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Review on Dose, Destination and delivery aspects of Etoricoxib

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Abstract: Etoricoxib (Arcoxia) is a cyclooxygenase-2 (COX-2) selective inhibitor, particular enzyme which involved in severe inflammation and pain. It comes under the class of nonsteroidal anti-inflammatory drug (NSAIDs) of the COX-2-selective inhibitors(coxibs). As, the etoricoxib recommended dosage for osteoarthritis is 60 mg/day, for rheumatoid arthritis is 90 mg/day and for acute gouty arthritis is 120 mg/day. In patients with rheumatoid arthritis, improvements in tender and swollen joint counts and patient and investigator global assessment of disease activity were significantly greater in etoricoxib than in placebo recipients in two studies. Etoricoxib was also significantly more effective than naproxen in one of these studies. This review provides an update regarding the etoricoxib medical uses, action of this drug, solubility and various adverse effects

Keywords: Etoricoxib, History, working, solubility, mechanism, toxicity, Adverse effects.

1. Introduction

It is a non-steroidal anti-inflammatory drug in which cytochrome P450 (CYP) 3A4 isoenzyme, etoricoxib is metabolised primarily**.** Firstly, In 2002 as medication it was introduced clinically by **Merck & Co** and is now available in almost 62 countries worldwide, but approval in United States is still awaits. As, the several coxibs of second-generation includes parecoxib and lumiracoxib which neither has obtained FDA approval. It is sold under the trade name Arcoxia. From MCOLSON Research Laboratories it is a selective COX-2 inhibitor. Globally, in more than 80 countries it is approved except the US, because additional safety and efficacy for this drug is requires by FDA before it will be approved. It helps to prevent from inflammation and pain which takes places in the joints in which people of 16 years of age and older with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout. The treatment with some coxibs (Rofecoxib) is takes places by some clinical trials and meta-analysis which led to incidence of adverse cardiovascular events increased as compared to placebo. Due to such results, from market several drugs were withdrawn (Rofecoxib, September 2004 and Valdecoxib in April 2005). The several processes of the entire class of both NSAIDs and COX-2 inhibitors are started revision by the United States FDA and European medicines agency. Etoricoxib had similar efficacy to indomethacin in a study in patients with acute gout, and single-dose etoricoxib had similar efficacy to naproxen sodium in a study in women with primary dysmenorrhoea. Compared with non-COX-selective NSAIDs, etoricoxib was associated with significantly fewer upper gastrointestinal (GI) perforations, ulcers or bleeds, and was significantly less likely to result in treatment discontinuation because of NSAID-type GI symptoms or any GI symptoms. In contrast, selective COX-2 inhibitors have greater affinity for COX-2 than COX-1. Clinical evidence has shown that selective COX-2 inhibitors have comparable efficacy with traditional NSAIDs in the treatment of arthritis and pain, but offer the major advantage of reduced gastrointestinal toxicity, thus providing physicians with an important therapeutic alternative. Recently, reports from two long-term studies in patients with a history of colorectal adenomas have detailed an increased risk of cardiovascular events associated with the COX-2 inhibitors celecoxib and rofecoxib compared with placebo, leading to questions

about the cardiovascular safety of these agents, and highlighting the importance of careful patient selection based on the benefits and risks of treatment.

It was patent in 1996 and approved for medical use in 2002.

Etoricoxib having 92% protein bound abundantly. Approximately, it having apparent volume of 120L distributed in human body, as plasma albumin primarily. As, the plasma concentration vs time of drug (AUC) is ranges between 5 and 120mg in which increasing oral doses, the proportion is also increases. Etoricoxib provides relief from pain that takes places gradually. The treatment of problem like osteo, rheumatoid, acute gouty arthritis, dysmenorrhoea, acute dental surgery pain and several various conditions without affecting function of platelet or damaging gastric that is applicable for once-a-day. Etoricoxib having the highest COX-2 inhibition. The rate of thrombotic cardiovascular events, the etoricoxib use is found to be similar with diclofenac.

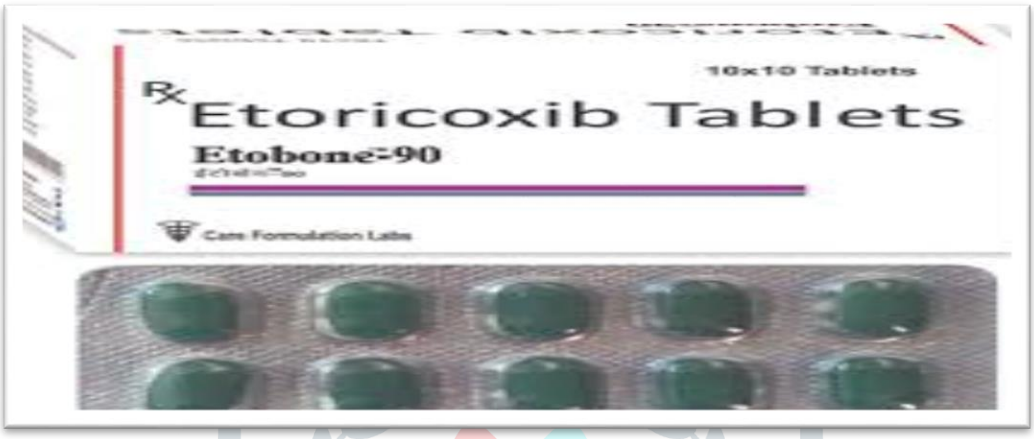

Fig: Etoricoxib Tablets

2. Structure features of Etoricoxib:

Etoricoxib is a member of the class of bipyridines that is 2,3'-bipyridine which is substituted at the 3, 5, and 6' positions by 4-(methyl sulfonyl)phenyl, chlorine, and methyl groups, respectively. It has a role as a cyclooxygenase 2 inhibitor and a non-steroidal anti-inflammatory drug

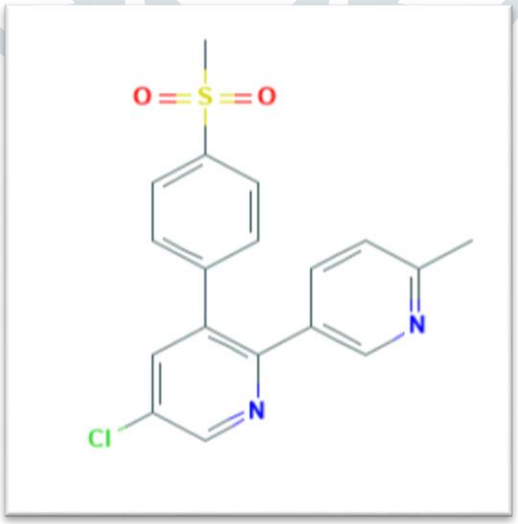

Fig: Structure of Etoricoxib

IUPAC Name: 5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

Formula: $C_{18}H_{15}ClN_2O_2S$

Bioavailability: 100%

Protein binding: 92%

Molar mass: 358.842 g/mol

Elimination half-life: 22 hours

Metabolism: Hepatic, CYP extensively involved (CYP3A4)

Excretion: Renal (70%) and fecal (20%)

3. Mechanism of action of Etoricoxib

As, compared with several selective COX-2 inhibitor, Etoricoxib selectively inhibits isoform 2 of the cyclooxygenase (COX-2) enzyme. Approximately, it selectively folds 106 for COX-2 inhibition over COX-1. The generation of prostaglandins (PGs) from arachidonic acid and to TXA2 and prostacyclin reduces. Compared with traditional non-steroidal anti-inflammatory drug, the selective show lesser activity of COX-2 inhibitors over COX-1. The cause of reduced gastrointestinal side effects by reduces the activity, as several large clinical trials demonstrated with different coxibs. Like any other COX-2 selective inhibitor Etoricoxib selectively inhibits isoform 2 of cyclo-oxygenase enzyme (COX-2), preventing production of prostaglandins (PGs) from arachidonic acid

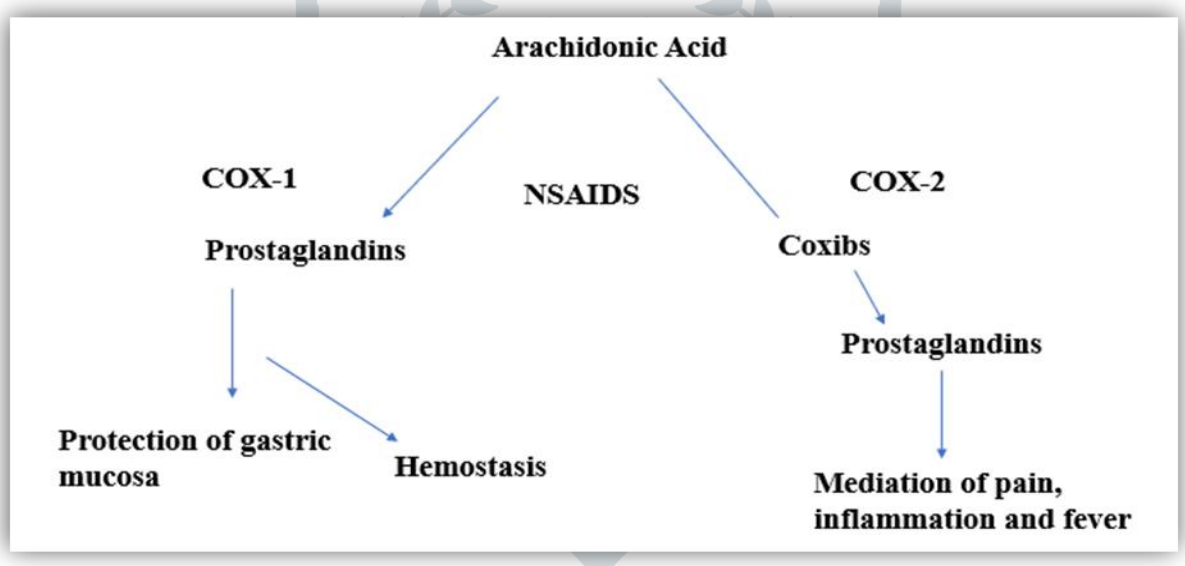

Fig: Flow chart of mechanism of action of Etoricoxib

4. **Dose:** The efficacy of etoricoxib has been established in a variety of other painful conditions including ankylosing spondylitis (AS), LBP, acute postoperative pain, and primary dysmenorrhea (60-120 mg OD)

5. Metabolism

Hepatic, primarily via CYP3A4.

Hover over products below to view reaction partners

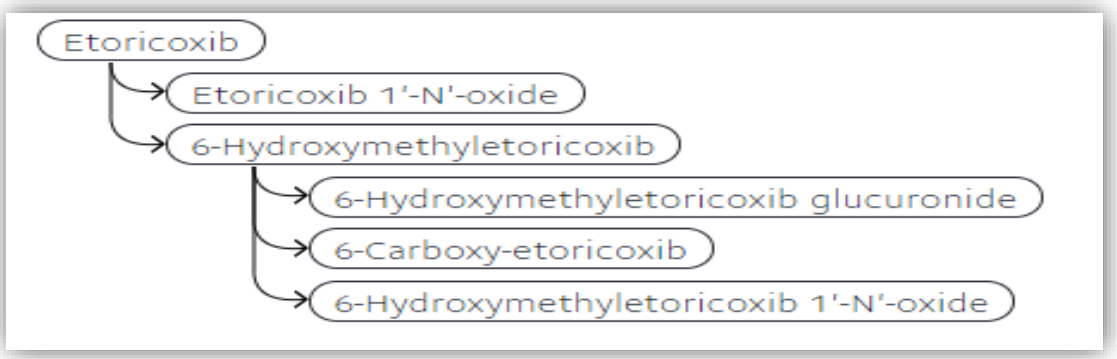

Fig: Metabolism of Etoricoxib

6. **How does Etoricoxib works:** It works by the blocking the release of certain chemical messengers that are responsible for pain and inflammation (redness and swelling).

7. Several expert advices for etoricoxib

- It helps to prevent from pain, swelling and inflammation that takes places
- As, compared to several other NSAIDS (Ibuprofen or Naproxen) which causes fewer stomach problems.
- Until, having no idea how it affects in which do not drive or do anything with requiring concentration which causes fatigue and dizziness.
- As, it causes excessive drowsiness by consuming alcohol while treating with such medicines.
- While treatment, in first two weeks it regularly monitoring your blood pressure while taking this medicine.
- If the history of having problems like stomach ulcers, heart diseases, high blood pressure, and liver or kidney disease then it should be informed to the doctor
- Doctor may have to take regular tests of blood for knowing the liver function during 0
- the long treatment.
- During, breastfeeding, Pregnancy or planning of conceive don't take Etoricoxib

8. Clinical Studies

Clinical studies have established the efficacy and tolerability of etoricoxib in arthritis and pain, and the drug is available in over 50 countries worldwide. Etoricoxib is approved in Europe for the symptomatic relief of OA, RA, and the pain and signs of inflammation associated with acute gouty arthritis (EMEA 2005a), whereas the US Food and Drug Administration (FDA) has requested additional efficacy and safety data prior to approval of etoricoxib. Some countries in Latin America and Asia have additional indications including LBP, ankylosing spondylitis, and primary dysmenorrhea

9. Solubility of Etoricoxib: Medical uses of Etoricoxib

Etoricoxib is a white powder which is insoluble in water. It is freely soluble in tetrahydrofuran, methanol, dimethyl sulfoxide, chloroform, dimethyl formamide and methyl ethyl ketone. It is also soluble in ethanol, toluene isopropyl acetate and sparingly soluble in 2-propanol.

10. Medical uses of Etoricoxib

The etoricoxib is used for treating psoriatic arthritis, osteoarthritis, rheumatoid arthritis, acute pain, chronic low back pain, gout and ankylosing spondylitis. These/ indications are approved differ by several countries. It also used for treatment of moderate pain after dental surgery for the short-term of adults in UK. The benefits of etoricoxib single dose in reduction of acute post-operative pain in adults is assessed by

Key Pharmacological Features

- Rapidly and completely absorbed via oral route
- Suitable for once daily without dose adjustment (except hepatic insufficiency)
- Greater COX-2 selectively than rofecoxib, valdecoxib or celecoxib
- Less interference with aspirin antiplatelet activity compared with other NSAIDs

Cochrane Review. Four times more pain relief post operatively than placebo by the single-dose oral etoricoxib, with equivalent adverse events level. The dose of 120mg of etoricoxib give effective or even better than commonly used analgesics.

ETORICOXIB

Efficacy: Osteoarthritis

- Comparable with diclofenac
- Comparable with naproxen
- Comparable with ibuprofen

Rheumatoid arthritis

- Comparable with diclofenac
- Comparable with or greater than naproxen

Acute gouty arthritis

- Comparable with indomethacin

Ankylosing spondylitis

- Greater than naproxen

Chronic lower back pain

- Greater than placebo

Postoperative pain

- Comparable with naproxen
- Greater than opioid/acetaminophen

Primary dysmenorrhea

- Comparable with naproxen

Tolerability Overall

- Generally, well tolerated
- No new findings during long term treatment

Gastrointestinal

- Superior to non-selective NSAIDs

Renal

- Similar to naproxen or ibuprofen
- Serious hypertension related adverse events were rare in EDGE (Etoricoxib versus Diclofenac sodium Gastrointestinal tolerability and Effectiveness study)
- Significant increase in hypertension related adverse events and significantly higher percentage of patients discontinuing therapy in etoricoxib 90mg/day group compared with diclofenac 150mg/day

Cardiovascular

- Thrombotic events risk similar to non-naproxen NSAIDs
- COX-2 inhibitor class effects for increased cardiovascular risk in product labeling

Hepatic

- Adjust etoricoxib dose in patient with hepatic insufficiency

S. No	Brand Name	Country
1	Algix and Tauxib	Italy
2	Arcox, Berrica, and Starcox	Pakistan
3	Arcoxia	Australia, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Croatia, Ecuador, Egypt, Estonia, Finland, Germany, Greece, Guatemala, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Jordan, Lebanon, Lithuania, Luxembourg, Malaysia, Mexico, Netherlands, New Zealand, Norway, Panama, Philippines, Portugal, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand, The Bahamas, Trinidad.
4	Blokium Cox	Argentina
5	Coxit	Jordan
6	Dabie	Singapore
7	Doloxib	Poland
8	E-Cox and Vecoxib	Nepal
9	Etoll	India
10	Etorix, Eto, Tory, Etoxib, and Vargus	Bangladesh and Costa Rica
11	Etozox, Etospeed, Intacoxia, Nucoxia, ETOS MR, and Etoshine	India
12	Exinef	South Africa
13	Exxiv	Portugal
14	Foldox	Argentina, Paraguay
15	Gerocoxan	Romania
16	Hetori	Brazil
17	Kostarox	Poland
18	Roticox	Polan

12. **Side effects**: Dyspepsia, abdominal pain, pedal edema, rise in BP, dry mouth, aphthous ulcers, taste disturbances and paresthesias. It is important that **you use** the lowest dose that controls your pain and you should not **take etoricoxib** for **longer** than necessary. This is because the risk of heart attacks and strokes might increase after **prolonged** treatment, especially with high doses.

13. How quickly does etoricoxib works?

The onset of **pain** relief was rapid, with similar benefit reported within 4 hours of the first dose of etoricoxib or indomethacin

14. Toxicity:

It causes the reduced of gastrointestinal toxicity because of such reduced activity, as COXIB signify several large clinical trials which are carried out by them. Compared with placebo, there is increased incidence of cardiovascular adverse events due to some clinical trials and meta- analysis showed with the treatment of COXIB. About 97% of the patients well tolerated the oral challenge with **etoricoxib**. During, the challenge test only two systemic reactions were concluded. For the patients with previous adverse reaction to NSAIDs concluded **Etoricoxib** as s **safe** molecule.

15. Adverse effects

Like all other NSAIDs the COX-2 inhibitors too have their share of adverse effects. Fixed drug eruption and generalised erythema, acute generalized exanthematous pustulosis (AGEP), erythema multiforme like eruption and drug induced pretibial erythema are some serious side effects reported, besides the usual innocuous ones.

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