Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Arcoxia 30mg Film-Coated Tablets
Auxib 30mg Film-Coated Tablets
Exxiv 30mg Film-Coated Tablets
Turox 30mg Film-Coated Tablets

UK/H/0532-5/004/DC
UK licence no: PL 00025/0478-81

Merck Sharp and Dohme Limited

LAY SUMMARY

On 22nd October 2007, the MHRA granted Merck Sharp and Dohme Marketing Authorisations (licences) for the medicinal products Arcoxia, Auxib, Exxiv and Turox 30mg Film-Coated Tablets (PL 00025/0478-81). These are prescription only medicines (POM) that help reduce the pain and swelling (inflammation) in the joints of people with osteoarthritis, rheumatoid arthritis and gout.

Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It also causes inflammation in other areas of the body.

Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

These medicinal products belong to a group of drugs called selective COX-2 inhibitors, which belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Arcoxia, Auxib, Exxiv and Turox 30mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Arcoxia 30mg Film-Coated Tablets Auxib 30mg Film-Coated Tablets Exxiv 30mg Film-Coated Tablets Turox 30mg Film-Coated Tablets
Type of Application	Full dossier, Article 8.3
Active Substance	Etoricoxib
Form	Film-Coated Tablets
Strength	30mg
MA Holder	Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK
RMS	United Kingdom
CMS	Arcoxia 30mg Film-Coated Tablets (PL 00025/0478): Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain and Sweden. Auxib 30mg Film-Coated Tablets (PL 00025/0479): Austria, Germany, Italy and The Netherlands Exxiv 30mg Film-Coated Tablets (PL 00025/0480): Germany, Italy and Poland Turox 30mg Film-Coated Tablets (PL 00025/0481): Belgium, Finland, France, Greece, Italy and Luxembourg
Procedure Number	UK/H/0532-5/0004/DC
Timetable	Day 210 – 20th August 2007

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ARCOXIA® 30 mg Film-coated Tablets
AUXIB® 30 mg Film-coated Tablets
EXXIV® 30 mg Film-coated Tablets
TUROX® 30 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg of etoricoxib.

Excipient:
30 mg: lactose 1.4 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

30 mg Tablets: Blue-green, apple-shaped biconvex tablets debossed '101' on one side and 'ACX 30' 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

ARCOXIA/AUXIB/EXXIV/TUROX is administered orally and may be taken with or without food. The onset of drug effect may be faster when ARCOXIA/AUXIB/EXXIV/TUROX is administered without food. This should be considered when rapid symptomatic relief is needed.

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 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 OA should not exceed 60 mg daily.
The dose for RA 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.

Elderly: No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients (see section 4.4).

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; administration of 30 mg once daily can also be considered.

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 contraindicated in these patients (see sections 4.3, 4.4 and 5.2).

Renal insufficiency: 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 contraindicated (see sections 4.3 and 4.4).

Paediatric use: Etoricoxib is contraindicated in children and adolescents under 16 years of age (see section4.3).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 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 (cyclo-oxygenase-2) inhibitors.

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 has not been adequately controlled.

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Gastro-intestinal effects

Upper gastro-intestinal 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 gastro-intestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, or patients with a prior history of gastro-intestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastro-intestinal adverse effects (gastro-intestinal ulceration or other gastro-intestinal 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 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 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 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 cyclo-oxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive (see sections 4.6, 5.1 and 5.3).

ARCOXIA/AUXIB/EXXIV/TUROX 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 section 4.4).

Diuretics, ACE inhibitors and Angiotensin II Antagonists: 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 or Angiotensin II Antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

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 sections 5.1 and 4.4.).

Ciclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, co-administration of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin 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.

Oral contraceptives: Etoricoxib 60 mg given concomitantly with an oral contraceptive 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%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC_{0-24hr} of EE by 50 to 60%. This increase in EE concentration should be considered 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 (e.g. venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy: Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (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%). The effect of the recommended chronic doses of etoricoxib (30, 60 and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24hr}) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in estrogen exposure might increase the risk of adverse events associated with HRT.

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

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 section 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 section 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 section 4.3). 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. (See sections 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 7,152 individuals, including 4,488 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.

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.

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 30 mg, 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 (≥1/1000, <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/hypaesthesia, 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 (see section 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.
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 increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs

ATC Code: MO1 AH05

Mechanism of Action

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

Across clinical pharmacology studies, ARCOXIA/AUXIB/EXXIV/TUROX 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.

Cyclo-oxygenase 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.

Efficacy

In patients with osteoarthritis (OA), etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12 week treatment period (using similar assessments as the above studies). In a dose ranging study, etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of the hands.

In patients with rheumatoid arthritis (RA), etoricoxib 90 mg once daily provided significant improvements in pain, inflammation, and mobility. These beneficial effects were maintained over the 12-week treatment periods.

In patients experiencing attacks of acute gouty arthritis, etoricoxib 120 mg once daily over an eight-day treatment period, relieved moderate to extreme joint pain and inflammation comparable to indometacin 50 mg three times daily. Pain relief was observed as early as four hours after initiation of treatment.

In studies specifically designed to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing.

Safety
Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Programme
The MEDAL Programme was a prospectively designed Cardiovascular (CV) Safety Outcomes Programme of pooled data from three randomised, double-blind active comparator controlled trials, the MEDAL study, EDGE II and EDGE.

The MEDAL Study, was an endpoint driven CV Outcomes study in 17,804 OA and 5,700 RA patients treated with etoricoxib 60 (OA) or 90 mg (OA and RA) or diclofenac 150 mg daily for a mean period of 20.3 months (maximum of 42.3 months, median 21.3 months). In this trial, only serious adverse events and discontinuations due to any adverse events were recorded.

The EDGE and EDGE II studies compared the gastrointestinal tolerability of etoricoxib versus diclofenac. The EDGE study included 7,111 OA patients treated with a dose of etoricoxib 90 mg daily (1.5 times the dose recommended for OA) or diclofenac 150 mg daily for a mean period of 9.1 months (maximum 16.6 months, median 11.4 months). The EDGE II study included 4,086 RA patients treated with etoricoxib 90 mg daily or diclofenac 150 mg daily for a mean period of 19.2 months (maximum 33.1 months, median 24 months).

In the pooled MEDAL Programme, 34,701 patients with OA or RA were treated for a mean duration of 17.9 months (maximum 42.3 months, median 16.3 months) with approximately 12,800 patients receiving treatment for more than 24 months. Patients enrolled in the Programme had a wide range of cardiovascular and gastrointestinal risk factors at baseline. Patients with a recent history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention within 6 months preceding enrollment were excluded. Use of gastroprotective agents and low dose aspirin were permitted in the studies.

Overall Safety:
There was no significant difference between etoricoxib and diclofenac in the rate of cardiovascular thrombotic events. Cardiorenal adverse events were observed more frequently with etoricoxib than with diclofenac, and this effect was dose-dependent (see specific results below). Gastrointestinal and hepatic adverse events were observed significantly more frequently with diclofenac than etoricoxib. The incidence of adverse experiences in EDGE and EDGE II and of adverse experiences considered serious or resulting in discontinuation in the MEDAL study was higher with etoricoxib than diclofenac.

Cardiovascular safety results:
The rate of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) was comparable between etoricoxib and diclofenac, and data are summarised in the table below. There were no statistically significant differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analysed including patient categories across a range of baseline cardiovascular risk. When considered separately, the relative risks for confirmed thrombotic cardiovascular serious adverse events with etoricoxib 60 mg or 90 mg compared with diclofenac 150 mg were similar.

Table 1: Rates of Confirmed Thrombotic CV Events (Pooled MEDAL Programme)			
	Etoricoxib (N=16,819) 25,836 Patient-Years	Diclofenac (N=16,483) 24,766 Patient-Years	Between Treatment Comparison
	Rate† (95% CI)	Rate† (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Events			
Per-protocol	1.24 (1.11, 1.38)	1.30 (1.17, 1.45)	0.95 (0.81, 1.11)
Intent-to-treat	1.25 (1.14, 1.36)	1.19 (1.08, 1.30)	1.05 (0.93, 1.19) -
Confirmed Cardiac Events			
Per-protocol	0.71 (0.61, 0.82)	0.78 (0.68, 0.90)	0.90 (0.74, 1.10)
Intent-to-treat	0.69 (0.61, 0.78)	0.70 (0.62, 0.79)	0.99 (0.84, 1.17)
Confirmed Cerebrovascular Events			
Per-protocol	0.34 (0.28, 0.42)	0.32 (0.25, 0.40)	1.08 (0.80, 1.46)
Intent-to-treat	0.33 (0.28, 0.39)	0.29 (0.24, 0.35)	1.12 (0.87, 1.44)
Confirmed Peripheral Vascular Events			
Per-protocol	0.20 (0.15, 0.27)	0.22 (0.17, 0.29)	0.92 (0.63, 1.35)
Intent-to-treat	0.24 (0.20, 0.30)	0.23 (0.18, 0.28)	1.08 (0.81, 1.44)

†Events per 100 Patient-Years; CI=confidence interval
N=total number of patients included in Per-protocol population-

Per-protocol: all events on study therapy or within 14 days of discontinuation (excluded: patients who took < 75% of their study medication or took non-study NSAIDs >10% of the time).

Intent-to-treat: all confirmed events up to the end of the trial (included patients potentially exposed to non-study interventions following discontinuation of study medication). Total number of patients randomised, n= 17,412 on etoricoxib and 17,289 on diclofenac.

CV mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Cardiorenal Events:
Approximately 50% of patients enrolled in the MEDAL study had a history of hypertension at baseline. In the study, the incidence of discontinuations due to hypertension-related adverse events was statistically significantly higher for etoricoxib than for diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg (statistically significant for 90 mg etoricoxib vs. 150 mg diclofenac in MEDAL OA cohort). The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalisation or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to oedema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).

The cardiorenal results for EDGE and EDGE II were consistent with those described for the MEDAL Study.

In the individual MEDAL Programme studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to 2.6% for hypertension, up to 1.9% for oedema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg.

MEDAL Programme Gastrointestinal Tolerability Results:
A significantly lower rate of discontinuations of treatment for any clinical (e.g., dyspepsia, abdominal pain, ulcer) GI adverse event was observed with etoricoxib compared with diclofenac within each of the three component studies of the MEDAL Programme. The rates of discontinuations due to adverse clinical GI events per hundred patient-years over the entire period of study were as follows: 3.23 for etoricoxib and 4.96 for diclofenac in the MEDAL Study; 9.12 with etoricoxib and 12.28 with diclofenac in the EDGE study; and 3.71 with etoricoxib and 4.81 with diclofenac in the EDGE II study.

MEDAL Programme Gastrointestinal Safety Results:
Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. A significantly lower rate of overall upper GI events was observed with etoricoxib compared to diclofenac. There was no significant difference between etoricoxib and diclofenac in the rate of complicated events. For the subset of upper GI haemorrhage events (complicated and uncomplicated combined), there was no significant difference between etoricoxib and diclofenac. The upper GI benefit for etoricoxib compared with diclofenac was not statistically significant in patients taking concomitant low-dose aspirin (approximately 33% of patients).

The rates per hundred patient-years of confirmed complicated and uncomplicated upper GI clinical events (perforations, ulcers and bleeds (PUBs)) were 0.67 (95% CI 0.57, 0.77) with etoricoxib and 0.97 (95% CI 0.85, 1.10) with diclofenac, yielding a relative risk of 0.69 (95% CI 0.57, 0.83).

The rate for confirmed upper GI events in elderly patients was evaluated and the largest reduction was observed in patients ≥ 75 years of age (1.35 [95% CI 0.94, 1.87] vs. 2.78 [95% CI 2.14, 3.56] events per hundred patient-years for etoricoxib and diclofenac, respectively.

The rates of confirmed lower GI clinical events (small or large bowel perforation, obstruction, or haemorrhage, [POBs]) were not significantly different between etoricoxib and diclofenac.

MEDAL Programme Hepatic Safety Results:
Etoricoxib was associated with a statistically significantly lower rate of discontinuations due to hepatic-related adverse experiences than diclofenac. In the pooled MEDAL Programme, 0.3% of patients on etoricoxib and 2.7% of patients on diclofenac discontinued due to hepatic-related adverse experiences. The rate per hundred patient-years was 0.22 on etoricoxib and 1.84 for diclofenac (p-value was <0.001 for etoricoxib vs. diclofenac). However, most hepatic adverse experiences in the MEDAL Programme were non-serious.

Additional Thrombotic Cardiovascular Safety Data
In clinical studies excluding the MEDAL Programme Studies, approximately 3,100 patients were treated with etoricoxib ≥ 60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥ 60 mg, placebo, or non-naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of thrombo-embolic events. Selective COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

Additional Gastrointestinal Safety Data
In two 12-week double-blind endoscopy studies, the cumulative incidence of gastroduodenal ulceration was significantly lower in patients treated with etoricoxib 120 mg once daily than in patients treated with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. Etoricoxib had a higher incidence of ulceration as compared to placebo.

Renal Function Study in the Elderly
A randomised, double-blind, placebo-controlled, parallel-group study evaluated the effects of 15 days of treatment of etoricoxib (90 mg), celecoxib (200 mg bid), naproxen (500 mg bid) and placebo on urinary sodium excretion, blood pressure, and other renal function parameters in subjects 60 to 85 years of age on a 200-mEq/day sodium diet. Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at Day 14 when compared to celecoxib and naproxen (mean change from baseline for systolic blood pressure: etoricoxib 7.7 mmHg, celecoxib 2.4 mmHg, naproxen 3.6 mmHg).

5.2 Pharmacokinetic properties

Absorption

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 µg/ml) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{0-24hr}) was 37.8 µg•hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120 mg dose. The rate of absorption was affected, resulting in a 36% decrease in C_{max} and an increase in T_{max} by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

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 (V_{dss}) was approximately 120 l in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

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 catalysed 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.

Elimination

Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

Characteristics in patients

Elderly: Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Gender: The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic insufficiency: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10). (See sections 4.2 and 4.3.)

Renal insufficiency: The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min). (See sections 4.3 and 4.4.)

Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (<12 years old) have not been studied.

In a pharmacokinetic study (n=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established (see section 4.2.).

5.3 Preclinical safety data

In preclinical studies, etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >2-times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately two years. Hepatocellular and thyroid follicular cell adenomas observed in rats are considered to be a consequence of rat-specific mechanism related to hepatic CYP enzyme induction. Etoricoxib has not been shown to cause hepatic CYP3A enzyme induction in humans.

In the rat, gastro-intestinal toxicity of etoricoxib increased with dose and exposure time. In the 14-week toxicity study, etoricoxib caused gastro-intestinal ulcers at exposures greater than those seen in man at the therapeutic dose. In the 53- and 106-week toxicity study, gastro-intestinal ulcers were also seen at exposures comparable to those seen in man at the therapeutic dose. In dogs, renal and gastro-intestinal abnormalities were seen at high exposures.

Etoricoxib was not teratogenic in reproductive toxicity studies conducted in rats at 15 mg/kg/day (this represents approximately 1.5 times the daily human dose [90 mg] based on systemic exposure). In rabbits, a treatment-related increase in cardiovascular malformations was observed at exposure levels below the clinical exposure at the daily human dose (90mg). However no treatment-related external or skeletal fetal malformations were observed. In rats and rabbits, there was a dose-dependent increase in post-implantation loss at exposures greater than or equal to 1.5 times the human exposure (see sections 4.3 and 4.6.).

Etoricoxib is excreted in the milk of lactating rats at concentrations approximately two-fold those in plasma. There was a decrease in pup body weight following exposure of pups to milk from dams administered etoricoxib during lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Calcium hydrogen phosphate (anhydrous)
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose

Tablet coating:
Carnauba wax
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Triacetin
The 30mg tablets also contain indigo carmine lake (E132) and yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Bottles: Keep the container tightly closed in order to protect from moisture.
Blisters: Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

30 mg
Aluminium/aluminium blisters in packs containing 28 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 00025/0478
PL 00025/0479
PL 00025/0480
PL 00025/0481

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/10/2007

10 DATE OF REVISION OF THE TEXT
06/12/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

ARCOXIA® 30 mg Film coated Tablets etoricoxib

ARCOXIA® 60 mg Film coated Tablets etoricoxib

ARCOXIA® 90 mg Film coated Tablets etoricoxib

ARCOXIA® 120 mg Film coated Tablets etoricoxib

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Arcoxia is and what it is used for

- Arcoxia is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- Arcoxia helps to reduce the pain and swelling (inflammation) in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, and gout.

What is osteoarthritis?
Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It also causes inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

2. BEFORE YOU TAKE ARCOXIA

Do not take Arcoxia:
- if you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of Arcoxia (see Further information, section 6)
- if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- if you have a current stomach ulcer or bleeding in your stomach or intestines
- if you have serious liver disease
- if you have serious kidney disease
- if you are or could be pregnant or are breast-feeding (see 'Pregnancy and breast feeding')
- if you are under 16 years of age
- if you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- if your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke
- if you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Take special care with ARCOXIA
Arcoxia may not be suitable for you, or you may need to be monitored regularly while taking it if any of the following apply to you:

Turn over ➥ for sections 3 to 4

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- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, heart attack or any other form of heart disease.
- You have a history of stroke or mini stroke.
- You have a history of high blood pressure. Arcoxia can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. Arcoxia can mask or hide a fever, which is a sign of infection.
- You are a woman trying to become pregnant.
- You are elderly (i.e., over 65 years of age).
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.

Turn back for the beginning of section 2 ➥

If you are not sure if any of the above apply to you, **talk to your doctor before taking Arcoxia** to see if this medicine is suitable for you.

Arcoxia works equally well in older and younger adult patients. If you are elderly (i.e., over 65 years of age), your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for elderly patients.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking Arcoxia:

- medicines that thin your blood (anticoagulants), such as warfarin
- rifampicin (an antibiotic)
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- lithium (a medicine used to treat some types of depression)
- diuretics (water tablets)
- ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- digoxin (a medicine for heart failure and irregular heart rhythm)
- minoxidil (a drug used to treat high blood pressure)
- salbutamol tablets or oral solution (a medicine for asthma)
- birth control pills
- hormone replacement therapy
- aspirin, the risk of stomach ulcers is greater if you take Arcoxia with aspirin.
  -Arcoxia can be taken with low-dose aspirin. If you are currently taking low-dose aspirin to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor
  -do not take high dose aspirin or other anti-inflammatory medicines while taking Arcoxia

Pregnancy and breast-feeding
Arcoxia tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

It is not known if Arcoxia is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking Arcoxia. If you are using Arcoxia, you must not breast-feed.

Driving and using machines
Dizziness and sleepiness have been reported in some patients taking Arcoxia.
Do not drive if you experience dizziness or sleepiness.
Do not use any tools or machines if you experience dizziness or sleepiness.

Important information about some of the ingredients of Arcoxia
Arcoxia contains lactose. If you have been told by your doctor that you are unable to tolerate some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ARCOXIA

Always take Arcoxia exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Arcoxia Tablets should not be taken by children or adolescents under 16 years of age.

Take Arcoxia Tablets by mouth once a day. Arcoxia can be taken with or without food.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take Arcoxia for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

Osteoarthritis
The recommended dose is 30 mg once a day, increase to a maximum of 60 mg once a day if needed.

Rheumatoid arthritis
The recommended dose is 90 mg once a day.

Gout
The recommended dose is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.

People with liver problems
- If you have mild liver disease, you should not take more than 60 mg a day.
- If you have **moderate** liver disease, you should not take more than 60 mg **every other day** or 30 mg a day.

If you take more Arcoxia than you should
You should never take more tablets than the doctor recommends. If you do take too many Arcoxia Tablets, you should seek medical attention immediately.

If you forget to take Arcoxia
It is important to take Arcoxia as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Arcoxia can cause side effects, although not everybody gets them.

If you develop any of these signs you should stop Arcoxia and talk to your doctor immediately:
- shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The following side effects can occur during treatment with Arcoxia:

***Common* (occurring in greater than 1 out of 100 and less than 1 out of 10 people)**
Weakness and fatigue, dizziness, headache, flu-like illness, diarrhoea, wind, nausea, indigestion (dyspepsia), stomach pain or discomfort, heartburn, changes in blood tests related to your liver, swelling of the legs and/or feet due to fluid retention (oedema), increased blood pressure, palpitations, bruising.

***Uncommon* (occurring in greater than 1 out of 1000 and less than 1 out of 100 people)**
Stomach bloating, chest pain, heart failure, heart attack, stroke, mini-stroke (transient ischaemic attack), abnormal heart rhythm (atrial fibrillation), upper respiratory infection, high levels of potassium in your blood, changes in blood or urine tests relating to your kidney, changes in your bowel habits including constipation, dry mouth, mouth ulcers, taste alteration, gastroenteritis, gastritis, stomach ulcer, being sick (vomiting), irritable bowel syndrome, inflammation of the esophagus, blurred vision, eye irritation and redness, nose bleed, ringing in the ears, vertigo, appetite increases or decreases, weight gain, muscle cramp/spasm, muscle pain/stiffness, inability to sleep, sleepiness, numbness or tingling, anxiety, depression, decreases in mental sharpness, breathlessness, cough, swelling of the face, flushing, skin rash or itchy skin, urinary tract infection.

***Rare* (occurring in greater than 1 out of 10,000 and less than 1 out of 1000 people)**
Low blood levels of sodium.

***Very Rare* (occurring in less than 1 out of 10,000 people)**
Allergic reactions (which may be serious enough to require immediate medical attention) including hives, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, bronchospasm (wheezing or shortness of breath), severe skin reactions, inflammation of the stomach lining or stomach ulcers that can become serious and may lead to bleeding, liver problems, serious kidney problems, severe increase in blood pressure, confusion, seeing, feeling or hearing things that are not there (hallucinations).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Turn over ➥ for sections 5 to 6

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5. HOW TO STORE ARCOXIA

Keep out of the reach and sight of children.

Do not use Arcoxia after the expiry date which is stated on the pack. The expiry date refers to the last day of the month.

Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Arcoxia contains
- The active substance is etoricoxib. Each film coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.
- The other ingredients are:
  Core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.
  Tablet coating: carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin. The 30-, 60- and 120-mg tablets also contain yellow ferric oxide (E172, colouring agent) and indigo carmine lake (E132, colouring agent).

What Arcoxia looks like and contents of the pack
Arcoxia Tablets are available in four strengths:
30 mg blue-green, apple-shaped, biconvex film coated tablets marked 'ACX 30' on one side and '101' on the other.
60 mg dark green, apple-shaped, biconvex film coated tablets marked 'ARCOXIA 60' on one side and '200' on the other.
90 mg white, apple-shaped, biconvex film coated tablets marked 'ARCOXIA 90' on one side and '202' on the other.
120 mg pale-green, apple-shaped, biconvex film coated tablets marked 'ARCOXIA 120' on one side and '204' on the other.

Pack sizes:
30 mg:
Pack sizes of 28 tablets in blisters.

60, 90, 120 mg:
Pack sizes of 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets in blisters; or 30 and 90 tablets in bottles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The **Marketing Authorisation Holder in the UK** for 30, 60, 90 and 120 mg , and in Ireland for 60, 90 and 120 mg is Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Herts, EN11 9BU, UK.
The **Marketing Authorisation Holder in Ireland** for 30 mg is Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.

Manufacturer (60, 90 and 120mg): Frosst Iberica S.A., Via Complutense, 140, 28805 Alcala de Henares, Madrid, Spain.
Manufacturer (30 mg): Merck Sharp&Dohme BV, Waarderweg 39, 2031 BN Haarlem, Holland.

This medicinal product is authorized in the Member States of the EEA under the following names:

AUSTRIA	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg-Filmtabletten	LATVIA	Arcoxia 30, 60, 90 un 120 mg apvalkotās tablets
BELGIUM	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés	LITHUANIA	Arcoxia 30, 60, 90, 120 mg plėvele dengtos tabletės
CZECH REP.	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg	LUXEMBOURG	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
CYPRUS	Arcoxia 30, 60, 90, 120 mg	MALTA	ARCOXIA 30, 60, 90 or 120 mg film-coated tablets
DENMARK	Arcoxia	NETHERLANDS	Arcoxia 30, 60, 90, 120
ESTONIA	Arcoxia	NORWAY	Arcoxia 30, 60, 90, 120 mg filmdrasjerte tabletter
FINLAND	Arcoxia 30 mg, 60 mg, 90 mg ja 120 mg tabletti, kalvopäällysteinen	POLAND	Arcoxia
FRANCE	Arcoxia 30 mg comprimé pelliculé	PORTUGAL	Arcoxia 30, 60, 90, 120 mg comprimidos revestidos por película
GERMANY	Arcoxia 30/60/90/120 mg Filmtabletten	SLOVAKIA	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg
GREECE	Arcoxia	SLOVENIA	Arcoxia 30/60/90/120 mg filmsko obložene tablete
HUNGARY	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg filmtabletta	SPAIN	Arcoxia 30, 60, 90 y 120 mg comprimidos recubiertos con película
ICELAND	Arcoxia	SWEDEN	Arcoxia 30 mg, 60 mg, 90 mg och 120 mg filmdragerade tabletter
IRELAND	Arcoxia 30, 60, 90 or 120 mg film-coated tablets	UNITED KINGDOM	ARCOXIA 30, 60, 90 or 120 mg film-coated tablets
ITALY	Arcoxia 30, 60, 90, 120 mg compresse rivestite con film		

This leaflet was last approved in (09/2007).
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PACKAGE LEAFLET: INFORMATION FOR THE USER

Auxib 30mg Film-Coated Tablets
Auxib 60 mg Film-Coated Tablets
Auxib 90 mg Film-Coated Tablets
Auxib 120 mg Film-Coated Tablets
(etoricoxib)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1.What Auxib is and what it is used for

Auxib is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
Auxib helps to reduce the pain and swelling (inflammation) in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, and gout.

What is osteoarthritis?
Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It also causes inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

2. Before you take Auxib

Do not take Auxib:
- if you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of Auxib (see Further information, section 6)
- if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- if you have a current stomach ulcer or bleeding in your stomach or intestines
- if you have serious liver disease
- if you have serious kidney disease
- if you are or could be pregnant or are breast-feeding (see 'Pregnancy and breast feeding')
- if you are under 16 years of age
- if you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- if your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke
- if you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Take special care with AUXIB
Auxib may not be suitable for you, or you may need to be monitored regularly while taking it if any of the following apply to you:

- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, heart attack or any other form of heart disease.
- You have a history of stroke or mini stroke.
- You have a history of high blood pressure. Auxib can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. Auxib can mask or hide a fever, which is a sign of infection.
- You are a woman trying to become pregnant.
- You are elderly (i.e., over 65 years of age).
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.

If you are not sure if any of the above apply to you, **talk to your doctor before taking Auxib** to see if this medicine is suitable for you.

Auxib works equally well in older and younger adult patients. If you are elderly (i.e., over 65 years of age), your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for elderly patients.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking Auxib:

- medicines that thin your blood (anticoagulants), such as warfarin
- rifampicin (an antibiotic)
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- lithium (a medicine used to treat some types of depression)
- diuretics (water tablets)
- ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- digoxin (a medicine for heart failure and irregular heart rhythm)
- minoxidil (a drug used to treat high blood pressure)
- salbutamol tablets or oral solution (a medicine for asthma)
- birth control pills
- hormone replacement therapy
- aspirin, the risk of stomach ulcers is greater if you take Auxib with aspirin.

-Auxib can be taken with low-dose aspirin. If you are currently taking low-dose aspirin
to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor

-do not take high dose aspirin or other anti-inflammatory medicines while taking Auxib

Pregnancy and breast-feeding
Auxib tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

It is not known if Auxib is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking Auxib. If you are using Auxib, you must not breast-feed.

Driving and using machines
Dizziness and sleepiness have been reported in some patients taking Auxib.
Do not drive if you experience dizziness or sleepiness.
Do not use any tools or machines if you experience dizziness or sleepiness.

Important information about some of the ingredients of Auxib
Auxib contains lactose. If you have been told by your doctor that you are unable to tolerate some sugars, contact your doctor before taking this medicinal product.

3. How to take Auxib

Always take Auxib exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Auxib Tablets should not be taken by children or adolescents under 16 years of age.

Take Auxib Tablets by mouth once a day. Auxib can be taken with or without food.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take Auxib for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

Osteoarthritis
The recommended dose is 30 mg once a day, increase to a maximum of 60 mg once a day if needed.
Rheumatoid arthritis
The recommended dose is 90 mg once a day.
Gout
The recommended dose is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.
People with liver problems
If you have mild liver disease, you should not take more than 60 mg a day.
If you have **moderate** liver disease, you should not take more than 60 mg **every other day** or 30 mg a day.

If you take more Auxib than you should
You should never take more tablets than the doctor recommends. If you do take too many Auxib Tablets, you should seek medical attention immediately.

If you forget to take Auxib
It is important to take Auxib as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side-effects

Like all medicines, Auxib can cause side effects, although not everybody gets them.

If you develop any of these signs you should stop Auxib and talk to your doctor immediately:

- shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The following side effects can occur during treatment with Auxib:

Common **(occurring in greater than 1 out of 100 and less than 1 out of 10 people)**
Weakness and fatigue, dizziness, headache, flu-like illness, diarrhoea, wind, nausea, indigestion (dyspepsia), stomach pain or discomfort, heartburn, changes in blood tests related to your liver, swelling of the legs and/or feet due to fluid retention (oedema), increased blood pressure, palpitations, bruising.

Uncommon **(occurring in greater than 1 out of 1000 and less than 1 out of 100 people)**
Stomach bloating, chest pain, heart failure, heart attack, stroke, mini-stroke (transient ischaemic attack), abnormal heart rhythm (atrial fibrillation), upper respiratory infection, high levels of potassium in your blood, changes in blood or urine tests relating to your kidney, changes in your bowel habits including constipation, dry mouth, mouth ulcers, taste alteration, gastroenteritis, gastritis, stomach ulcer, being sick (vomiting), irritable bowel syndrome, inflammation of the esophagus, blurred vision, eye irritation and redness, nose bleed, ringing in the ears, vertigo, appetite increases or decreases, weight gain, muscle cramp/spasm, muscle pain/stiffness, inability to sleep, sleepiness, numbness or tingling, anxiety, depression, decreases in mental sharpness, breathlessness, cough, swelling of the face, flushing, skin rash or itchy skin, urinary tract infection.

Rare **(occurring in greater than 1 out of 10,000 and less than 1 out of 1000 people)**
Low blood levels of sodium.

Very Rare **(occurring in less than 1 out of 10,000 people)**
Allergic reactions (which may be serious enough to require immediate medical attention) including hives, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, bronchospasm (wheezing or shortness of breath), severe skin reactions, inflammation of the stomach lining or stomach ulcers that can become serious and may lead to bleeding, liver problems, serious kidney problems, severe increase in blood pressure, confusion, seeing, feeling or hearing things that are not there (hallucinations).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Auxib?

Keep out of the reach and sight of children.
Do not use Auxib after the expiry date which is stated on the pack.
The expiry date refers to the last day of the month.
Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further Information

What Auxib contains
The active substance is etoricoxib. Each film coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.
The other ingredients are: Core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.

Tablet coating: carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin. The 30-, 60- and 120-mg tablets also contain yellow ferric oxide (E172, colouring agent) and indigo carmine lake (E132, colouring agent).

What Auxib looks like and contents of the pack
Auxib Tablets are available in four strengths:
30 mg blue-green, apple-shaped, biconvex film coated tablets plain on one side and '101' on the other.
60 mg dark green, apple-shaped, biconvex film coated tablets plain on one side and '200' on the other.
90 mg white, apple-shaped, biconvex film coated tablets plain on one side and '202' on the other.
120 mg pale-green, apple-shaped, biconvex film coated tablets plain on one side and '204' on the other.
Pack sizes:
30 mg: Pack sizes of 28 tablets in blisters.
60, 90, 120 mg: Pack sizes of 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets in blisters; or 30 and 90 tablets in bottles.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder in the UK for 30, 60, 90 and 120 mg, and in Ireland for 60, 90 and 120 mg is Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Herts, EN11 9BU, UK.

The Marketing Authorisation Holder in Ireland for 30 mg is Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.

Manufacturer (60, 90 and 120mg): Frosst Iberica S.A., Via Complutense, 140, 28805 Alcala de Henares, Madrid, Spain.

Manufacturer (30 mg): Merck Sharp&Dohme BV, Waarderweg 39, 2031 BN Haarlem, Holland.

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria	Auxib 30 mg, 60 mg, 90 mg, 120 mg-Filmtabletten
Belgium	Auxib 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Czech Rep.	AUXIB 30 mg, 60 mg, 90 mg, 120 mg
Cyprus	Auxib 30, 60, 90, 120 mg
Denmark	Auxib
Estonia	Auxib
Finland	Auxib 30 mg, 60 mg, 90 mg ja 120 mg tabletti, kalvopäällysteinen
France	Auxib 30 mg, comprimé pelliculé
Germany	Auxib 30/60/90/120 mg Filmtabletten
Greece	Auxib
Hungary	Auxib 30 mg, 60 mg, 90 mg, 120 mg filmtabletta
Iceland	Auxib
Ireland	Auxib 30, 60, 90 or 120 mg film-coated tablets
Italy	Auxib 30, 60, 90, 120 mg compresse rivestite con film
Latvia	Auxib 30, 60, 90 un 120 mg apvalkotās tablets
Lithuania	Auxib 30, 60, 90, 120 mg plėvele dengtos tabletės
Luxembourg	Auxib 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Malta	AUXIB 30, 60, 90 or 120 mg film-coated tablets
Netherlands	Auxib 30, 60, 90, 120
Norway	Auxib 30, 60, 90, 120 mg filmdrasjerte tabletter
Poland	Auxib
Portugal	Auxib 30, 60, 90, 120 mg comprimidos revestidos por película
Slovakia	AUXIB 30 mg, 60 mg, 90 mg, 120 mg
Slovenia	Auxib 30/60/90/120 mg filmsko obložene tablete
Spain	Auxib 30, 60, 90 y 120 mg comprimidos recubiertos con película
Sweden	Auxib 30 mg, 60 mg, 90 mg och 120 mg filmdragerade tabletter
United Kingdom	AUXIB 30, 60, 90 or 120 mg film-coated tablets

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Exxiv 30mg Film-Coated Tablets
Exxiv 60 mg Film-Coated Tablets
Exxiv 90 mg Film-Coated Tablets
Exxiv 120 mg Film-Coated Tablets
(etoricoxib)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1.What Exxiv is and what it is used for

Exxiv is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
Exxiv helps to reduce the pain and swelling (inflammation) in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, and gout.

What is osteoarthritis?
Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It also causes inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

2. Before you take Exxiv

Do not take Exxiv:
- if you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of Exxiv (see Further information, section 6)
- if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- if you have a current stomach ulcer or bleeding in your stomach or intestines
- if you have serious liver disease
- if you have serious kidney disease
- if you are or could be pregnant or are breast-feeding (see 'Pregnancy and breast feeding')
- if you are under 16 years of age
- if you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- if your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke
- if you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Take special care with EXXIV
Exxiv may not be suitable for you, or you may need to be monitored regularly while taking it if any of the following apply to you:

- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, heart attack or any other form of heart disease.
- You have a history of stroke or mini stroke.
- You have a history of high blood pressure. Exxiv can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. Exxiv can mask or hide a fever, which is a sign of infection.
- You are a woman trying to become pregnant.
- You are elderly (i.e., over 65 years of age).
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.

If you are not sure if any of the above apply to you, **talk to your doctor before taking Exxiv** to see if this medicine is suitable for you.

Exxiv works equally well in older and younger adult patients. If you are elderly (i.e., over 65 years of age), your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for elderly patients.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking Exxiv:

- medicines that thin your blood (anticoagulants), such as warfarin
- rifampicin (an antibiotic)
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- lithium (a medicine used to treat some types of depression)
- diuretics (water tablets)
- ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- digoxin (a medicine for heart failure and irregular heart rhythm)
- minoxidil (a drug used to treat high blood pressure)
- salbutamol tablets or oral solution (a medicine for asthma)
- birth control pills
- hormone replacement therapy
- aspirin, the risk of stomach ulcers is greater if you take Exxiv with aspirin.

-Exxiv can be taken with low-dose aspirin. If you are currently taking low-dose aspirin
to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor

-do not take high dose aspirin or other anti-inflammatory medicines while taking Exxiv

Pregnancy and breast-feeding
Exxiv tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

It is not known if Exxiv is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking Exxiv. If you are using Exxiv, you must not breast-feed.

Driving and using machines
Dizziness and sleepiness have been reported in some patients taking Exxiv.
Do not drive if you experience dizziness or sleepiness.
Do not use any tools or machines if you experience dizziness or sleepiness.

Important information about some of the ingredients of Exxiv
Exxiv contains lactose. If you have been told by your doctor that you are unable to tolerate some sugars, contact your doctor before taking this medicinal product.

3. How to take Exxiv

Always take Exxiv exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Exxiv Tablets should not be taken by children or adolescents under 16 years of age.

Take Exxiv Tablets by mouth once a day. Exxiv can be taken with or without food.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take Exxiv for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

Osteoarthritis
The recommended dose is 30 mg once a day, increase to a maximum of 60 mg once a day if needed.
Rheumatoid arthritis
The recommended dose is 90 mg once a day.
Gout
The recommended dose is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.
People with liver problems
If you have mild liver disease, you should not take more than 60 mg a day.
If you have **moderate** liver disease, you should not take more than 60 mg **every other day** or 30 mg a day.

If you take more Exxiv than you should
You should never take more tablets than the doctor recommends. If you do take too many Exxiv Tablets, you should seek medical attention immediately.

If you forget to take Exxiv
It is important to take Exxiv as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side-effects

Like all medicines, Exxiv can cause side effects, although not everybody gets them.

If you develop any of these signs you should stop Exxiv and talk to your doctor immediately:

- shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The following side effects can occur during treatment with Exxiv:

Common **(occurring in greater than 1 out of 100 and less than 1 out of 10 people)**
Weakness and fatigue, dizziness, headache, flu-like illness, diarrhoea, wind, nausea, indigestion (dyspepsia), stomach pain or discomfort, heartburn, changes in blood tests related to your liver, swelling of the legs and/or feet due to fluid retention (oedema), increased blood pressure, palpitations, bruising.

Uncommon **(occurring in greater than 1 out of 1000 and less than 1 out of 100 people)**
Stomach bloating, chest pain, heart failure, heart attack, stroke, mini-stroke (transient ischaemic attack), abnormal heart rhythm (atrial fibrillation), upper respiratory infection, high levels of potassium in your blood, changes in blood or urine tests relating to your kidney, changes in your bowel habits including constipation, dry mouth, mouth ulcers, taste alteration, gastroenteritis, gastritis, stomach ulcer, being sick (vomiting), irritable bowel syndrome, inflammation of the esophagus, blurred vision, eye irritation and redness, nose bleed, ringing in the ears, vertigo, appetite increases or decreases, weight gain, muscle cramp/spasm, muscle pain/stiffness, inability to sleep, sleepiness, numbness or tingling, anxiety, depression, decreases in mental sharpness, breathlessness, cough, swelling of the face, flushing, skin rash or itchy skin, urinary tract infection.

Rare **(occurring in greater than 1 out of 10,000 and less than 1 out of 1000 people)**
Low blood levels of sodium.

Very Rare **(occurring in less than 1 out of 10,000 people)**
Allergic reactions (which may be serious enough to require immediate medical attention) including hives, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, bronchospasm (wheezing or shortness of breath), severe skin reactions, inflammation of the stomach lining or stomach ulcers that can become serious and may lead to bleeding, liver problems, serious kidney problems, severe increase in blood pressure, confusion, seeing, feeling or hearing things that are not there (hallucinations).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Exxiv?

Keep out of the reach and sight of children.
Do not use Exxiv after the expiry date which is stated on the pack.
The expiry date refers to the last day of the month.
Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further Information

What Exxiv contains
The active substance is etoricoxib. Each film coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.
The other ingredients are: Core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.

Tablet coating: carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin. The 30-, 60- and 120-mg tablets also contain yellow ferric oxide (E172, colouring agent) and indigo carmine lake (E132, colouring agent).

What Exxiv looks like and contents of the pack
Exxiv Tablets are available in four strengths:
30 mg blue-green, apple-shaped, biconvex film coated tablets plain on one side and '101' on the other.
60 mg dark green, apple-shaped, biconvex film coated tablets plain on one side and '200' on the other.
90 mg white, apple-shaped, biconvex film coated tablets plain on one side and '202' on the other.
120 mg pale-green, apple-shaped, biconvex film coated tablets plain on one side and '204' on the other.
Pack sizes:
30 mg: Pack sizes of 28 tablets in blisters.
60, 90, 120 mg: Pack sizes of 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets in blisters; or 30 and 90 tablets in bottles.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder in the UK for 30, 60, 90 and 120 mg, and in Ireland for 60, 90 and 120 mg is Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Herts, EN11 9BU, UK.

The Marketing Authorisation Holder in Ireland for 30 mg is Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.

Manufacturer (60, 90 and 120mg): Frosst Iberica S.A., Via Complutense, 140, 28805 Alcala de Henares, Madrid, Spain.

Manufacturer (30 mg): Merck Sharp&Dohme BV, Waarderweg 39, 2031 BN Haarlem, Holland.

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria	Exxiv 30 mg, 60 mg, 90 mg, 120 mg-Filmtabletten
Belgium	Exxiv 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Czech Rep.	EXXIV 30 mg, 60 mg, 90 mg, 120 mg
Cyprus	Exxiv 30, 60, 90, 120 mg
Denmark	Exxiv
Estonia	Exxiv
Finland	Exxiv 30 mg, 60 mg, 90 mg ja 120 mg tabletti, kalvopäällysteinen
France	Exxiv 30 mg, comprimé pelliculé
Germany	Exxiv 30/60/90/120 mg Filmtabletten
Greece	Exxiv
Hungary	Exxiv 30 mg, 60 mg, 90 mg, 120 mg filmtabletta
Iceland	Exxiv
Ireland	Exxiv 30, 60, 90 or 120 mg film-coated tablets
Italy	Exxiv 30, 60, 90, 120 mg compresse rivestite con film
Latvia	Exxiv 30, 60, 90 un 120 mg apvalkotās tablets
Lithuania	Exxiv 30, 60, 90, 120 mg plėvele dengtos tabletės
Luxembourg	Exxiv 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Malta	EXXIV 30, 60, 90 or 120 mg film-coated tablets
Netherlands	Exxiv 30, 60, 90, 120
Norway	Exxiv 30, 60, 90, 120 mg filmdrasjerte tabletter
Poland	Exxiv
Portugal	Exxiv 30, 60, 90, 120 mg comprimidos revestidos por película
Slovakia	EXXIV 30 mg, 60 mg, 90 mg, 120 mg
Slovenia	Exxiv 30/60/90/120 mg filmsko obložene tablete
Spain	Exxiv 30, 60, 90 y 120 mg comprimidos recubiertos con película
Sweden	Exxiv 30 mg, 60 mg, 90 mg och 120 mg filmdragerade tabletter
United Kingdom	EXXIV 30, 60, 90 or 120 mg film-coated tablets

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Turox 30mg Film-Coated Tablets
Turox 60 mg Film-Coated Tablets
Turox 90 mg Film-Coated Tablets
Turox 120 mg Film-Coated Tablets
(etoricoxib)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1.What Turox is and what it is used for

Turox is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
Turox helps to reduce the pain and swelling (inflammation) in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, and gout.

What is osteoarthritis?
Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It also causes inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

2. Before you take Turox

Do not take Turox:
- if you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of Turox (see Further information, section 6)
- if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- if you have a current stomach ulcer or bleeding in your stomach or intestines
- if you have serious liver disease
- if you have serious kidney disease
- if you are or could be pregnant or are breast-feeding (see 'Pregnancy and breast feeding')
- if you are under 16 years of age
- if you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- if your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke
- if you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Take special care with TUROX
Turox may not be suitable for you, or you may need to be monitored regularly while taking it if any of the following apply to you:

- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, heart attack or any other form of heart disease.
- You have a history of stroke or mini stroke.
- You have a history of high blood pressure. Turox can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. Turox can mask or hide a fever, which is a sign of infection.
- You are a woman trying to become pregnant.
- You are elderly (i.e., over 65 years of age).
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.

If you are not sure if any of the above apply to you, **talk to your doctor before taking Turox** to see if this medicine is suitable for you.

Turox works equally well in older and younger adult patients. If you are elderly (i.e., over 65 years of age), your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for elderly patients.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking Turox:

- medicines that thin your blood (anticoagulants), such as warfarin
- rifampicin (an antibiotic)
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- lithium (a medicine used to treat some types of depression)
- diuretics (water tablets)
- ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- digoxin (a medicine for heart failure and irregular heart rhythm)
- minoxidil (a drug used to treat high blood pressure)
- salbutamol tablets or oral solution (a medicine for asthma)
- birth control pills
- hormone replacement therapy
- aspirin, the risk of stomach ulcers is greater if you take Turox with aspirin.

-Turox can be taken with low-dose aspirin. If you are currently taking low-dose aspirin to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor

-do not take high dose aspirin or other anti-inflammatory medicines while taking Turox

Pregnancy and breast-feeding
Turox tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

It is not known if Turox is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking Turox. If you are using Turox, you must not breast-feed.

Driving and using machines
Dizziness and sleepiness have been reported in some patients taking Turox.
Do not drive if you experience dizziness or sleepiness.
Do not use any tools or machines if you experience dizziness or sleepiness.

Important information about some of the ingredients of Turox
Turox contains lactose. If you have been told by your doctor that you are unable to tolerate some sugars, contact your doctor before taking this medicinal product.

3. How to take Turox

Always take Turox exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Turox Tablets should not be taken by children or adolescents under 16 years of age.

Take Turox Tablets by mouth once a day. Turox can be taken with or without food.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take Turox for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

Osteoarthritis
The recommended dose is 30 mg once a day, increase to a maximum of 60 mg once a day if needed.
Rheumatoid arthritis
The recommended dose is 90 mg once a day.
Gout
The recommended dose is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.
People with liver problems
If you have mild liver disease, you should not take more than 60 mg a day.
If you have moderate liver disease, you should not take more than 60 mg every other day or 30 mg a day.

If you take more Turox than you should
You should never take more tablets than the doctor recommends. If you do take too many Turox Tablets, you should seek medical attention immediately.

If you forget to take Turox
It is important to take Turox as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side-effects

Like all medicines, Turox can cause side effects, although not everybody gets them.

If you develop any of these signs you should stop Turox and talk to your doctor immediately:

- shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The following side effects can occur during treatment with Turox:

Common **(occurring in greater than 1 out of 100 and less than 1 out of 10 people)**
Weakness and fatigue, dizziness, headache, flu-like illness, diarrhoea, wind, nausea, indigestion (dyspepsia), stomach pain or discomfort, heartburn, changes in blood tests related to your liver, swelling of the legs and/or feet due to fluid retention (oedema), increased blood pressure, palpitations, bruising.

Uncommon **(occurring in greater than 1 out of 1000 and less than 1 out of 100 people)**
Stomach bloating, chest pain, heart failure, heart attack, stroke, mini-stroke (transient ischaemic attack), abnormal heart rhythm (atrial fibrillation), upper respiratory infection, high levels of potassium in your blood, changes in blood or urine tests relating to your kidney, changes in your bowel habits including constipation, dry mouth, mouth ulcers, taste alteration, gastroenteritis, gastritis, stomach ulcer, being sick (vomiting), irritable bowel syndrome, inflammation of the esophagus, blurred vision, eye irritation and redness, nose bleed, ringing in the ears, vertigo, appetite increases or decreases, weight gain, muscle cramp/spasm, muscle pain/stiffness, inability to sleep, sleepiness, numbness or tingling, anxiety, depression, decreases in mental sharpness, breathlessness, cough, swelling of the face, flushing, skin rash or itchy skin, urinary tract infection.

Rare **(occurring in greater than 1 out of 10,000 and less than 1 out of 1000 people)**
Low blood levels of sodium.

Very Rare **(occurring in less than 1 out of 10,000 people)**
Allergic reactions (which may be serious enough to require immediate medical attention) including hives, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, bronchospasm (wheezing or shortness of breath), severe skin reactions, inflammation of the stomach lining or stomach ulcers that can become serious and may lead to bleeding, liver problems, serious kidney problems, severe increase in blood pressure, confusion, seeing, feeling or hearing things that are not there (hallucinations).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Turox?

Keep out of the reach and sight of children.
Do not use Turox after the expiry date which is stated on the pack.
The expiry date refers to the last day of the month.
Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further Information

What Turox contains
The active substance is etoricoxib. Each film coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.
The other ingredients are: Core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.

Tablet coating: carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin. The 30-, 60- and 120-mg tablets also contain yellow ferric oxide (E172, colouring agent) and indigo carmine lake (E132, colouring agent).

What Turox looks like and contents of the pack
Turox Tablets are available in four strengths:
30 mg blue-green, apple-shaped, biconvex film coated tablets plain on one side and '101' on the other.
60 mg dark green, apple-shaped, biconvex film coated tablets plain on one side and '200' on the other.
90 mg white, apple-shaped, biconvex film coated tablets plain on one side and '202' on the other.
120 mg pale-green, apple-shaped, biconvex film coated tablets plain on one side and '204' on the other.
Pack sizes:
30 mg: Pack sizes of 28 tablets in blisters.
60, 90, 120 mg: Pack sizes of 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets in blisters; or 30 and 90 tablets in bottles.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder in the UK for 30, 60, 90 and 120 mg, and in Ireland for 60, 90 and 120 mg is Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Herts, EN11 9BU, UK.

The Marketing Authorisation Holder in Ireland for 30 mg is Merck Sharp & Dohme Ireland (Human Health) Ltd, Pelham House, South County Business Park, Leopardstown, Dublin 18, Ireland.

Manufacturer (60, 90 and 120mg): Frosst Iberica S.A., Via Complutense, 140, 28805 Alcala de Henares, Madrid, Spain.

Manufacturer (30 mg): Merck Sharp&Dohme BV, Waarderweg 39, 2031 BN Haarlem, Holland.

This medicinal product is authorized in the Member States of the EEA under the following names:

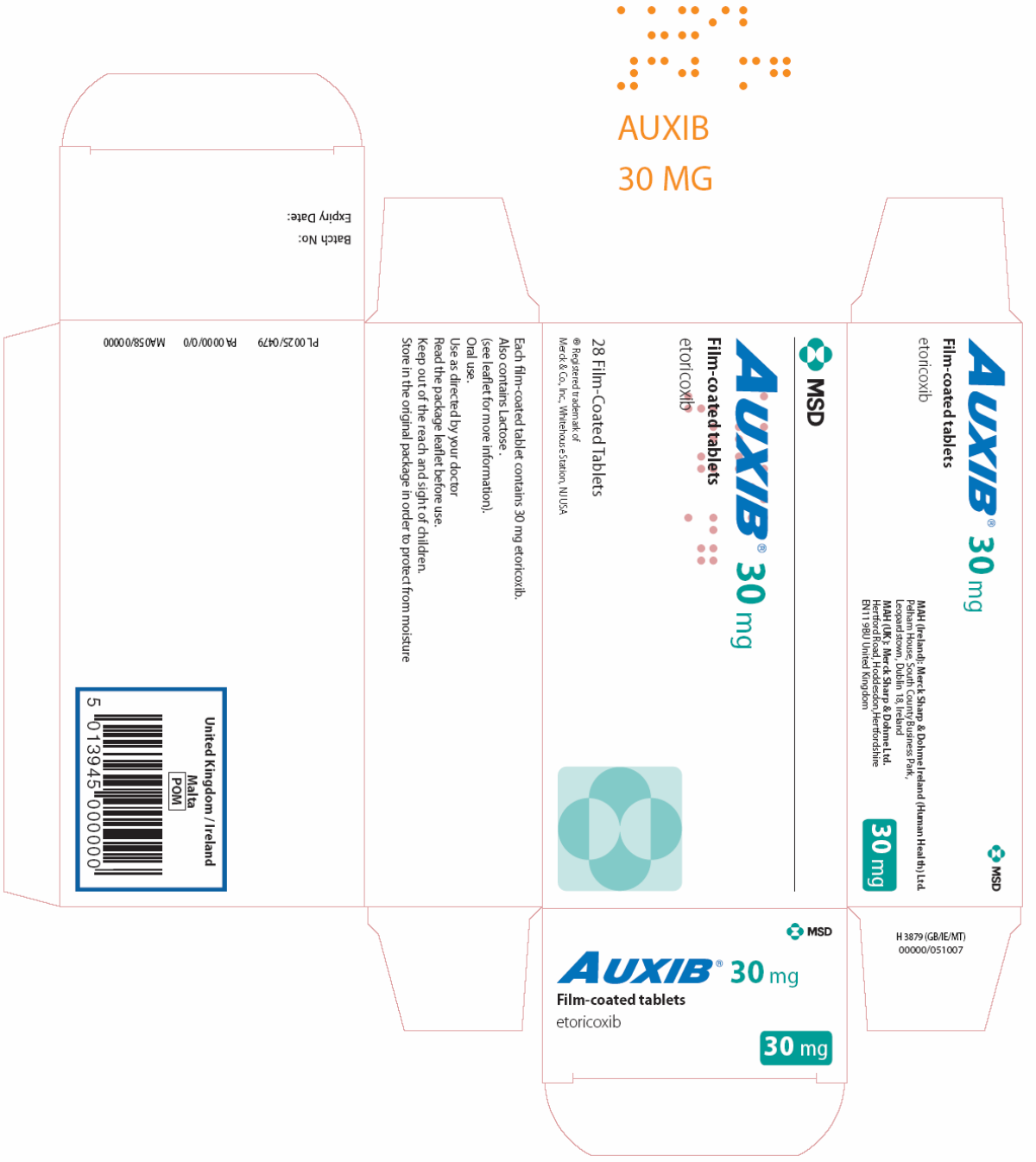
Austria	Turox 30 mg, 60 mg, 90 mg, 120 mg-Filmtabletten
Belgium	Turox 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Czech Rep.	TUROX 30 mg, 60 mg, 90 mg, 120 mg
Cyprus	Turox 30, 60, 90, 120 mg
Denmark	Turox
Estonia	Turox
Finland	Turox 30 mg, 60 mg, 90 mg ja 120 mg tabletti, kalvopäällysteinen
France	Turox 30 mg, comprimé pelliculé
Germany	Turox 30/60/90/120 mg Filmtabletten
Greece	Turox
Hungary	Turox 30 mg, 60 mg, 90 mg, 120 mg filmtabletta
Iceland	Turox
Ireland	Turox 30, 60, 90 or 120 mg film-coated tablets
Italy	Turox 30, 60, 90, 120 mg compresse rivestite con film
Latvia	Turox 30, 60, 90 un 120 mg apvalkotās tablets
Lithuania	Turox 30, 60, 90, 120 mg plėvele dengtos tabletės
Luxembourg	Turox 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Malta	TUROX 30, 60, 90 or 120 mg film-coated tablets
Netherlands	Turox 30, 60, 90, 120
Norway	Turox 30, 60, 90, 120 mg filmdrasjerte tabletter
Poland	Turox
Portugal	Turox 30, 60, 90, 120 mg comprimidos revestidos por película
Slovakia	TUROX 30 mg, 60 mg, 90 mg, 120 mg
Slovenia	Turox 30/60/90/120 mg filmsko obložene tablete
Spain	Turox 30, 60, 90 y 120 mg comprimidos recubiertos con película
Sweden	Turox 30 mg, 60 mg, 90 mg och 120 mg filmdragerade tabletter
United Kingdom	TUROX 30, 60, 90 or 120 mg film-coated tablets

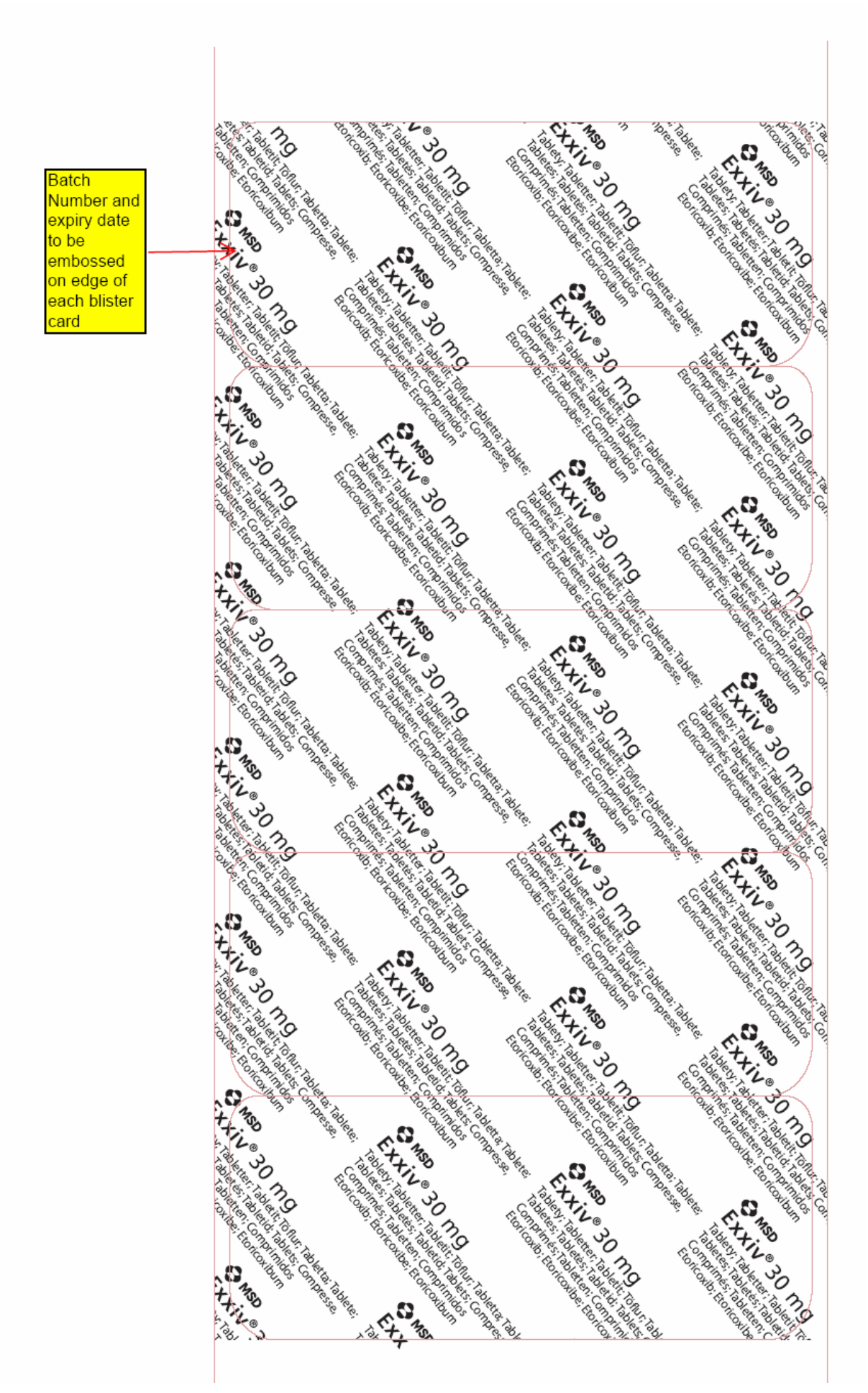
This leaflet was last approved in (09/2007).
PIL.ACX.06.UK.2387

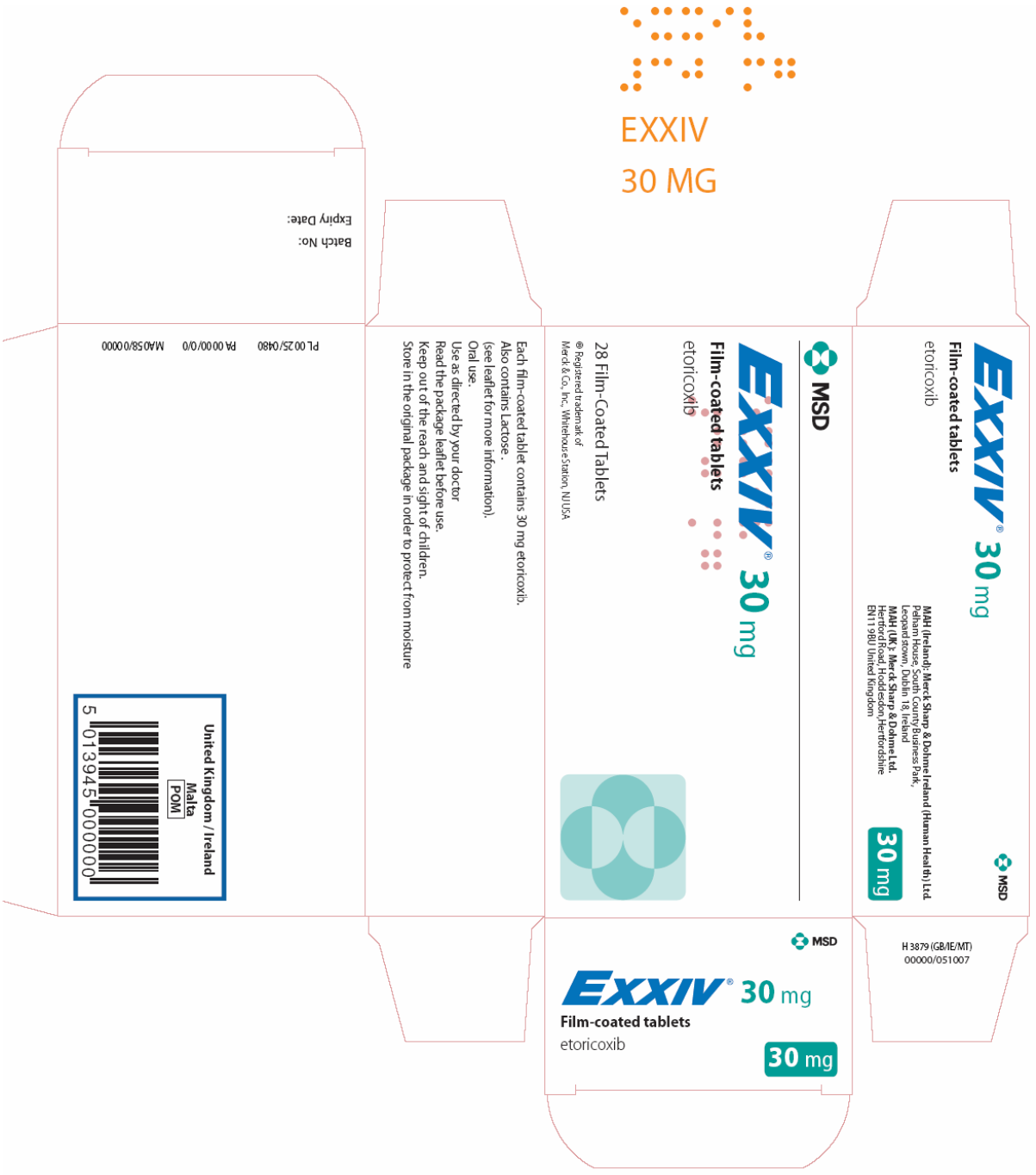
Module 4
Labelling

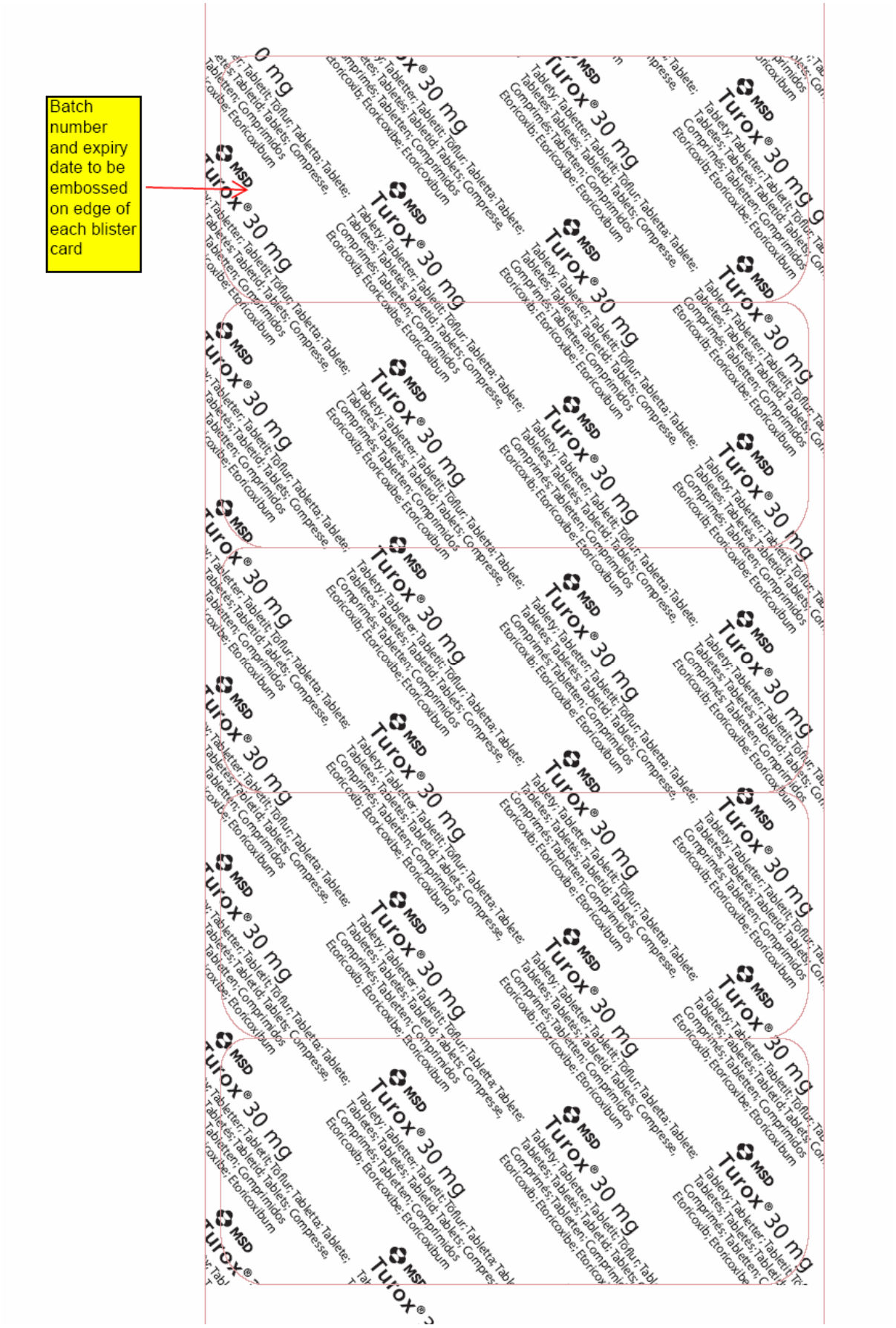

ARCOXIA
30 MG
Batch No:
Expiry Date:
PL 00025/0478 PA 1286/7/1 MA058/00000
Each film-coated tablet contains 30 mg etoricoxib.
Also contains Lactose.
(see leaflet for more information).
Oral use.
Use as directed by your doctor
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original package in order to protect from moisture
United Kingdom / Ireland
Malta
POM
5 013945 001709
MSD
ARCOXIA 30 mg
Film-coated tablets
etoricoxib
28 Film-Coated Tablets
® Registered trademark of Merck & Co., Inc., Whitehouse Station, NJ USA
MSD
ARCOXIA 30 mg
Film-coated tablets
etoricoxib
30 mg
ARCOXIA 30 mg
Film-coated tablets
etoricoxib
MAH (Ireland): Merck Sharp & Dohme Ireland (Human Health) Ltd.
Pelham House, South County Business Park,
Leopardstown, Dublin 18, Ireland
MAH (UK): Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon, Hertfordshire
EN11 9BU United Kingdom
30 mg
MSD
H 3879 (GB/IE/MT)
21760/051007

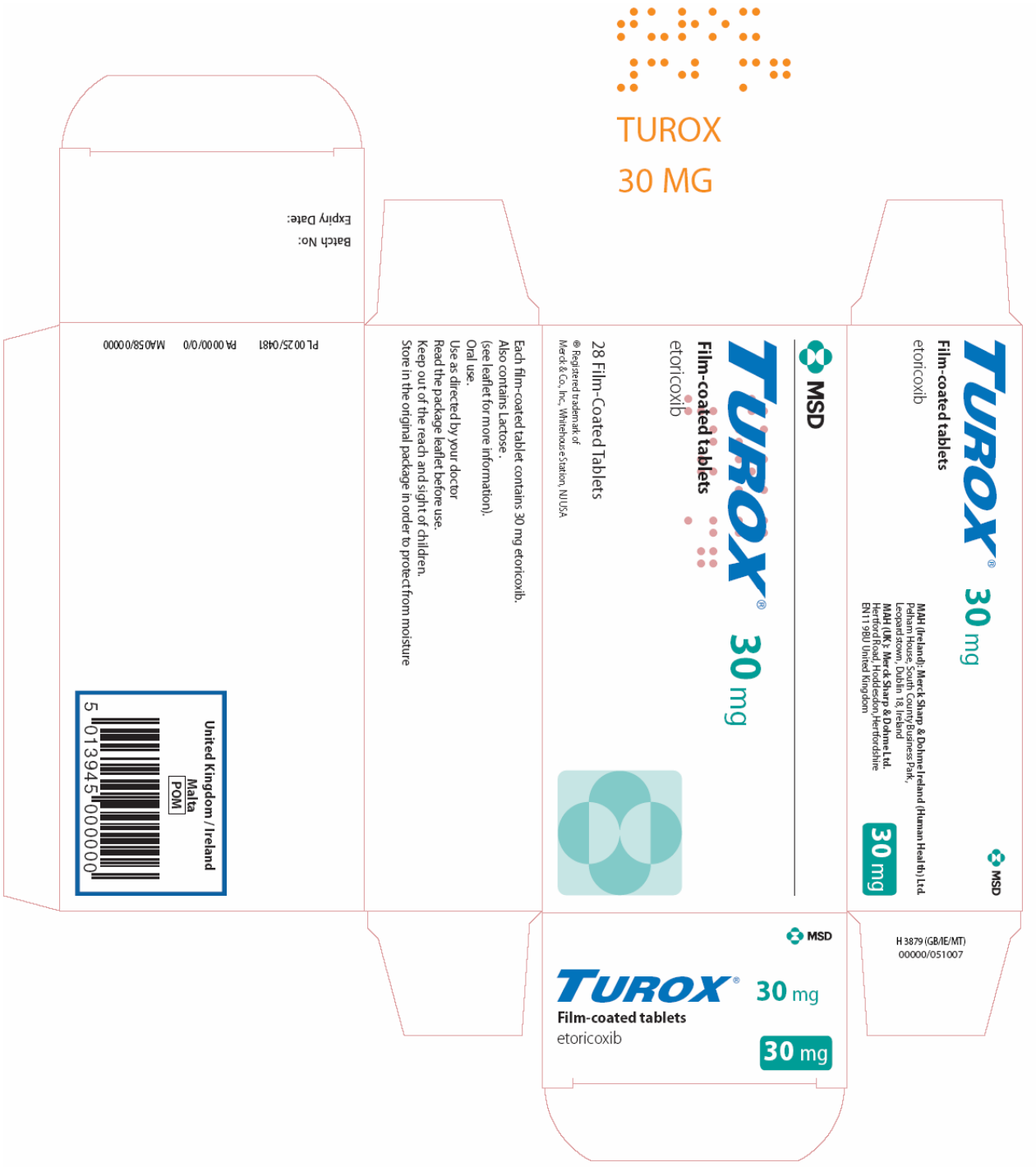

Batch number and expiry date to be embossed on the edge of each blister card
MSD
Auxib® 30 mg


AUXIB
30 MG
AUXIB® 30 mg
Film-coated tablets
etoricoxib
30 mg
MAH (Ireland): Merck Sharp & Dohme Ireland (Human Health) Ltd.
Pelham House, South County Business Park,
Leopardstown, Dublin 18, Ireland
MAH (UK): Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon, Hertfordshire
EN11 9BU United Kingdom
MSD
H 3879 (GB/IE/MT)
00000/051007
MSD
AUXIB® 30 mg
Film-coated tablets
etoricoxib
30 mg
MSD
AUXIB® 30 mg
Film-coated tablets
etoricoxib
28 Film-Coated Tablets
® Registered trademark of
Merck & Co, Inc., Whitehouse Station, NJ USA
Each film-coated tablet contains 30 mg etoricoxib.
Also contains Lactose.
(see leaflet for more information).
Oral use.
Use as directed by your doctor
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original package in order to protect from moisture
PL 00325/0479 PA 00000/0/0 MA058/0/0000
Batch No:
Expiry Date:
United Kingdom / Ireland
Malta
POM
5 013945 000000


Batch Number and expiry date to be embossed on edge of each blister card
MSD
Exxiv® 30 mg


EXXIV
30 MG
Expiry Date:
Batch No:
PL 00025/0480 PA 00000/0/0 MA058/0000
United Kingdom / Ireland
Malta
POM
5 013945 000000
Each film-coated tablet contains 30 mg etoricoxib.
Also contains Lactose.
(see leaflet for more information).
Oral use.
Use as directed by your doctor
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original package in order to protect from moisture
28 Film-Coated Tablets
® Registered trademark of
Merck & Co, Inc, Whitehouse Station, NJ USA
MSD
EXXIV® 30 mg
Film-coated tablets
etoricoxib
MSD
EXXIV® 30 mg
Film-coated tablets
etoricoxib
30 mg
EXXIV® 30 mg
Film-coated tablets
etoricoxib
MAH (Ireland): Merck Sharp & Dohme Ireland (Human Health) Ltd.
Pelham House, South County Business Park,
Leopardstown, Dublin 18, Ireland
MAH (UK): Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon, Hertfordshire
EN11 9BU United Kingdom
30 mg
MSD
H 3879 (GB/IE/MT)
00000/051007


Batch number and expiry date to be embossed on edge of each blister card
MSD
Turox® 30 mg


TUROX
30 MG
TUROX® 30 mg
Film-coated tablets
etoricoxib
MAH (Ireland): Merck Sharp & Dohme Ireland (Human Health) Ltd.
Pelham House, South County Business Park,
Leopardstown, Dublin 18, Ireland
MAH (UK): Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon, Hertfordshire
EN11 9BU United Kingdom
30 mg
MSD
H 3879 (GB/IE/MT)
00000/051007
MSD
TUROX® 30 mg
Film-coated tablets
etoricoxib
28 Film-Coated Tablets
® Registered trademark of
Merck & Co., Inc., Whitehouse Station, NJ, USA
Each film-coated tablet contains 30 mg etoricoxib.
Also contains Lactose.
(see leaflet for more information).
Oral use.
Use as directed by your doctor
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original package in order to protect from moisture
PL 00 25/0481 PA 00 00/0/0 MA 058/0 0000
Batch No:
Expiry Date:
United Kingdom / Ireland
Malta
POM
5 013945 000000
MSD
TUROX® 30 mg
Film-coated tablets
etoricoxib
30 mg

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Arcoxia, Auxib, Exxiv and Turox 30mg Film-Coated Tablets to Merck Sharp and Dohme (PL 000025/0478-81) on 22nd October 2007. The products are prescription-only medicines.

These were submitted as abridged applications according to Article 8.3 of Directive 2001/83/EC, a full dossier of a known active substance (etoricoxib) submitted as line extensions to existing licences for 60, 90 and 120mg film-coated tablets.

The products contain the active ingredient etoricoxib and are indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis.

Etoricoxib is an orally active, selective COX-2 inhibitor of the non-steroidal anti-inflammatory drug (NSAID) group. It has a unique chemical structure compared with other selective COX-2 inhibitors and is used for its anti-inflammatory and analgesic properties similar to other NSAID. Etoricoxib selectively inhibits COX-2 enzyme and provide pain relief and anti-inflammatory effect to a range of arthritic conditions. The mechanism of action of etoricoxib is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, etoricoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. Caution is required for use in patients with history of gastrointestinal disease and significant risk factor for cardiovascular events.

No new preclinical studies were conducted, which is acceptable given that the application was based on an active substance whose pharmacokinetic, pharmacodynamic and toxicological properties are well-known.

All clinical studies conducted were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Arcoxia 30mg Film-Coated Tablets Auxib 30mg Film-Coated Tablets Exxiv 30mg Film-Coated Tablets Turox 30mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Etoricoxib
Pharmacotherapeutic classification (ATC code)	Anti-inflammatory and antirheumatic products, non-steroids, coxibs (MO1 AH05)
Pharmaceutical form and strength(s)	30mg Film-Coated Tablets
Reference numbers for the Decentralised Procedure	UK/H/0532-5/004/DC
Reference Member State	United Kingdom
Member States concerned	Arcoxia 30mg Film-Coated Tablets (PL 00025/0478): Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain and Sweden. Auxib 30mg Film-Coated Tablets (PL 00025/0479): Austria, Germany, Italy and The Netherlands Exxiv 30mg Film-Coated Tablets (PL 00025/0480): Germany, Italy and Poland Turox 30mg Film-Coated Tablets (PL 00025/0481): Belgium, Finland, France, Greece, Italy and Luxembourg
Marketing Authorisation Number(s)	PL 00025/0478-81
Name and address of the authorisation holder	Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Etoricoxib

Chemical Name: 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

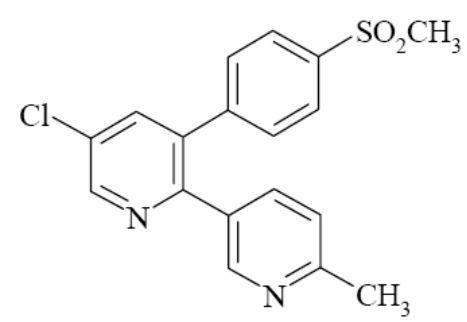
CAS Registry No: 202409-33-4

Molecular Formula: $C_{18}H_{15}ClN_2O_2S$

ATC Code: MO1 AH05

Pharmacotherapeutic Class: Anti-inflammatory and antirheumatic products, non-steroids, coxibs

Structure:



Molecular Weight: 358.84

Appearance: White to pale yellow powder

Solubility: Low solubility in water, solubility increases with decreasing pH.

Polymorphism: Five anhydrous polymorphic forms exist.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance etoricoxib. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

The specifications for the container-closure for active etoricoxib have been provided and are satisfactory. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been provided to support a retest period of 48 months when stored in the proposed packaging. Suitable post approval stability commitments for the active substance have been provided.

P Medicinal Product

Other Ingredients

Other ingredients consists of the pharmaceutical excipients calcium hydrogen phosphate anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, carnauba wax, hypromellose, lactose monohydrate, titanium dioxide, glycerol triacetate, indigo carmine lake, yellow iron oxide (E172) and opadry II green.

All excipients used comply with respective European Pharmacopoiea monographs, with the exception of yellow iron oxide and indigo carmine lake (which are controlled to suitable EEC regulations), and opadry II green (which is controlled to an in-house specification). Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients used contain materials of animal or human origin. The applicant has confirmed that the lactose used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for milk from human consumption.

Pharmaceutical Development

The applicant has provided a suitable product development rationale and data. Dissolution data have been provided showing that the 30mg strength tablets have a comparable dissolution to the already-licensed 120mg tablets.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.

Control of Drug Product

The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

Reference Standards or Materials

Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System

The finished product is packaged in aluminium blisters in pack sizes of 28 tablets.

Stability of the Drug Product

Stability data provided to support a shelf-life of 3 years, with the storage conditions ‘Store in the original package.’

Bioequivalence/Bioavailability

No bioequivalence data are provided and none are required for these applications.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
It is recommended that marketing authorisations are granted for these applications.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of etoricoxib are well-known. The applicant has not provided additional studies and further studies are not required. These applications are for a lower strength tablet to those already granted marketing authorisations.

There are no objections to the approval of licences for Arcoxia/Auxib/Exxiv/Turox 30mg Film-Coated Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
Pharmacodynamics
No new pharmacodynamic data have been provided and none are required for applications of this type.

Pharmacokinetics
No new pharmacokinetic data have been provided and none are required for applications of this type.

EFFICACY
The applicant has conducted new studies to support the efficacy of the proposed 30mg dose of etoricoxib after the marketing authorisation of the 60mg dose for the treatment of osteoarthritis.

Five relevant studies are presented (007, 071, 073, 076 and 077).
Study 007 is a dose-response study comparing etoricoxib 5, 10, 30, 60 and 90 mg with placebo in Part 1 (6 weeks) and etoricoxib 30, 60 and 90 mg with diclofenac 150mg in Part 2 (38 weeks). The patients included were prior NSAID or acetaminophen users with osteoarthritis of the knee who met clinical, radiographic and flare criteria.

Studies 071 and 073 were 12-week studies in prior NSAID or acetaminophen users with osteoarthritis of knee or hip, comparing etoricoxib 30mg with placebo and ibuprofen 2400mg. Studies 076 and 077 had a similar design to 071 and 073 though used celecoxib 200mg as an active control and included a 14-week extension phase in which patients previously on placebo were switched to active treatment. In each study, pain and physical function were assessed as primary endpoints, as per the CPMP Points to Consider Document (CPMP/EWP/784/97); also included as a primary endpoint was the patient's global assessment of disease status. Patients were required to experience a 'flare' in symptoms prior to randomisation.

The CHMP guideline on development of products for symptom-modification in osteoarthritis gives certain recommendations on the design of pivotal studies. These include assessment of efficacy after at least 6-months, the examination of one 'target joint' per study, the choice of primary endpoints and the choice of control group. In conducting a three-arm study assessing both pain and physical function as primary end point, the applicant is in accordance with the latter two of these recommendations. However, the primary assessment of efficacy is after 12 weeks in each pivotal study and patients with either osteoarthritis of the knee or osteoarthritis of the hip are included simultaneously in each study. The "points to consider" document provided also describes that for a general indication in osteoarthritis data in osteoarthritis of the hand should also be provided. No specific study is provided on this point for the 30mg dose.

The majority of the statistical methodology is standard and readily acceptable. One point of contention is the absence of imputation for missing data. The primary efficacy variables were analysed by a 'time-weighted average response over the 12-week period' therefore all patients with follow-up data can contribute to the analysis. However, an exploration of the pattern, timing and reasons for missing data is a standard and vital assessment of any clinical trial and the expected range of sensitivity analyses investigating the influence of missing data has not been conducted. Patient disposition in each study indicated an excess of withdrawals from the placebo arm, predominately due to lack of efficacy. Withdrawals from etoricoxib were no greater than withdrawals from the active control arms. Despite the considerable number of withdrawals from each active treatment group (approximately 10-20%), it might, therefore, be concluded that the estimated effect sizes presented are not, therefore, biased to an important degree in favour of etoricoxib. In summary, withdrawals from etoricoxib and active-control are comparable.

Etoricoxib 30mg is clearly differentiated from placebo in the trials presented. Of greatest concern is determining the optimal posology. As per the 2005 CHMP Article 31 deliberations, and as reflected in the etoricoxib summary of product characteristics, Cox-2 inhibitors should be used at the lowest possible dose and for the shortest possible duration. The benefits of continued treatment should, therefore, be clear. The pivotal studies designs were to give an active treatment or placebo after patients have "flare". The results demonstrated a significant response to the 30mg within 2 weeks. The duration of the studies against placebo was only 12 weeks. There was no sign of "flare" in the placebo limb of the studies and no indication of worsening of symptoms. Because of that, it is difficult to draw any conclusion on the duration of treatment. Therefore, it is reasonable to propose that the response to treatment needs to be reviewed periodically with the aim to keep the duration period to a minimum.

The 30mg has been shown to be superior to placebo, but inferior to the 60mg in efficacy. The study 007 is the only study in which comparison of efficacy between the doses 60mg and 30mg was carried out. The 60mg dose was significantly superior in efficacy to the 30mg. No comparison of safety was carried out. The numerically greater efficacy observed for etoricoxib 60 and 90mg versus etoricoxib 30mg was also generally maintained over the entire treatment period.

Clinically meaningful effects were predefined as differences from placebo of 0.5 points on a 0- to 4-point Likert scale and -10 mm on a 0- to 100-mm VAS [Ref. 5.3.5.4: R12]. The 60mg dose was the lowest dose to provide clinically meaningful treatment effects for all three primary endpoints. Etoricoxib 60 mg also provided significantly greater treatment effects across the three primary endpoints compared with etoricoxib 30 mg, the next lowest dose. In

addition, when the Patients Global Assessment of Response to Therapy was further evaluated, a dose-related trend was observed with 48% and 70% of patients in the 30mg and 60mg etoricoxib groups, respectively, having a good to excellent response to therapy. These data clearly show that compared to etoricoxib 30mg, the 60mg dose provides additional efficacy across multiple measures of the signs and symptoms of OA. Therefore, based on the evidence from the studies submitted by the applicant, a periodic assessment of the treatment should be stated to give the health professionals and patients a clear direction.

Table 2.7.3-OA: 12

Analysis of Primary Endpoints :Comparison Between Treatment Groups
Mean Change From Baseline (Flare/Randomization Visit)
Average Response Phase IIb OA (Protocol 007, Part I)

Comparisons Between Treatment Groups	Difference in LS Mean	95% CI for LS Mean Difference	p-Value
WOMAC Pain Subscale (0- to 100-mm VAS)			
With Placebo†			
60 mg vs. Placebo	-22.29	(-28.91, -15.68)	<0.001
30 mg vs. Placebo	-13.86	(-20.55, -7.17)	<0.001
Between MK-0663 Doses‡			
60 mg vs. 30 mg	-8.44	(-14.00, -2.87)	0.003
Patient Global Assessment of Response to Therapy (0- to 4-point Likert Scale)			
With Placebo†			
60 mg vs. Placebo	-1.21	(-1.51, -0.90)	<0.001
30 mg vs. Placebo	-0.66	(-0.97, -0.35)	<0.001
Between MK-0663 Doses‡			
60 mg vs. 30 mg	-0.55	(-0.81, -0.29)	<0.001
Investigator Global Assessment of Disease Status (0- to 4-point Likert Scale)			
With Placebo†			
60 mg vs. Placebo	-0.83	(-1.09, -0.58)	<0.001
30 mg vs. Placebo	-0.45	(-0.70, -0.20)	<0.001
Between MK-0663 Doses‡			
60 mg vs. 30 mg	-0.38	(-0.60, -0.17)	<0.001

† Based on Tukey-Ciminera-Heyse trend test.
‡ Based on pairwise t-tests and error variance from analysis of covariance.
LS Mean=Least-squares mean.
VAS=Visual analog scale.
CI=Confidence interval.

[Ref. 5.3.5.4: R12]

Taking into account of the clinical data provided, the wording for Sections 4.1, 4.2 and 5.1 of the summary of product characteristics is acceptable:

SAFETY
No new safety issues have been identified.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are satisfactory and consistent with those for the other strengths of this product that have previously been granted licences.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
Overall, there are no clinical objections to the grant of marketing authorisations for these applications. No new or unexpected safety concerns arise from these applications. The SPC, PIL and packaging are satisfactory and consistent with those for the other strengths of this product that have previously been granted licences.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Arcoxia, Auxib, Exxiv and Turox 30mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy data provided support the use of this strength of etoricoxib in the proposed indications.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the other strengths of this product that have previously been granted licences.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with etoricoxib is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
20/09/2007	II	To submit the readability test of the PIL. To also update sections 1 (Name of the medicinal products), 2 (Qualitative and quantitative composition), 3 (Pharmaceutical form), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties), 6.1 (List of excipients), 6.4 (Special precautions for storage) and 6.5 (Nature and content of container) of the SPC and also labelling in order to harmonise them across the different strengths.	Granted 06/12/2007