ARCONA

20240304AA

(Etoricoxib Film-coated Tablet)

1. Product name

ARCONA Etoricoxib 90 mg Film-coated Tablet

ARCONA Etoricoxib 120 mg Film-coated Tablet

2. Name and Strength of active ingredient

ARCONA (90 mg): Each 1 film coated tablet contains Etoricoxib 90 mg

ARCONA (120 mg): Each 1 film coated tablet contains Etoricoxib 120 mg

3. Product description

ARCONA (90 mg): White, round shaped, biconvex, film-coated tablet, engraved with 'M' on one side of break line and 'H' on the other side, the reverse face engraved with 'N'.The tablet is not meant to be split.

ARCONA (120 mg): White, round shaped, biconvex, film-coated tablet, engraved with 'M' on one side of break line and 'H' on the other side, the reverse face engraved with 'XII'.The tablet is not meant to be split.

4. Pharmacodynamics/Pharmacokinetics

Absorption

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

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean Cmax = 3.6 mcg/mL) was observed at approximately 1 hour (Tmax) after administration to fasted adults. The geometric mean AUC0-24hr was 37.8 mcg•hr/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 were similar (comparable AUC, Cmax within approximately 20%) when administered alone, with a magnesium/aluminium hydroxide antacid, or a calcium carbonate antacid (approximately 50 mEq acid- neutralizing capacity).

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 mcg/mL. The volume of distribution at steady state (Vdss) is approximately 120 L in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by cytochrome P450 (CYP) enzymes.

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

5. Indication

ARCONA is non-steroidal anti-inflammatory drug (NSAIDs) in a member of a class called coxibs.

ARCONA is a highly selective inhibitor of cyclooxygenase-2 (COX-2).

ARCONA is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Chronic low back pain (30 mg and 60 mg only)
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

6. Recommended Dose/Mode of Administration

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

ARCONA is available at the strengths of 90 mg and 120 mg only and may not be able to deliver all the dosing recommendations mentioned below. In such cases, other approved strengths should be used.

Osteoarthritis

The recommended dose is 30 mg or 60 mg once daily.

Rheumatoid Arthritis

The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Ankylosing Spondylitis

The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Chronic low back pain

The recommended dose is 60 mg once daily.

Acute Pain

In the following acute painful conditions, ARCONA should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment:

- Acute Gouty Arthritis : The recommended dose is 120 mg once daily.
- Primary Dysmenorrhea : The recommended dose is 120 mg once daily.
- Minor Dental Procedures : 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 of chronic low back pain should not exceed 60mg daily.
- The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.
- The dose for minor dental procedures should not exceed 90 mg daily.

As the cardiovascular risks of selective COX-2 inhibitors 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 Precautions).

Elderly, Gender, Race

No dosage adjustment in ARCONA is necessary for the elderly or based on gender or race.

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60 mg every other day should not be exceeded, administration of 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (see Precautions).

Renal Insufficiency

In patients with advanced renal disease (creatinine clearance < 30 mL/min), treatment with ARCONA is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥ 30 mL/min). (see Precautions).

7. Contraindications

ARCONA is contraindicated in patients with:

- Hypersensitivity to any component of this product.
- Congestive heart failure (NYHA II-IV).
- Patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke).
- Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty).
- Patients with hypertension (high blood pressure) whose blood pressure is not under control
- Pregnancy

8. Warning and Precautions

- Warning

Risk of GI ulceration, Bleeding and Periforation with NSAIDs

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

- Precautions

Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment. 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, smoking, peripheral arterial disease) should only be treated with etoricoxib after careful consideration.

Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses). The relative difference in gastrointestinal safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been adequately evaluated in long-term clinical trials.

In patients with advanced renal disease, treatment with ARCONA is not recommended. Clinical experience in patients with estimated creatinine clearance of <30 mL/min is very limited. If therapy with ARCONA must be initiated in such patients, close monitoring of the patient's renal function is advisable.

Long-term administration of NSAIDs 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

ARCONA 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.

Caution should be used when initiating treatment with ARCONA in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCONA.

As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking ARCONA. The possibility of fluid retention, edema or hypertension should be taken into consideration when ARCONA is used in patients with pre-existing edema, hypertension, or heart failure. All Nonsteroidal Antiinflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. 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.

Physicians should be aware that individual patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment.

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.

A 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 (three times the upper limit of normal) are detected, ARCONA should be discontinued.

ARCONA should be used with caution in patients who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Since the pathophysiology of these reactions is unknown, physicians should weigh the potential benefits of prescribing ARCONA versus the potential risks.

When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.

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. These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

ARCONA may mask fever, which is a sign of infection. The physician should be aware of this when using ARCONA in patients being treated for infection.

9. Interactions with Other Medication

Warfarin: Standard monitoring of INR values should be conducted when therapy with ARCONA is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

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

Methotrexate: Monitoring for methotrexate-related toxicity should be considered when ARCONA at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Antagonists (AIIAs): Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of diuretics, ACE inhibitors and AIIAs. This interaction should be given consideration in patients taking ARCONA concomitantly with these products.

In some 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 non- steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors or AIIAs may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Lithium: Reports suggest that non-selective NSAIDs and selective COX-2 inhibitors may increase plasma lithium levels. This interaction should be given consideration in patients taking ARCONA concomitantly with lithium.

Aspirin: ARCONA can be used concomitantly with low-dose aspirin at doses for cardiovascular prophylaxis. At steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily). However, concomitant administration of low- dose aspirin with ARCONA increases the rate of GI ulceration or other complications compared to use of ARCONA alone.

Oral Contraceptives: This increase in ethinyl estradiol (EE) concentration should be considered when selecting 24hr an appropriate oral contraceptive for use with ARCONA. 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: This increase in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with ARCONA.

Antacids and ketoconazole (a potent inhibitor of CYP3A4) did not have clinically important effects on the pharmacokinetics of ARCONA.

Other: ARCONA did not have clinically important effects on the pharmacokinetics of prednisone/ prednisolone or digoxin.

10. Pregnancy and Lactation

Contraindicated in pregnancy. Discontinue nursing or discontinue the drug because etoricoxib is excreted in the milk of lactating rats.

11. Undesirable Effect

Cardiovascular: Edema, hypertension, palpitation

Central nervous system: Dizziness, fatigue, headache

Dermatologic: Bruising

Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, flatulence, heartburn, nausea

Hepatic: ALT increased, AST increased

Neuromuscular & skeletal: Weakness

Miscellaneous: Alveolar osteitis, flu-like syndrome

12. OVERDOSAGE

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. Etoricoxib is not dialyzable by hemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis

13. Storage condition

Store below 30°C

14. Dosage form and Packaging available

ARCONA (90 mg):

10's packed in aluminium-aluminium blister packed in the paper box; 10 aluminium-aluminium blister. (Shelf life : 36 months)

ARCONA (120 mg):

10's packed in aluminium strip and packed in the paper box; 3 aluminium strip. (Shelf life : 36 months)

15. Name and Address of manufacturer

M & H MANUFACTURING CO., LTD.

41 Sukhumvit Road, Paknam, Muang, Samutprakarn, 10270, Thailand

16. Date of revision of package insert

October 2024