APPPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ARCOXIA® 30 mg Tablet

ARCOXIA® 60 mg Tablet

ARCOXIA® 90 mg Tablet

ARCOXIA® 120 mg Tablet

COMPOSITION

ARCOXIA 30 mg: Each tablet contains 30 mg of etoricoxib.

ARCOXIA 60 mg: Each tablet contains 60 mg of etoricoxib.

ARCOXIA 90 mg: Each tablet contains 90 mg of etoricoxib.

ARCOXIA 120 mg: Each tablet contains 120 mg of etoricoxib.

ARCOXIA Tablets contain the following inactive ingredients:

Calcium hydrogen phosphate anhydrous USP, carnauba wax NF, croscarmellose sodium NF, lactose monohydrate, magnesium stearate NF and microcrystalline cellulose NF.

In addition:

30 mg tablets contain Opadry II Blue-green 39K11526.

60 mg tablets contain Opadry II Green 39K11520.

90 mg tablets contain Opadry II White 39K18305.

120 mg tablets contain Opadry II Green 39K11529.

All ARCOXIA Tablets contain sugar (lactose).

CATEGORY AND CLASS

A.3.1 Anti-Rheumatics (Anti-inflammatory Agents)

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. Etoricoxib is an orally active, selective cyclo-oxygenase-2 (COX-2) inhibitor.

Pharmacokinetic Properties

Absorption

Orally administered etoricoxib is absorbed with a mean oral bioavailability of approximately 100 %. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3,6 mcg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean AUC_{0-24h} was 37,8 mcg/h/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. In clinical trials, etoricoxib was administered without regard to food.

The pharmacokinetics of etoricoxib in 12 healthy subjects (40 to 65 years of age) were similar (comparable AUC, C_{max} within approximately 20 %) when administered alone or with a magnesium/aluminium hydroxide antacid or a calcium carbonate antacid (approximately 50 mEq acid-neutralising capacity).

Distribution

In humans, etoricoxib is approximately 92 % bound to plasma protein over the range of concentrations of 0,05 mcg/mL to 5 mcg/mL. The volume of distribution at steady state (V_{dss}) is approximately 120 litres.

Etoricoxib crosses the placenta and the blood-brain barrier.

Metabolism

Etoricoxib is extensively metabolised in the liver with less than 1 % of a dose recovered in urine as the parent compound. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by cytochrome P450 (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.

Elimination

Following administration of a single 25 mg radiolabelled intravenous dose of etoricoxib to healthy subjects, 70 % of radio-activity was recovered in urine and 20 % in faeces, mostly as metabolites. Plasma and urine were collected for 7 days and stool collected for 10 days post-dose. Less than 2 % was recovered as unchanged medicine.

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 an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 mL/min.

Elderly

Pharmacokinetics in the elderly (65 years of age and older) with normal renal function are similar to those in the young. In clinical studies, a higher incidence of adverse experiences was seen in older patients compared to younger patients (see DOSAGE AND DIRECTIONS FOR USE).

Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) administered etoricoxib 60 mg once daily (for 21 days) had an approximately 16 % higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) administered etoricoxib 60 mg **every other day** (for 21 days) had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily. There are no available clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9) (see CONTRAINDICATIONS and DOSAGE AND DIRECTIONS FOR USE, Hepatic Insufficiency).

Renal Insufficiency

The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance of less than 30 mL/min) 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).

Paediatric Patients

The pharmacokinetics of etoricoxib in paediatric patients (less than 12 years of age) have not been studied.

In a pharmacokinetic study (N=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 kg to 60 kg given etoricoxib 60 mg once daily and in adolescents greater than 60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and efficacy of etoricoxib

in paediatric and adolescent patients have not been established (see CONTRAINDICATIONS).

INDICATIONS

ARCOXIA is indicated for:

- Symptomatic relief of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Short term relief of acute pain, treatment limited to a maximum period of 8 days
- Treatment of primary dysmenorrhoea
- Treatment of moderate to severe acute post-operative pain associated with dental surgery

The decision to prescribe ARCOXIA should be based on an assessment of the individual patient's overall risks (see WARNINGS AND SPECIAL PRECAUTIONS).

CONTRAINDICATIONS

ARCOXIA is contraindicated in the following:

- known hypersensitivity to etoricoxib or to any of the excipients of ARCOXIA
- patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioedema or urticaria following the administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) including ARCOXIA
- active peptic ulceration or active gastrointestinal (GI) bleeding
- severe hepatic dysfunction (Child-Pugh score greater than 9 or serum albumin less than 25 g/L)
- severe renal impairment (estimated creatinine clearance less than 30 mL/min)
- uncontrolled hypertension
- pregnancy and lactation
- children and adolescents under 16 years of age
- inflammatory bowel disease
- congestive heart failure (NYHA II – IV), established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see WARNINGS AND SPECIAL PRECAUTIONS)
- perioperative analgesia in the setting of coronary artery bypass surgery (CABG)
- concomitant administration with ARCOXIA may lead to toxic blood concentrations of lithium (see INTERACTIONS)

- digoxin: there was an approximate increase of 33 % in digoxin C_{max} in healthy volunteers (see INTERACTIONS)

WARNINGS AND SPECIAL PRECAUTIONS

ARCOXIA may predispose patients to cardiovascular events, gastrointestinal events or cutaneous reactions which may be fatal.

Long-term administration of NSAIDs such as ARCOXIA, has resulted in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of ARCOXIA 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 liver cirrhosis.

Monitoring of renal and hepatic function in such patients is indicated. Caution should be used when initiating treatment with ARCOXIA in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCOXIA.

Due to inhibition of prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking ARCOXIA. Caution should be exercised in patients with 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 ARCOXIA should be taken. Patients with pre-existing congestive heart failure or hypertension should be closely monitored. All non-steroidal anti-inflammatory drugs (NSAIDs), including ARCOXIA, can be associated with new onset or recurrent congestive heart failure (see SIDE EFFECTS).

ARCOXIA may be associated with more frequent and severe hypertension than other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, special attention should be paid to blood pressure monitoring during treatment with ARCOXIA. If blood pressure rises significantly, alternative treatment should be considered.

Clinical trials suggest that the selective COX-2 inhibitor class of medicines, such as ARCOXIA, are associated with an increased risk of arterial thrombotic events (especially myocardial infarction (MI) and stroke). As the cardiovascular risks 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.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus or smoking) should only be treated with ARCOXIA after careful consideration.

ARCOXIA is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. Because ARCOXIA does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued and if indicated, should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events. There is no evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with ARCOXIA.

Concomitant administration of low-dose aspirin with ARCOXIA increases the rate of gastrointestinal adverse effects (gastrointestinal ulceration, bleeding or perforation) compared to use of ARCOXIA alone.

For more details, refer to section on INTERACTIONS**,** Aspirin**.**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with the use of selective COX-2 inhibitors such as ARCOXIA during post-marketing surveillance (see SIDE EFFECTS). Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving ARCOXIA (see SIDE EFFECTS).

Selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any allergy. ARCOXIA should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

When using ARCOXIA in the elderly and in patients with renal, hepatic or cardiac dysfunction, medically appropriate supervision should be intensified. If these patients show deterioration during treatment, appropriate measures should be taken, including discontinuation of ARCOXIA.

Gastrointestinal Effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in a fatal outcome, have occurred in patients treated with ARCOXIA.

Caution is advised with treatment of patients at risk of developing a gastrointestinal complication with ARCOXIA: the elderly, patients using any other NSAIDs or aspirin concomitantly or patients with a prior history of gastrointestinal disease, such as perforation, ulceration and GI bleeding.

There is an increase in risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when ARCOXIA is taken concomitantly with aspirin (even at low doses).

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately 3 or more times the upper limit of normal) have been reported in approximately 1 % of patients in clinical trials treated for up to 1 year with ARCOXIA 60 mg and 90 mg daily.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (3 times the upper limit of normal) are detected, ARCOXIA should be discontinued.

ARCOXIA may mask fever and other signs of inflammation or infection.

The use of ARCOXIA is not recommended in fertile women attempting to conceive.

Effects on Ability to Drive and Use Machinery

Patients who experience dizziness, vertigo or somnolence while taking ARCOXIA should refrain from driving or operating machinery.

Lactose

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ARCOXIA.

INTERACTIONS

Ciclosporin and tacrolimus: Co-administration of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when ARCOXIA and either of these medicines is used in combination.

Warfarin: In subjects stabilised on chronic warfarin therapy, the administration of ARCOXIA 120 mg daily was associated with an approximate 13 % increase in prothrombin time International Normalised Ratio (INR). Standard monitoring of INR values should be conducted when therapy with ARCOXIA is initiated or changed in patients receiving warfarin or similar agents.

Rifampicin: Co-administration of ARCOXIA with rifampicin, a potent inducer of hepatic metabolism, produced a 65 % decrease in etoricoxib plasma area under the curve (AUC). This interaction should be considered when ARCOXIA is co-administered with rifampicin.

Methotrexate: Two studies investigated the effects of ARCOXIA 60 mg, 90 mg or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7,5 mg to 20 mg for rheumatoid arthritis. ARCOXIA at 60 mg and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study,

ARCOXIA 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, ARCOXIA 120 mg increased methotrexate plasma concentrations by 28 % (as measured by AUC) and reduced renal clearance of methotrexate by 13 %. Monitoring for methotrexate-related toxicity should be considered when ARCOXIA at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs): Reports suggest that non-selective NSAIDs and COX-2 selective inhibitors such as ARCOXIA may diminish the antihypertensive effect of diuretics, ACE inhibitors and ARBs. This interaction should be given consideration in patients taking ARCOXIA concomitantly with these products.

In patients with compromised renal function (e.g. elderly patients or patients who are volume depleted, including those on diuretic therapy) who are being treated with ARCOXIA, the co-administration of ACE inhibitors or ARBs may result in a further deterioration of renal function, including possible acute renal failure. These effects may be reversible. Therefore, the combination should be administered with caution, especially in the elderly and in patients with impaired renal function. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Lithium: ARCOXIA may increase plasma lithium levels. This interaction should be given consideration in patients taking ARCOXIA concomitantly with lithium.

Aspirin: In a study in healthy subjects, at steady state, ARCOXIA 120 mg once daily had no effect on the anti-platelet activity of aspirin (81 mg once daily). ARCOXIA may be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low-dose aspirin). However, concomitant administration of low-dose aspirin with ARCOXIA increases the rate of gastrointestinal adverse effects (gastrointestinal ulceration, bleeding or perforation) compared to use of ARCOXIA alone. Concomitant administration of ARCOXIA with doses of aspirin *above* those for cardiovascular prophylaxis or with other NSAIDs should be avoided (see WARNINGS AND SPECIAL PRECAUTIONS).

Oral Contraceptives: ARCOXIA 60 mg given concomitantly with an oral contraceptive containing 35 mcg ethinyl oestradiol (EE) and 0,5 mg to 1 mg norethindrone (NET) for 21 days increased the steady state $AUC_{0\text{-}24h}$ of EE by 37 %. ARCOXIA 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24h}$ of EE by 50 % to 60 %; however, NET concentrations generally did not increase to a clinically relevant degree. This increase in EE concentration should be considered when selecting an appropriate oral contraceptive for use with ARCOXIA. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thromboembolic events in women at risk).

Furosemide: Clinical studies have shown that NSAIDs such as ARCOXIA reduce the natriuretic and antihypertensive effects of furosemide and thiazides in patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Hormone Replacement Therapy: Administration of ARCOXIA 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg conjugated oestrogens for 28 days), increased the mean steady state $AUC_{0\text{-}24h}$ of unconjugated oestrone (41 %), equilin (76 %), and 17-beta-oestradiol (22 %). The effects of the recommended chronic doses of ARCOXIA (30 mg, 60 mg and 90 mg) have not been studied. The effects of ARCOXIA 120 mg on the exposure ($AUC_{0\text{-}24h}$) to these oestrogenic components of conjugated oestrogens were less than half of those observed when conjugated oestrogens were administered alone, and the dose was increased from 0,625 mg to 1,25 mg. The clinical significance of these increases is unknown, and higher doses of conjugated oestrogens were not studied in combination with ARCOXIA. These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with ARCOXIA because the increase in oestrogen exposure might increase the risk of adverse events associated with hormone replacement therapy (HRT).

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

Digoxin:

ARCOXIA 120 mg once daily for 10 days in healthy volunteers did not alter the steady-state plasma AUC_{0-24h} or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33 %) (see CONTRAINDICATIONS).

Other:

In interaction studies ARCOXIA did not have clinically significant effects on the pharmacokinetics of prednisone/prednisolone.

Antacids did not have clinically significant effects on the pharmacokinetics of ARCOXIA.

Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any clinically significant effect on the single-dose pharmacokinetics of 60 mg ARCOXIA (43 % increase in AUC).

Although additional specific interaction studies were not performed in clinical studies, ARCOXIA was used concomitantly with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established. ARCOXIA is contraindicated in pregnancy and lactation (See CONTRAINDICATIONS).

The use of non-steroidal anti-inflammatory drugs such as ARCOXIA during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Fertility

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

DOSAGE AND DIRECTIONS FOR USE

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

Osteoarthritis (OA):

The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, the dose may be increased to 60 mg once daily.

Rheumatoid Arthritis (RA):

The recommended dose is 90 mg once daily. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

Ankylosing Spondylitis (AS):

The recommended dose is 90 mg once daily. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

Short term relief of Acute Pain:

The recommended dose is 90 or 120 mg once daily, limited to a maximum of 8 days treatment.

Acute Gouty Arthritis:

The recommended dose is 120 mg once daily, limited to a maximum of 8 days treatment.

Primary Dysmenorrhoea:

The recommended dose is 120 mg once daily.

Post-operative Dental Pain:

The recommended dose is 90 mg once daily.

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

The dose for OA should not exceed 60 mg daily.

The dose for RA should not exceed 90 mg daily.

The dose for ankylosing spondylitis should not exceed 90 mg daily.

The dose for acute gout should not exceed 120 mg daily.

The dose for acute pain and primary dysmenorrhoea should not exceed 120 mg daily.

The dose for post-operative acute dental surgery pain should not exceed 90 mg daily.

As the cardiovascular risks of ARCOXIA 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 (See WARNINGS AND SPECIAL PRECAUTIONS).

Elderly

No dosage adjustment in ARCOXIA is necessary for the elderly although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular adverse effects (see WARNINGS AND SPECIAL PRECAUTIONS, SIDE EFFECTS and SIDE EFFECTS, Post-Marketing Experience).

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), a dose of 60 mg once daily should not be exceeded.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the dose should be reduced; a dose of 60 mg *every other day* should not be exceeded, and administration of ARCOXIA 30 mg once daily can also be considered].

Clinical experience is limited particularly in patients with moderate hepatic dysfunction. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9), therefore the use of ARCOXIA is contraindicated in these patients (see CONTRAINDICATIONS; PHARMACOLOGICAL ACTION, Pharmacokinetic Properties).

Renal Insufficiency

No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance greater than or equal to 30 mL/min). The use of ARCOXIA in patients with creatinine clearance less than 30 mL/min is contraindicated. (See CONTRAINDICATIONS).

SIDE EFFECTS

Clinical studies

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with ARCOXIA for one year or longer.

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000) including isolated reports.

Infections and infestations:

Very common: post-dental extraction alveolar osteitis (dry socket)

Uncommon: gastroenteritis, upper respiratory infection, urinary tract infection

Metabolism and nutrition disorders:

Common: oedema/fluid retention

Uncommon: appetite increase or decrease, weight gain

Psychiatric disorders:

Uncommon: anxiety, depression, mental acuity decreased

Nervous system disorder:

Common: dizziness, headache

Uncommon: insomnia, paraesthaesia/hypaesthesia

Eye disorders:

Uncommon: conjunctivitis

Ear and labyrinth disorders:

Uncommon: tinnitus, vertigo

Cardiac disorders:

Common: palpitations

Uncommon: atrial fibrillation, congestive heart failure, non-specific ECG changes, myocardial infarction*

Very rare: angina

Frequency unknown: aggravated hypertension, dysrhythmia and tachycardia have been reported regardless of causality

Vascular disorders:

Common: hypertension

Uncommon: flushing, stroke*, transient ischaemic attack

Respiratory, thoracic and mediastinal disorders:

Uncommon: cough, dyspnoea, epistaxis

Gastrointestinal disorders:

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

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

Skin and subcutaneous tissue disorders:

Common: ecchymosis

Uncommon: facial oedema, pruritus, rash, erythema

Musculoskeletal, connective tissue and bone disorders:

Uncommon: muscular cramp/spasm, musculoskeletal pain/stiffness

Renal and urinary disorders:

Uncommon: proteinuria

General disorders and administration site conditions:

* 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).

Common: asthenia/fatigue, flu-like disease

Uncommon: chest pain

Investigations:

Common: increased ALT, increased AST.

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

Rare: decreased blood sodium.

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for ARCOXIA: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure, jaundice and pancreatitis.

In clinical studies, a higher incidence of adverse experiences was seen in older patients compared to younger patients.

Post-Marketing Experience:

The following adverse reactions have been reported in post-marketing experience:

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorder: hypersensitivity reactions including angioedema, anaphylactic/ anaphylactoid reactions including shock

Psychiatric disorders: confusion, hallucinations, depression, restlessness

Nervous system disorder: dysgeusia, somnolence

Eye disorders: blurred vision

Cardiac disorders: congestive heart failure, palpitations, angina, dysrhythmia

Vascular disorders: hypertensive crisis

Respiratory, thoracic and mediastinal disorders: bronchospasm

Gastrointestinal disorders: abdominal pain, oral ulcers, peptic ulcers including gastrointestinal perforation and bleeding (mainly in the elderly), vomiting, diarrhoea

Hepatobiliary disorders: hepatitis, jaundice, hepatic failure

Skin and subcutaneous tissue disorders: angioedema, pruritus, erythema, rash urticaria, Stevens Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption

Renal and urinary disorders: renal insufficiency, including renal failure, (see PHARMACOLOGICAL ACTION Pharmacokinetic Properties, Renal Insufficiency).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The most frequently observed adverse experiences were gastrointestinal events and renovascular events.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

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

IDENTIFICATION

ARCOXIA 30 mg: A blue-green, apple-shape, biconvex, film-coated tablet with '101' debossed on one side and ‘ACX 30’ on the other side.

ARCOXIA 60 mg: A dark green, apple shape, biconvex, film-coated tablet with '200' debossed on one side and 'ARCOXIA 60' on the other side.

ARCOXIA 90 mg: A white, apple shape, biconvex, film-coated tablet with '202' debossed on one side and 'ARCOXIA 90' on the other side.

ARCOXIA 120 mg: A pale green, apple shape, biconvex, film-coated tablet with '204' debossed on one side and 'ARCOXIA 120' on the other side.

PRESENTATION

ARCOXIA 30 mg and 60 mg tablets are available in aluminium blister packs of 28.

ARCOXIA 90 mg and 120 mg tablets are available in aluminium blister packs of 7 and 28.

STORAGE INSTRUCTIONS

Store at or below 30 ºC. Store in the original package.

Store all medicines out of reach of children.

REGISTRATION NUMBER

ARCOXIA 30 mg: 44/3.1/0063

ARCOXIA 60 mg: 37/3.1/0399

ARCOXIA 90 mg: 37/3.1/0400

ARCOXIA 120 mg: 37/3.1/0401

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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