



Sept 2008

***Direct Healthcare Professional Communication on in patients treated
with ARCOXIA (Etoricoxib)***

Dear Healthcare Professional,

Healthcare professionals have previously been informed of the risk of hypertension-related adverse events associated with use of etoricoxib, and of the contraindication for use of etoricoxib in patients with hypertension whose blood pressure (BP) is not adequately controlled. The European Medicines Agency has recently completed a review of the benefits and risks of 90 mg etoricoxib (ARCOXIA) in the treatment of rheumatoid arthritis and in ankylosing spondylitis. The review included analyses from an observational database (General Practice Research Database) study, which suggest that a substantial number of patients with systolic BP >150mmHg and/or diastolic BP >90mmHg have been initiated on etoricoxib despite earlier recommendations.

Prescribers are therefore asked to note the following updated and strengthened safety recommendations:

- Etoricoxib should not be used in patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- In all patients starting treatment with etoricoxib, BP should be monitored within 2 weeks after initiation, and periodically thereafter.

These changes have to now be incorporated into the UK licences for etoricoxib and we will be issuing a revised SmPC later this year.

Call for reporting

Please report suspected adverse drug reactions to etoricoxib to the Medicines and Healthcare products Regulatory Agency (MHRA) by use of a Yellow card, which is available from MHRA, CHM Freepost, London SW8 5BR, or electronically via www.yellowcard.gov.uk. Suspected adverse reactions can also be reported to Merck on 01992 467272.

Communication information

Should you have any questions or require additional information regarding the use of ARCOXIA, please contact the Medical Information Department on 01992 455000.

Sincerely,

A handwritten signature in black ink, appearing to read 'Paul Robinson', written over a light blue horizontal line.

Dr Paul Robinson
Medical Director

ARCOXIA[®]▼ (etoricoxib) ABRIDGED PRODUCT INFORMATION

Refer to the full Summary of Product Characteristics (SPC) before prescribing.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to MSD Ltd (tel: 01992 467272).

PRESENTATION

Tablets: 30 mg, 60 mg, 90 mg and 120 mg tablets each containing 30 mg, 60 mg, 90 mg or 120 mg of etoricoxib respectively.

USES

Symptomatic relief of osteoarthritis, rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis. Base the decision to prescribe a selective COX-2 inhibitor on an assessment of the individual patient's overall risks.

DOSE AND ADMINISTRATION

Take orally with or without food. Onset of action may be faster when administered without food, and should be considered when rapid relief is needed. Use the lowest effective daily dose for the shortest duration possible, as cardiovascular risks may increase with dose and duration of exposure. Re-evaluate periodically patient's need, especially in osteoarthritis patients. *Osteoarthritis*: 30 mg once daily, increasing to 60 mg in patients with insufficient relief from symptoms. *Rheumatoid arthritis*: 90 mg once daily. *Acute gouty arthritis*: 120 mg once daily for the acute symptomatic period only and limited to a maximum of 8 days. Doses greater than those above have either not been studied or have not demonstrated additional efficacy. *Hepatic insufficiency: mild (Child-Pugh score 5-6)*: do not exceed a dose of 60 mg daily; *moderate (Child-Pugh score 7-9)*: do not exceed 60 mg every other day, or use 30 mg once daily; *severe*: contra-indicated, see below. *Renal insufficiency: creatinine clearance <30 ml/min*: contra-indicated; ≥ 30 ml/min: no dosage adjustment necessary. *Elderly*: exercise caution.

CONTRA-INDICATIONS

Hypersensitivity to any component of this product. Active peptic ulceration or gastrointestinal (GI) bleeding. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria or allergic type reactions after aspirin or NSAIDs including COX-2 inhibitors. Pregnancy and lactation. Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10). Estimated 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, peripheral arterial disease and/or cerebrovascular disease.

PRECAUTIONS

Gastro-intestinal effects: Upper GI complications (perforations, ulcers or bleedings), some with fatal outcome have occurred in patients taking etoricoxib. Caution is advised in patients most at risk of developing a GI complication with NSAIDs: elderly, those on any other NSAID or aspirin concomitantly, or those with a prior history of GI disease. There is a further increase in the risk of GI adverse effects (GI ulceration or other GI complications) when etoricoxib is taken together with aspirin (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. *Cardiovascular*: 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, use for the shortest duration possible and use the lowest effective daily dose. Re-evaluate periodically the patient's need for symptomatic relief and response to therapy, especially in those with osteoarthritis. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration. COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued. *Renal effects*: Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension*: Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Pay special attention to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, consider alternative treatment. *Hepatic effects*: Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 30 mg, 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom an abnormal liver function test has occurred. Discontinue etoricoxib if signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (3 times the upper limit of normal) are detected. *General*: Take appropriate measures and consider discontinuation, if during treatment, patients deteriorate in any of the organ system functions described above. Maintain appropriate medical supervision when treating the elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution when initiating treatment in patients with considerable dehydration. 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, associated with the use of NSAIDs and some selective COX-2 inhibitors. Discontinue at the first signs of skin rash, mucosal lesions or any other signs of hypersensitivity as hypersensitivity reactions (anaphylaxis, angioedema) have been reported. Etoricoxib may mask fever. Use of etoricoxib is not recommended in women attempting to conceive. 'Arcoxia' tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. *Interactions (pharmacodynamic)*: *Oral anticoagulants*: Exercise caution when co-administering with warfarin and other oral anticoagulants. Closely monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose changed in patients receiving oral anticoagulants or similar agents, particularly in the first few days. *Diuretics, ACE-inhibitors and Angiotensin II Antagonists*: NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function, the co-administration of an ACE inhibitor or AIIA and cyclo-oxygenase inhibitors may result in further deterioration of renal function including possible acute renal failure, which is usually reversible. Administer cautiously, especially in the elderly. Patients should be adequately hydrated. Consider monitoring renal function at initiation of therapy and periodically thereafter. *Aspirin*: etoricoxib can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low dose aspirin 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 aspirin above those for cardiovascular prophylaxis, or with other NSAIDs is not recommended. *Ciclosporin/tacrolimus*: monitor renal function when etoricoxib and either ciclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic)*: The effect of

etoricoxib on the pharmacokinetics of other drugs: *Lithium*: the plasma concentration of lithium is increased by NSAIDs, therefore monitor and adjust blood lithium and lithium dosage if necessary. *Methotrexate*: adequate monitoring is recommended for methotrexate-related toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contraceptives (OC)*: Administration of etoricoxib 60 mg with an OC containing 35 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC_{0-24hr} of EE by 37%. Administration of etoricoxib 120 mg with the same OC, concomitantly or separated by 12 hours, increased the steady state AUC_{0-24hr} of EE by 50 to 60%. Consider this increase in EE concentration when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives. *Hormone Replacement Therapy*: 120 mg etoricoxib administered with 0.625 mg Premarin[™] (Wyeth) for 28 days increased the mean steady state AUC_{0-24hr} of unconjugated estrone (41%), equilin (76%) and 17- β -estradiol (22%). Although the clinical significance is unknown, take into consideration the increase in estrogenic concentration when selecting HRT as the increase in estrogen exposure might increase the risk of adverse events associated with HRT. *Digoxin*: Patients at high risk of digoxin toxicity should be monitored for an increase in digoxin C_{max} when etoricoxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised by sulfotransferases*: Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SUL1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. 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*. *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, an interaction which may result in recurrence of symptoms. *Antacids*: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent. *Pregnancy*: contra-indicated in the first, second and third trimesters of pregnancy. *Lactation*: contra-indicated.

SIDE EFFECTS

Refer to Summary of Product Characteristics for complete information on side effects

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 the MEDAL Programme studies, or in post-marketing experience:

[Very common ($>1/10$) Common ($>1/100$, $<1/10$) Uncommon ($>1/1,000$, $<1/100$) Rare ($>1/10,000$, $<1/1,000$) Very rare ($<1/10,000$) not known (cannot be estimated from the available data)]

Infections and infestations: Uncommon: gastro-enteritis, upper respiratory infection, urinary tract infection. *Immune system disorder*: Very rare: hypersensitivity reactions including angioedema, anaphylactic/anaphylactoid reactions including shock.

Metabolism and nutrition disorders: Common: oedema/fluid retention. Uncommon: appetite increase or decrease, weight gain. *Psychiatric disorders*: Uncommon: anxiety, depression, mental acuity decreased. Very rare: confusion, hallucinations.

Nervous system disorder: Common: dizziness, headache. Uncommon: dysgeusia, insomnia, paraesthesia/hyphaesthesia, somnolence. *Eye disorders*: Uncommon: blurred vision, conjunctivitis. *Ear and labyrinth disorders*: Uncommon: tinnitus, vertigo. *Cardiac disorders*: Common: palpitations. Uncommon: atrial fibrillation, congestive heart failure, non-specific ECG changes, myocardial infarction*.

Vascular disorders: Common: hypertension. Uncommon: flushing, cerebrovascular accident*, transient ischaemic attack. Very rare: hypertensive crisis. *Respiratory, thoracic and mediastinal disorders*: Uncommon: cough, dyspnoea, epistaxis. Very rare: bronchospasm. *Gastro-intestinal disorders*: Common: gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, 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, gastritis. Very rare: peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly). *Hepatobiliary disorders*: Very rare: hepatitis. *Skin and subcutaneous tissue disorders*: Common: ecchymosis. Uncommon: facial oedema, pruritus, rash. Very rare: urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis.

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. *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. Rare: blood sodium decreased. 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, jaundice and pancreatitis. * 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 for such events is unlikely to exceed 1% per year based on existing data (uncommon).

PACKAGE QUANTITIES AND BASIC NHS COST
30 mg – £13.99, 60 mg – £20.11 and 90 mg – £22.96: packs of 28 tablets.
120 mg Tablets: packs of 7 tablets £6.03 and packs of 28 tablets £24.11.

Marketing Authorisation numbers
Tablet 30 mg PL 0025/0478.
Tablet 60 mg PL 0025/0422.
Tablet 90 mg PL 0025/0423.
Tablet 120 mg PL 0025/0424.

Marketing Authorisation holder
Merck Sharp & Dohme Limited
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[POM] Date of review of prescribing information: October 2007

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