

## 1. NAME OF THE MEDICINAL PRODUCT

ARCOXIA 60 mg Film-coated Tablets/Tablets  
ARCOXIA 90 mg Film-coated Tablets/Tablets  
ARCOXIA 120 mg Film-coated Tablets/Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet/tablet contains 60, 90 or 120 mg of etoricoxib.  
For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet/tablet.

60 mg Tablets: Green, apple-shaped, biconvex tablets <debossed '447' on one side and 'MSD' on the other side>.

90 mg Tablets: White, apple-shaped, biconvex tablets <debossed '454' on one side and 'MSD' on the other side>.

120 mg Tablets: Pale-green, apple-shaped, biconvex tablets <debossed '541' on one side and 'MSD' on the other side>.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4).

### 4.2 Posology and method of administration

<INVENTED NAME> is administered orally and may be taken with or without food. The onset of drug effect may be faster when <INVENTED NAME> is administered without food. This should be considered when rapid symptomatic relief is needed.

#### *Osteoarthritis*

The recommended dose is 60 mg once daily.

#### *Rheumatoid arthritis*

The recommended dose is 90 mg once daily.

#### *Acute gouty arthritis*

The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore, the dose for each indication is the maximum recommended dose:

The dose for OA should not exceed 60mg daily

The dose for RA should not exceed 90mg daily

The dose for acute gout should not exceed 120mg daily, limited to a maximum of 8 days treatment.

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 (4.3, 4.4, 4.8 and 5.1).

*Elderly:* No dosage adjustment is necessary for elderly patients.

*Hepatic insufficiency:* 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) the recommended dose of 60 mg **every other day** 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  $\geq 10$ ); therefore, its use is contra-indicated in these patients (see 4.3, 4.4 and 5.2).

*Renal insufficiency:* No dosage adjustment is necessary for patients with creatinine clearance  $\geq 30$  ml/min (see 5.2). The use of etoricoxib in patients with creatinine clearance  $< 30$  ml/min is contra-indicated (see 4.3 and 4.4).

*Paediatric use:* Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

### **4.3 Contra-indications**

History of hypersensitivity to the active substance or to any of the excipients (see 6.1).

Active peptic ulceration or active gastro-intestinal (GI) bleeding.

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

Pregnancy and lactation (see 4.6 and 5.3).

Severe hepatic dysfunction (serum albumin  $< 25$  g/l or Child-Pugh score  $\geq 10$ ).

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 has not been adequately controlled

Established ischaemic heart disease and/or cerebrovascular disease

## Section 4.4 Special Warnings and Precautions

### *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 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 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 (4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with etoricoxib after careful consideration (see 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 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 drugs known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. 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, special attention should be paid to blood pressure monitoring during treatment with etoricoxib. 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 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, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs including other COX-2 (cyclooxygenase-2) inhibitors and cannot be ruled out for etoricoxib (see 4.8). Hypersensitivity reactions (anaphylaxis, angioedema) have been reported in patients receiving etoricoxib (see 4.8). Etoricoxib should be discontinued at the first 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 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 4.6, 5.1, and 5.3).

ARCOXIA tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

#### *Pharmacodynamic interactions*

*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). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed (see 4.4).

*Diuretics and ACE inhibitors:* NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g., dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, which is usually reversible.

These interactions should be given consideration in patients taking etoricoxib concomitantly with ACE inhibitors.

*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). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid *above* those for cardiovascular prophylaxis or with other NSAIDs is not recommended. (See 5.1 and 4.4.)

*Cyclosporin and tacrolimus:* Although this interaction has not been studied with etoricoxib, coadministration of cyclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when etoricoxib and either of these drugs is used in combination.

### *Pharmacokinetic interactions*

#### *The effect of etoricoxib on the pharmacokinetics of other drugs*

*Lithium:* NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

*Methotrexate:* Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13%. Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

*Digoxin:* Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the 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.

#### *Effect of etoricoxib on drugs metabolised by sulfotransferases*

Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil).

#### *Effect of etoricoxib on drugs metabolised by CYP isoenzymes*

Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

#### *Effects of other drugs on the pharmacokinetics of etoricoxib*

The main pathway of etoricoxib metabolism is dependent on 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 have not been studied *in vivo*. *Ketoconazole*: Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers, did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC).

*Rifampicin*: Co-administration 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 co-administered 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 (see 4.2).

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

## **4.6 Pregnancy and lactation**

### *Pregnancy*

The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive.

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity (see 5.3). 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 (see 4.3). If a woman becomes pregnant during treatment, etoricoxib should 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 should not breast feed. (See 4.3 and 5.3.)

## **4.7 Effects on ability to drive and use machines**

No studies on the effect of etoricoxib on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery.

## **4.8 Undesirable effects**

In clinical trials, etoricoxib was evaluated for safety in approximately 4800 individuals, including approximately 3400 patients with OA, RA or chronic low back pain (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.

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks or in post-marketing experience:

[*Very Common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000) including isolated cases*]

***Infections and infestations:***

*Uncommon:* gastroenteritis, upper respiratory infection, urinary tract infection.

***Immune system disorder:***

*Very rare:* hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions.

***Metabolism and nutrition disorders:***

*Common:* oedema/fluid retention

*Uncommon:* appetite increase or decrease, weight gain.

***Psychiatric disorders:***

*Uncommon:* anxiety, depression, mental acuity decreased.

***Nervous system disorder:***

*Common:* dizziness, headache.

*Uncommon:* dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence.

***Eye disorders:***

*Uncommon:* blurred vision.

***Ear and labyrinth disorders:***

*Uncommon:* tinnitus.

***Cardiac disorders:***

*Uncommon:* congestive heart failure, non-specific ECG changes.

*Very rare:* myocardial infarction.

***Vascular disorders:***

*Common:* hypertension

*Uncommon:* flushing.

*Very rare:* cerebrovascular accident.

***Respiratory, thoracic and mediastinal disorders:***

*Uncommon:* cough, dyspnoea, epistaxis.

***Gastrointestinal disorders:***

*Common:* gastrointestinal disorders (e.g., abdominal pain, flatulence, heartburn), diarrhea, dyspepsia, epigastric discomfort, nausea.

*Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting.

*Very rare:* peptic ulcers including gastrointestinal perforation and bleeding (mainly in the elderly).

***Skin and subcutaneous tissue disorders:***

*Uncommon:* ecchymosis, facial oedema, pruritus, rash.

*Very rare:* urticaria.

***Musculoskeletal, connective tissue and bone disorders:***

*Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness.

***Renal and urinary disorders:***

*Uncommon:* proteinuria.

*Very rare:* renal insufficiency, including renal failure, usually reversible upon discontinuation of treatment (see 4.4).

***General disorders and administration site conditions:***

*Common:* asthenia/fatigue, flu-like disease.

*Uncommon:* chest pain.

***Investigations:***

*Common:* ALT increased, AST increased.

*Uncommon:* blood urea nitrogen increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased.

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; hepatotoxicity including hepatic failure and jaundice; cutaneous mucosal adverse effects and severe skin reactions (see 4.4).

## **4.9 Overdose**

No overdoses of etoricoxib were reported during clinical trials.

In clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity.

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.

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