PRODUCT NAME / TERMÉK NEVE:
COXETA FILMTABLETTA BETEGTAJEKOZTATO, MALAJZIA

COLOURS / SZINEK
Process Black

VERSION CODE / VÁLTOZATKÓD: 20191150 0522

DIMENSION / MÉRET: 160 x 460 mm

ID NUMBER / CIKKSZÁM: 20191150

PHARMA CODE / PHARMAKÓD: 850

Coxeta FC tablets

Product Name
Coxeta FC tablets 60mg
Coxeta FC tablets 90mg
Coxeta FC tablets 120mg

Name and Strength of Active Substance(s)
Etoricoxib 60mg
Etoricoxib 90mg
Etoricoxib 120mg

Product Description
60 mg: Dark green, round, biconvex film-coated tablet, debossed "60" on one side and plain on the other.
Dimension: Approx. 8 mm diameter.
90 mg: White, round, biconvex film-coated tablet, debossed "90" on one side and plain on the other.
Dimension: Approx. 9 mm diameter.
120 mg: Pale-green, round, biconvex film-coated tablet, debossed "120" on one side and plain on the other.
Dimension: Approx. 10 mm diameter.

Pharmacodynamics
Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs, ATC code: M01AH05

Mechanism of Action
Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.
Etoricoxib produce 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 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.

Pharmacokinetics
Absorption
Etoricoxib is well absorbed from the gastrointestinal tract after oral doses.
The mean oral bioavailability is approximately 100%.
Peak plasma concentrations occur in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption.
Antacids (calcium carbonate, aluminum/magnesium hydroxide) do not significantly affect the absorption of etoricoxib.

Distribution
Plasma protein binding is about 92%.
Etoricoxib may cross the placenta and some is distributed into breast milk.
Volume of Distribution: 119 L at steady state.

Metabolism
Etoricoxib is extensively metabolized with <2% of a dose recovered in urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6'-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6'-carboxylic acid derivative, the major metabolite.
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.
No metabolites are considered to contribute significantly to COX-2 (or COX-1) inhibition.

Elimination
Etoricoxib is excreted mainly via the urine (70%) with only 20% of a dose appearing in the faeces.
At steady state the half-life of etoricoxib is about 22 hours.

Indication
Coxeta is indicated for:
- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures.

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

Recommended Dosage
Coxeta is administered orally. Coxeta may be taken with or without food. Coxeta should be administered for the shortest duration possible and the lowest effective daily dose should be used.

Osteoarthritis (OA)
The recommended dose is 30 mg or 60 mg once daily.

Rheumatoid Arthritis (RA)
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
In the following acute painful conditions, Coxeta should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment:
- Acute Gouty Arthritis: The recommended dose is 120 mg once daily.
- Primary Dysmenorrhea: The recommended dose is 120 mg once daily.
- Minor Dental Procedures: The recommended dose is 90 mg once daily.

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 should not exceed 90 mg daily.
The dose for ankylosing spondylitis should not exceed 90 mg daily.
The dose for acute gout should not exceed 120 mg daily.
The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.
The dose for minor dental procedures should not exceed 90 mg daily.

Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see Warnings and Precautions).

Elderly, Gender, Race
No dosage adjustment in Coxeta is necessary for the elderly or based on gender or race.

Hepatic Insufficiency
In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded.
In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60 mg every other day should not be exceeded, administration of 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9) (see Warnings and Precautions).

Renal Insufficiency
In patients with advanced renal disease (creatinine clearance <30 mL/min), treatment with Coxeta is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance >30 mL/min) (see P Warnings and Precautions).

Contraindications
- Hypersensitivity to any component of this product.
- Congestive heart failure (NYHA II-IV)
- Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty)
- Pregnancy
- Patients with hypertension whose blood pressure has not been adequately controlled
- Renal impairment associated with a creatinine clearance of less than 30 mL/minute
- Patients with active gastrointestinal ulceration or bleeding
- Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal antiinflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) (risk of anaphylactic-like reactions)
- Patients with inflammatory bowel disease
- Patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke)

Warning and Precautions
Etoricoxib may be associated with an increased risk of thrombotic events (especially MI and stroke). As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.
Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.
Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease.
Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Hence, antiplatelet therapies should not be discontinued.
There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib when taken concomitantly with acetylsalicylic acid (even at low doses).
In patients with advanced renal disease, treatment with etoricoxib is not recommended. If therapy with etoricoxib must be initiated in such patients, renal function should be monitored closely.
Long-term use of NSAIDs has resulted in renal papillary necrosis and other renal injury. Monitoring of renal function should be considered for those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.
Caution should be used when initiating treatment with etoricoxib in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.
The possibility of fluid retention, edema or hypertension should be taken into consideration when etoricoxib is used in patients with pre-existing edema, hypertension, or heart failure.
All Nonsteroidal Antiinflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure.
Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled.
Conditions predisposing to gastrointestinal events (eg, history of peptic ulcer, upper gastrointestinal disease, ulcerative colitis, smoking, advancing age, concurrent aspirin or corticosteroids, alcohol abuse, stress).
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

Etoricoxib should be used with caution in patients with history of acute asthmatic attacks, urticaria, or rhinitis, which were caused by salicylates or non-selective cyclooxygenase inhibitors.
When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.
It should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen.
Use of etoricoxib is associated with very rare occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. These serious events may occur without warning and patients are at highest risk for these reactions early in the course of therapy.
Patients with history of mild allergic phenomena related to ingestion of other nonsteroidal antiinflammatory drugs (eg, rash) should be treated with caution. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Etoricoxib may mask fever, which is a sign of infection.

<u>Risk of GI Ulceration, Bleeding and Perforation with NSAID</u>
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

<u>Effects on Ability to Drive and Use Machine</u>
Patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery.

Interactions with Other Medicaments
Concurrent use of etoricoxib and warfarin may result in increased prothrombin time International Normalized Ratio (INR).
Concurrent use of etoricoxib and rifampicin may result in decreased plasma concentration of etoricoxib.
Concurrent use of etoricoxib and methotrexate may result in increased methotrexate plasma concentrations and toxicity.
Concurrent use of etoricoxib and diuretics (e.g. bumetanide, frusemide, hydrochlorothiazide) may result in decreased diuretic and antihypertensive efficacy.
Concurrent use of etoricoxib and the following may result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity:
- Amiloride
- Spironolactone

Concurrent use of etoricoxib and angiotensin II antagonists (e.g. losartan, telmisartan, valsartan) may result in decreased antihypertensive effects and an increased risk of renal impairment.

Concurrent use of etoricoxib and beta-blockers (e.g. atenolol, bisoprolol, carvedilol) may result in decreased antihypertensive effect.
Concurrent use of etoricoxib and angiotensin converting enzyme inhibitors (ACEI e.g. captopril, enalapril, perindopril) may result in diminished antihypertensive effect of ACEI.

Concurrent use of etoricoxib and lithium may result in increased lithium plasma concentrations.
Concurrent use of etoricoxib and low-dose aspirin may result in increased rate of gastrointestinal ulceration or other complications.
Concurrent use of etoricoxib and ethinyl estradiol (Oral contraceptives) may result in increased plasma concentration of ethinyl estradiol.
Concurrent use of etoricoxib and conjugated estrogens or Hormone Replacement Therapy may result in increased conjugated estrogen exposure.

Concurrent use of etoricoxib and the following may result in increased risk of gastrointestinal bleeding:
- Abciximab
- Dipyridamole
- Fondaparinux
- Heparin
- Ticlopidine
- Tirofiban

Concurrent use of etoricoxib and the following may result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect:
- Amlodipine
- Verapamil

Concurrent use of etoricoxib and the following may result in increased risk of bleeding:
- Citalopram
- Clopidogrel
- Dabigatran Etexilate
- Duloxetine
- Enoxaparin
- Escitalopram
- Fluoxetine
- Ginkgo
- Paroxetine
- Pentoxifylline
- Prasugrel
- Rivaroxaban
- Tinzaparin
- Venlafaxine

Concurrent use of etoricoxib and the following may result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect:
- Diltiazem
- Felodipine
- Flunarizine
- Nicardipine
- Nifedipine
- Nimodipine

Concurrent use of etoricoxib and the following may result in an increased risk of seizures:
- Levofloxacin
- Norfloxacin
- Ofloxacin

Concurrent use of etoricoxib and the following may result in an increased risk of hypoglycemia:
- Gliclazide
- Glimepiride
- Glipizide

Concurrent use of etoricoxib and cyclosporine may result in an increased risk of cyclosporine nephrotoxicity.
Concurrent use of etoricoxib and ketorolac may result in enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding and/or perforation).
Concurrent use of etoricoxib and minoxidil may result in increased exposure to minoxidil.
Concurrent use of etoricoxib and tacrolimus may result in acute renal failure.

Pregnancy and Lactation

Pregnancy
No clinical data on exposed pregnancies are available for etoricoxib. 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. Women who use etoricoxib must not breast feed.

Adverse Effects / Undesirable Effects

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	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, diarrhea, 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, hepatic failure, jaundice	Rare
Skin and subcutaneous tissue disorders	ecchymosis	Common
	facial oedema, pruritus, rash, erythema, urticaria	Uncommon
	Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption	Rare
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency	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

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.

Symptoms and Treatment of Overdosage

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 dialyzable by haemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

Storage Condition

Store below 30°C.
Store in the original package. Protect from moisture and light.

Dosage Forms and Packaging Available

OPA/Alu/PVC-Aluminium blisters containing 10 film-coated tablets each.
60mg: Carton of 30 or 100 tablets.
90mg: Carton of 30 or 100 tablets.
120mg: Carton of 30 or 100 tablets.

Name and Address of Manufacturer

TEVA Gyogyszergyar Zrt.
Pallagi ut 13., Debrecen H-4042, Hungary

Date of Revision of Package Insert

4-May-2021

Actavis

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