4. In vivo studies have shown the following:

3.6.1. Lithium:

Mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with CELECOXIB 200 mg twice daily as compared to subjects receiving lithium alone.

3.6.2. Fluconazole:

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole.

3.6.3. Other Drugs

The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied in vivo and clinically important interactions have not been found.

3.6.4. Warfarin

Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELECOXIB therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications.

3.6.5. Aspirin

CELECOXIB can be used with low-dose aspirin. However, concomitant administration of aspirin with CELECOXIB increases the rate of GI ulceration or
other complications, compared to use of CELECOXIB alone. Because of its lack of platelet effects, CELECOXIB is not a substitute for aspirin for cardiovascular prophylaxis.

3.6.6. ACE-inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking CELECOXIB concomitantly with ACE-inhibitors and angiotensin II antagonists.

3.6.7. Furosemide

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prosta
glandin synthesis.

3.6.8. Methotrexate

In an interaction study of rheumatoid arthritis patients taking methotrexate, CELECOXIB did not have an effect on the pharmacokinetics of methotrexate.

3.6.9. Concomitant NSAID Use

The concomitant use of CELECOXIB with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

3.7 CONTRAINDICATIONS

CELECOXIB is contraindicated:

- In patients with known hypersensitivity to celecoxib, aspirin, or other NSAIDs.
- In patients who have demonstrated allergic-type reactions to sulfonamides.
- In patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactoid reactions to NSAIDs, some of them fatal, have been reported in such patients.
For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
Lornoxicam$^{103-110}$

Lornoxicam (chlortenoxicam) is a new non steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. Lornoxicam differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug. Lornoxicam is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica, and other inflammations. Lornoxicam is also use in relieving symptoms of rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. It inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase (both COX-1 and COX-2).

![Chemical structure of Lornoxicam](image)

IUPAC Name: (3E)-6-chloro-3-[hydroxy(pyridin-2-ylamino)methylene]-2-methyl-2,3 dihydro-4H-thieno[2,3-e][1,2]thiazin-4-one 1,1-dioxide

Chemical Formula: $C_{13}H_{10}ClN_{3}O_{4}S_{2}$

Molecular weight: 371.8

Melting point: 225-230°C

CAS number: 70374-39-9
Solubility:

Slightly soluble : chloroform and 0.1mol/L NaOH Liquor

very lightly soluble : methanol and acetonitrile

Practically insoluble : Water

Standards :

Characteristics : A yellow crystalline powder

Loss on Drying: Not more than 1.00% w/w

Residue on Ignition: Not more than 0.20% w/w

Heavy Metal: Less than 20ppm

Assay(By HPLC) (On dried basis) : Not less than 98.0% & Not more than 102.0% w/w (% purity =99.3%)

Clinical pharmacology

Pharmacokinetics

Absorption:

Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Maximum plasma concentrations are achieved after approximately 1 to 2 hours. Food protracts the average time to maximum concentration from 1.5 to about 2.3 hours and can reduce the area under the curve (AUC) by up to 20%.

Distribution:

The absolute bioavailability of Lornoxicam is 90–100%. No first-pass effect was observed. Lornoxicam is 99% bound to plasma proteins (almost exclusively to serum albumin). Lornoxicam is highly bound (99%) to plasma proteins with a low apparent volume of distribution (0.2 L/kg). However, it readily penetrates into perivascular interstitial spaces, including synovial fluid.
Metabolism:

Lornoxicam is extensively metabolised in the liver. Lornoxicam is metabolized completely by CYP2C9 with the principal metabolite being 5'-hydroxy-lornoxicam and only negligible amounts of intact lornoxicam are excreted unchanged in the urine. The hydroxylated metabolite exhibits no pharmacological activity.

Elimination:

Approximately 2/3 of the drug is eliminated via the liver and 1/3 via the kidneys in the active form. Excretion is shared between the renal (42%) and faecal (51%) routes. Lornoxicam has a relatively short terminal plasma elimination half-life (mean 3 to 5 hours).

Pharmacodynamics:

Mechanism of action

Like all NSAIDs, it acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both iso forms in the same concentration range i.e. COX-1/COX-2 = 1. Thus, a perfectly balanced inhibition of COX-1 and COX-2 is achieved. COX-1 is a constitutive enzyme expressed in many cells as a house keeping enzyme and provides homeostatic prostaglandins. COX-2 is an inducible enzyme, which is expressed at the onset of inflammation in many cell types involved in inflammatory responses. It differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug.

![Figure 3.2: Mechanism of action of lornoxicam](image-url)
Prostaglandins are involved in all phases of inflammatory events including fever, pain reactions and physiological functions like intestinal motility, vascular tone, renal function, gastric acid secretion etc. The inducing events include phorbol esters, cytokines and endotoxins. It might produce the peripheral analgesic effects by NOcGMP pathway and the opening of K+ channels. It also acts by inhibition of spinal nociceptive processings, elevation of plasma levels of dynorphin and β endorphin following IV administration. In vitro tests have shown that lornoxicam also inhibited the formation of nitric oxide. It has also shown marked inhibitory activity on endotoxin induced IL-6 formation in THP 1 monocytes with less activity on TNF alpha and IL-1α.

Figure 3.3: The Prostaglandin pathway
Indications:

Lornoxicam is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica, and other inflammations. For the treatment of acute mild to moderate pain, as well as pain and inflammation of the joints caused by certain types of rheumatic diseases.

Tolerability and Drug Interactions:

Lornoxicam has a tolerability profile characteristic of NSAIDs, with gastrointestinal disturbances (pain, dyspepsia, nausea, vomiting) being the most prominent events. In comparative clinical trials, the tolerability of oral lornoxicam appeared to be similar to that of diclofenac and better than that of indomethacin in patients with arthritic conditions or chronic low back pain. As would be expected, parenterally administered lornoxicam tended to be better tolerated than parenteral opioid analgesics in patients with postoperative pain. Interactions with other drugs are typical of NSAIDs. Combination with vitamin K antagonists like warfarin increases the risk of bleeding. Combination with ciclosporin can lead to reduced kidney function, and to acute renal failure in rare cases. Lornoxicam can also increase the adverse effects of lithium, methotrexate and digoxin and its derivatives. The effect of diuretics, ACE inhibitors and angiotensin II receptor antagonists can be reduced, but this is only relevant in patients with special risks like heart failure. As with piroxicam, cimetiidine can increase plasma levels but is unlikely to cause relevant interactions.

Contraindications

Lornoxicam is contraindicated in the following situations:

Lornoxicam is contraindicated in conditions like Peptic ulcer, Hypersensitivity, Pregnancy, Lactation, Cerebro vascular hemorrhage, Gastro intestinal hemorrhage, Severe renal impairment. The drug is contraindicated in patients that must not take other NSAIDs, possible reasons including salicylate sensitivity, gastrointestinal bleeding and bleeding disorders, and severe impairment of heart, liver or kidney function and is contraindicated during the last third of pregnancy.
**Adverse effects**

Lornoxicam has side effects similar to other NSAIDs, most commonly mild ones like gastrointestinal disorders (nausea and diarrhea) and headache, Abdominal pain, diarrhoea, dizziness, dyspepsia, nausea, vomiting; headache; haematologic disorders; CNS effects; visual disturbance; tinnitus; nephrotoxicity; fluid retention; photosensitivity; alveolitis; pancreatitis; Stevens-Johnson syndrome; toxic epidermal necrolysis; colitis induction/exacerbation; stomatitis; hypertension, palpitation; insomnia, somnolence. Severe but seldom side effects include bleeding, bronchospasms and the extremely rare Stevens–Johnson syndrome.

**Dosage and Administration**

The most common dosages of lornoxicam used in clinical trials were 4 mg twice or 3 times daily or 8 mg twice daily (orally) for management of arthritic conditions, low back pain and ankylosing spondylitis, and single or repeated doses of 4 or 8 mg (orally or intravenously) for management of postoperative pain.