

Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Etoricoxib and Pregabalin Tablets

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Etoricoxib120 mg.

Pregabalin75 mg

Excipients..... Q.S

Colour : Brilliant Blue FCF

3.PHARMACEUTICAL FORM

Tablet.

For oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Etoricoxib

- Relief Of Osteoarthritis (OA),
- Rheumatoid Arthritis (RA),
- Ankylosing Spondylitis,
- Acute Gouty Arthritis

Pregabalin

- Anticonvulsant
- Antiepileptics

4.2 Posology and method of administration

Etoricoxib

The recommended dose is 120 mg once daily.

Method of administration: Oral

Pregabalin

The recommended dose is 75 mg once daily.

Method of administration: Oral

4.3 Contraindications:

Etoricoxib

Hypersensitivity

Active peptic ulceration or active gastrointestinal (GI) bleeding

Inflammatory bowel disease.

Pregabalin

Depression

A decrease in sharpness of vision called reduced visual acuity

Atrioventricular block, a type of slow heart rhythm disorder

chronic heart failure

Sudden and serious symptoms of heart failure called acute decompensated heart failure
Decreased lung function

4.4 Special warnings and precautions for use

Etoricoxib

General

If during treatment, patients deteriorate in any of the organ system functions such as Gastrointestinal effects, Cardiovascular effects, Renal effects, Hepatic effects, 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 postmarketing surveillance. 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. 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.

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

Hypersensitivity reactions

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Renal failure

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant antiepileptic medicinal products

There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on Pregabalin.

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

4.5 Interaction with other medicinal products and other forms of interaction**Etoricoxib**

Antacids: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

Voriconazole and Miconazole: Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib, but is not considered to be clinically meaningful based on published data

Digoxin: When multiple doses of Etoricoxib and digoxin were do not alter healthy volunteers steady-state plasma AUC_{0-24hr} or renal elimination of digoxin There was an increase in digoxin C_{max} (approximately 33%). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Rifampicin: Coadministration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. This interaction may result in recurrence of symptoms when etoricoxib is coadministered with rifampicin. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended

Prednisone/prednisolone: In drug-interaction studies, etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

Pregabalin**In vivo studies and population pharmacokinetic analysis**

Accordingly, in in vivo studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

4.6 Pregnancy and lactation

Etoricoxib

Pregnancy

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. 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.

Lactation

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib must not breast feed.

Pregabalin

Pregabalin are contraindicated during pregnancy and breast feeding the combination generic cannot be used.

4.8 Undesirable effects

Etoricoxib

Infections and infestations, Blood and lymphatic system disorders, Immune system disorders, Metabolism and nutrition disorders, Psychiatric disorders, Nervous system disorders,, Gastrointestinal disorders

Pregabalin

Infections and infestations, Blood and lymphatic system disorders, Immune system disorders, Psychiatric disorders, Nervous system disorders, Cardiac disorders, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, Investigations.

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via National Regulatory Authority.

4.9 Overdose

Etoricoxib

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

Pregabalin

In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Etoricoxib

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, nonsteroids, coxibs, ATC code: MO1 AH05

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

Across clinical pharmacology studies, Etoricoxib 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.

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.

Pregabalin

Pharmacotherapeutic group: Antiepileptics, other antiepileptics ATC code: N03AX16

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

Mechanism of action

Pregabalin binds to an auxiliary subunit ($\alpha 2$ - δ protein) of voltage-gated calcium channels in the central nervous system,

5.2 Pharmacokinetic properties

Etoricoxib

Absorption

Etoricoxib is rapidly absorbed after oral administration.

Distribution

Etoricoxib is $\geq 92\%$ bound to plasma proteins.

Biotransformation

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. 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.

Excretion

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion

Pregabalin**Absorption**

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be $\geq 90\%$ and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose	BP
Maize Starch	BP
Purified water	BP
Croscarmellose Sodium	BP
Magnesium Stearate	BP
Purified Talc	BP
Film Coat Brilliant blue	IHS

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

2 X 10 Alu-PVC Pack

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. REVISION DATE