1. Name of the medicinal product

ETO-WELL P 60 TABLETS

2. Qualitative and quantitative composition

Each film coated tablet contains
Etoricoxib 60mg
Paracetamol BP..... 500mg
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

film coated tablet.
An orange color oblong shape biconvexed film coated tablet, Scored in the middle on one side and plain on other side of the tablet.

4. Clinical particulars

4.1 Therapeutic indications

Etoricoxib and Paracetamol Tablet is a pain-relieving medicine. It is used to reduce pain and inflammation in conditions like rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. It may also be used to relieve muscle pain, back pain, toothache, or pain in the ear and throat.

4.2 Posology and method of administration

Etoricoxib
Posology
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 sections 4.3, 4.4, 4.8 and 5.1).
Osteoarthritis
The recommended dose is 30 mg once daily. 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 stabilised, 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 stabilised, 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 OA should not exceed 60 mg daily.
The dose for RA 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. Caution should be exercised in elderly patients (see section 4.4).
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.
Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients (see sections 4.3, 4.4 and 5.2).
Renal impairment
No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min (see section 5.2). The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated (see sections 4.3 and 4.4).
Paediatric population
Etoricoxib is contra-indicated in children and adolescents under 16 years of age (see section 4.3).
Method of administration
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.
Paracetamol
Posology
Adults, Elderly and Children over 16 years:
Two tablets every four hours as required. Not more than eight tablets in 24 hours
Do not take for more than 3 days without consulting your doctor.
These doses should not be given more frequently than every four hours nor should more than four doses be given in any 24 hour period.
Paediatric population
Not recommended for children under 10 years of age.
Children aged 10 to 15 years:
One tablet every four to six hours when necessary to a maximum of four doses in 24 hours. Do not take for more than 3 days without consulting your doctor.
These doses should not be repeated more frequently than every four to six hours nor should more than four doses be given in any 24 hour period.
Method of administration
For oral administration

4.3 Contraindications

Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients listed.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active peptic ulceration or active gastro-intestinal (GI) bleeding.
Patients who, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.
Pregnancy and lactation (see sections 4.6 and 5.3).
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.
Congestive heart failure (NYHA II-IV).
Patients with hypertension whose blood pressure is persistently elevated above 140/90mmHg and has not been adequately controlled.
Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Etoricoxib and Paracetamol tablet should be used with caution in patients with kidney disease. It is not recommended in patients with severe liver disease and active liver disease.
Gastrointestinal effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], 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 gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid 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 gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1).

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. 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 sections 4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration (see section 5.1).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see sections above, 4.5 and 5.1).

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, oedema and hypertension

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib see section 5.1. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema 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 section 4.3) 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 and/or signs 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

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 section 4.8). 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 section 4.8). 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 section 4.5).

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive (see sections 4.6, 5.1, and 5.3).

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants: In subjects stabilised on chronic warfarin therapy, the administration of etoricoxib
120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalised Ratio (INR).
Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs.
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)
Lithium: NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels.
Cholestyramine: Reduces absorption of paracetamol.
Charcoal: Activated, administered immediately reduces absorption of paracetamol.
Domperidone and metochlopramide: Enhance absorption of paracetamol.

4.6 Fertility, Pregnancy and lactation

Etoricoxib and Paracetamol Tablet may be unsafe to use during pregnancy and lactating.

4.7 Effects on ability to drive and use machines

Etoricoxib and Paracetamol Tablet may decrease alertness, affect your vision or make you feel sleepy and dizzy. Do not drive if these symptoms occur.

4.8 Undesirable effects

Some of the common side effects of this medicine include diarrhea, indigestion, stomach pain, flatulence, swelling of hands and feet, and flu-like symptoms.

Etoricoxib

Summary of the safety profile

In clinical trials, etoricoxib was evaluated for safety in 9295 individuals, including 6757 patients with OA, RA, chronic low back pain or ankylosing spondylitis (approximately 600 patients with OA or RA were treated for one year or longer).

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with etoricoxib for one year or longer.

In a clinical study for acute gouty arthritis, patients were treated with etoricoxib 120 mg once daily for eight days. The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In a cardiovascular safety outcomes programme of pooled data from three active comparator controlled trials, 17, 412 patients with OA or RA were treated with etoricoxib (60 mg or 90 mg) for a mean duration of approximately 18 months. The safety data and details from this programme are presented in section 5.1.

In clinical studies for acute postoperative dental pain following surgery including 614 patients treated with etoricoxib (90 mg or 120 mg), the adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

Tabulated list of adverse reactions

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 30 mg, 60 mg or 90 mg up to the recommended dose for up to 12 weeks; in the MEDAL Programme studies for up to 3½ years; in short term acute pain studies for up to 7 days; or in post-marketing experience (see Table 1):

Table 1:

System Organ Class	Adverse Reactions	Frequency Category*
Infections and infestations	alveolar osteitis	Common
	gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	hypersensitivity‡ ß	Uncommon
	angioedema/anaphylactic /anaphylactoid reactions including shock‡	Rare
Metabolism and nutrition disorders	oedema/fluid retention	Common
	appetite increase or decrease, weight gain	Uncommon
Psychiatric disorders	anxiety, depression, mental acuity decreased, hallucinations‡	Uncommon

	confusion‡, restlessness‡	Rare
Nervous system disorders	dizziness, headache	Common
	dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence	Uncommon
Eye disorders	blurred vision, conjunctivitis	Uncommon
Ear and labyrinth disorders	tinnitus, vertigo	Uncommon
Cardiac disorders	palpitations, arrhythmia‡	Common
	atrial fibrillation, tachycardia‡, congestive heart failure, non-specific ECG changes, angina pectoris‡, myocardial infarction§	Uncommon
Vascular disorders	hypertension	Common
	flushing, cerebrovascular accident§, transient ischaemic attack, hypertensive crisis‡, vasculitis‡	Uncommon
Respiratory, thoracic and mediastinal disorders	bronchospasm‡	Common
	cough, dyspnoea, epistaxis	Uncommon
Gastrointestinal disorders	abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer	Common
	abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis‡	Uncommon
Hepatobiliary disorders	ALT increased, AST increased	Common
	hepatitis‡	Rare
	hepatic failure‡, jaundice‡	Rare†
Skin and subcutaneous tissue disorders	ecchymosis	Common
	facial oedema, pruritus, rash, erythema‡, urticaria‡	Uncommon
	Stevens-Johnson syndrome‡, toxic epidermal	Rare†

	necrolysis‡, fixed drug eruption‡	
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency‡(see section 4.4)	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	Common
	chest pain	Uncommon
Investigations	blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased	Uncommon
	blood sodium decreased	Rare

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).
‡ This adverse reaction was identified through post-marketing surveillance. Its reported frequency has been estimated based upon the highest frequency observed across clinical trial data pooled by indication and approved dose.
† The frequency category of "Rare" was defined per the Summary of Product Characteristics (SmPC) guidance (rev. 2, Sept 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of subjects treated with etoricoxib in the analysis of the Phase III data pooled by dose and indication (n=15,470).
ß Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy".
§ Based on analyses of long-term placebo and active controlled clinical trials, 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.

Paracetamol

The information below lists reported adverse reactions, ranked using the following frequency classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Immune system disorders
Hypersensitivity including skin rash may occur.
Not known: anaphylactic shock; angioedema
Blood and lymphatic system disorders
Not known: blood dyscrasias including thrombocytopenia and agranulocytosis
Skin and subcutaneous disorders
Very rare cases of serious skin reactions have been reported.
Metabolism and nutrition disorders
Not known: high anion gap metabolic acidosis.
Description of selected adverse reactions

High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system

4.9 Overdose

Give supportive measures and symptomatic treatment. Drug can be removed from the body by gastric lavage or by inducing emesis. Absorption of the drug can be reduced by administration of activated charcoal.
Treatment: 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. N-acetylcysteine is the specific antidote for Paracetamol poisoning.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Etoricoxib, which is of non-steroidal anti-inflammatory drug (NSAID) class, eases the inflammation and pain by interfering with the cyclooxygenase-2 (COX-2) pathway. Cyclooxygenase-2 enzyme converts arachidonic acid to various inflammatory mediators such as, prostaglandins, interleukins and TNFs. Paracetamol is a potent analgesic and antipyretic. It is also said to inhibit the prostaglandin synthesis in the brain. It exhibits the analgesia by increasing the threshold for pain and antipyresis by acting on the hypothalamic heat regulating centre in the brain.

5.2 Pharmacokinetic properties

Absorption: Orally administered Etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Paracetamol is rapidly and completely absorbed after oral administration.
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 (Vdss) was approximately 1,20l in humans. Paracetamol is distributed mostly in the body in unbound form.
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 catalyzed by CYP enzymes. Paracetamol is extensively metabolised in the liver.
Elimination: Elimination of Etoricoxib and Paracetamol occurs almost exclusively through metabolism followed by renal excretion.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch
Sodium Methyl
Hydroxybenzoate Sodium
Propyl Hydroxybenzoate
Povidone K30
Croscarmellose
Sodium Purified
Talc
Colloidal Anhydrous Silica
Magnesium Stearate
Tab Coat Orange
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
1 x 10's (10 tablets are packed in one Alu-Alu blister and 1 such Alu-Alu blister is kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder and Manufacturing Site Address

Marketing authorisation holder:
Company name: INNOCIA LIFESCIENCES PVT. LTD.,
Address: Block A, No.12, Balaji Nagar, Ambattur,
Chennai-600 053 Country: INDIA.
Manufacturing Site:
ATOZ Pharmaceutials Pvt.Ltd.,
No.12, Balaji Nagar, Ambattur, Chennai-
600053, India.

8. Marketing authorisation number(s)

H2022/CTD9630/21341

9.Date of first registration / Renewal of the registration

2022 November 09

10. Date of revision of the text:

2022 November 09