APPROVED PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

RAYZON® 40 mg IV/IM (Powder and Solvent for Solution for Injection)

COMPOSITION:

RAYZON 40 mg IV/IM: Each 5 ml vial contains 40 mg parecoxib (present as 42,36 mg lyophilised parecoxib sodium) for reconstitution. After reconstitution with 2 ml Sodium Chloride Intravenous Infusion (0,9 % w/v) BP, the final concentration of parecoxib is 20 mg/ml.

When reconstituted in sodium chloride solution (0,9 % w/v), RAYZON Injection contains approximately 0,44 mmol/L of sodium per 40 mg vial.

The other ingredients in RAYZON injection include dibasic sodium phosphate heptahydrate. Phosphoric acid and/or sodium hydroxide may have been added for pH adjustment.

PHARMACOLOGICAL CLASSIFICATION:

A 2.9 Other Analgesics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Parecoxib sodium is an inactive prodrug for valdecoxib. Following injection, parecoxib is rapidly hydrolysed to valdecoxib, which is active in animal models of prostaglandin-dependent pain, inflammation and fever.

The mechanism of action of valdecoxib is predominantly by inhibition of COX-2-mediated prostaglandin synthesis.

At therapeutic doses, valdecoxib is a specific COX-2 inhibitor and does not inhibit COX-1.

In animal models, the analgesic activity of valdecoxib is not reversible by naloxone.

Pharmacokinetic properties:

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacological moiety, by enzymatic hydrolysis in the liver.

Absorption:

Exposure of valdecoxib following single doses of parecoxib injection, as measured by both the area under the plasma concentration vs. time curve (AUC) and peak concentration (C_{max}), is approximately linear in the range of clinical doses. AUC and C_{max} following twice a day (BID) administration of valdecoxib is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with BID dosing.

Following single IV and IM doses of parecoxib sodium 20 mg, C_{max} of valdecoxib is achieved at approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C_{max} following IV and IM administration.

Distribution:

The volume of distribution of valdecoxib after its IV administration is approximately 55 L (greater than total body water). Plasma protein binding is approximately 98 % over the concentration range achieved with the highest recommended dose, 80 mg/day. Valdecoxib, but not parecoxib, is extensively partitioned into erythrocytes.

Metabolism:

Parecoxib is rapidly and almost completely converted to valdecoxib *in vivo* with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P450 CYP3A4 and CYP2C9 isoenzymes and CYP-independent glucuronidation of the sulphonamide moiety.

A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10 % of the concentration of valdecoxib; but because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium. The valdecoxib metabolite undergoes extensive metabolism, with less than 5 % of the dose excreted in urine and faeces.

Elimination:

Valdecoxib is eliminated via hepatic metabolism with less than 5 % unchanged medicine recovered in the urine. No unchanged parecoxib is detected in urine and only trace amounts in the faeces. About

70 % of the dose is excreted in the urine as inactive metabolites. Plasma clearance (CL_p) for valdecoxib is about 6 L/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life ($t_{1/2}$) of valdecoxib is about 8 hours.

Elderly subjects:

In healthy elderly subjects, the apparent oral clearance of valdecoxib was reduced, resulting in an approximately 40 % higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted for body weight, steady state plasma exposure of valdecoxib was 16 % higher in elderly females compared to elderly males.

Renal impairment:

In patients with varying degrees of renal impairment administered 20 mg IV parecoxib injection as a single dose, parecoxib was rapidly cleared from plasma. Because renal elimination of valdecoxib is not important to its disposition, no changes in valdecoxib clearance were found even in patients with renal impairment. Dosages of more than 20 mg have not been studied in renal impairment. Therefore, on the basis of pharmacokinetics, dosing adjustment in patients with mild to moderate impaired renal function is not necessary.

Hepatic impairment:

Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh scale 7 – 9), treatment should be initiated with half the usual recommended dose of parecoxib injection and the maximum daily dose should be reduced to 40 mg since valdecoxib exposures were more than doubled (130 %) in these patients. Patients with severe hepatic impairment have not been studied and therefore the use of parecoxib injection in patients with severe hepatic impairment is not recommended.

INDICATIONS:

For the short term management of post-operative pain in patients who need parenteral therapy and for when a similar benefit could not be obtained from oral therapy. It is reminded that patients be transferred to alternative oral therapy as soon as clinically indicated.

RAYZON is also indicated for the reduction of post-operative opioid use in patients who have undergone hip replacement surgery, for up to 48 hours.

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any other ingredient of the product.

History of hypersensitivity to sulphonamides.

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

Severe impairment of hepatic function.

Severe renal impairment.

Post- and peri-operative analgesia in the setting of coronary artery bypass surgery (CABG).

Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.

Pregnancy and lactation.

Children younger than 18 years.

WARNINGS AND SPECIAL PRECAUTIONS:

RAYZON may predispose to cardiovascular events, cerebrovascular events, gastrointestinal events or cutaneous reactions which may be fatal.

Cardiovascular effects:

RAYZON has been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy been associated with increased risk.

Two separate studies in coronary artery bypass graft (CABG) surgery showed that patients receiving RAYZON for a minimum of 3 days followed by valdecoxib (the active metabolite of parecoxib) for 7 – 14 days, had increased incidence of cardiovascular/thromboembolic events (e.g. myocardial infarction and cerebrovascular accident) compared to those receiving placebo. The risk is associated with higher doses and prolonged duration of treatment (see CONTRAINDICATIONS).

Caution is advised when RAYZON is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia.

Gastrointestinal (GI) effects:

Upper gastrointestinal (GI) perforations, ulcers, or bleeds have occurred in patients treated with RAYZON. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a history of, or active, GI disease, such as ulceration, bleeding, or inflammatory conditions.

Skin effects:

Serious skin reactions which may be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in post-marketing experience with RAYZON. RAYZON Injection should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Because of its lack of platelet effects, RAYZON is not a substitute for aspirin for cardiovascular prophylaxis.

Concomitant use of RAYZON with other anti-coagulant medicines may increase the risk of intra- and post-operative bleeding.

Renal and hepatic effects:

RAYZON Injection should be used with caution in patients with severe renal impairment (creatinine clearance < 30 ml/min) or moderate hepatic impairment (Child-Pugh scale 7 – 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh scale > 9) therefore RAYZON Injection is not recommended for use in these patients.

Caution should be used when initiating treatment with RAYZON Injection in patients with any form of dehydration. It is advisable to rehydrate patients first and then start therapy with RAYZON Injection.

Fluid retention and oedema:

Due to inhibition of prostaglandin synthesis, fluid retention and oedema may occur in patients taking RAYZON; therefore RAYZON should not be used in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Anaphylactoid reactions:

Hypersensitivity reactions such as anaphylaxis and angioedema have been reported in post-marketing experience with valdecoxib and cannot be ruled out for RAYZON Injection. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in post marketing experience with RAYZON. RAYZON Injection should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

General:

RAYZON Injection may mask fever. In addition, caution should be exercised with respect to monitoring the incision for signs of infection in patients receiving RAYZON Injection.

Upper gastrointestinal perforations, ulcers or bleeds (PUBs) have occurred in patients treated with RAYZON Injection; therefore caution should be taken in patients with a history of PUBs.

Safety and efficacy of RAYZON injection have not been established for periods of use exceeding 96 hours.

INTERACTIONS:

General:

In vitro studies with human hepatic microsomal systems showed no significant inhibitory effects on CYP3A4, 2D6, 2E1, and 1A2 isoforms by RAYZON or valdecoxib. Weak inhibitory activity was found for 2C9 and 2C19 isozymes.

RAYZON is rapidly hydrolysed to the active substance valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via cytochrome P450 CYP3A4 and 2C9 isozymes. Glucuronidation is a further route of metabolism. The alternate CYP-mediated and non-CYP-mediated metabolic pathways may reduce the likelihood of individuals with genetic polymorphisms having substantially higher plasma concentrations due to impaired metabolism.

Aspirin:

RAYZON Injection had no effect on aspirin-mediated inhibition of platelet aggregation or bleeding times in volunteers. Clinical trials indicate that RAYZON Injection can be given with low dose aspirin (≤ 325 mg). Because of its lack of platelet effects, RAYZON Injection is not a substitute for aspirin for cardiovascular prophylaxis. There is no evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with RAYZON.

ACE-inhibitors:

Inhibition of RAYZON may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients receiving RAYZON concomitantly with ACE-inhibitors.

Ciclosporin or tacrolimus:

Co-administration of RAYZON and ciclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus. Renal function should be monitored when RAYZON Injection and any of these medicines are co-administered.

Diuretics:

RAYZON may reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

Fluconazole and ketoconazole:

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62 % and 19 %, respectively) when co-administered with fluconazole, indicating that the dose of RAYZON Injection should be reduced in those patients who are receiving fluconazole therapy. Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38 % and 24 %, respectively) when co-administered with ketoconazole; however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

Lithium:

RAYZON produced significant decreases in lithium serum clearance (25 %) and renal clearance (30 %) with a 34 % higher serum exposure compared to lithium alone. Lithium serum concentration should be monitored closely when initiating or changing RAYZON Injection therapy in patients receiving lithium.

Warfarin or similar agents:

Anticoagulant therapy should be monitored, particularly during the first few days after initiating RAYZON Injection therapy in patients receiving warfarin or similar agents, since these patients have an increased risk of bleeding complications.

Other:

RAYZON did not produce clinically relevant inhibition of the CYP2D6-mediated pathway involved in the conversion of dextromethorphan to dextrorphan.

Co-administration of RAYZON with glibenclamide (CYP3A4 substrate) did not affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate, RAYZON did not have a clinically significant effect on the plasma exposure to methotrexate.

Injectable anaesthetics:

Co-administration of IV RAYZON Injection 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics of IV propofol or IV midazolam. Additionally, co-administration with IV RAYZON Injection had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics:

In a post-orthopaedic surgery study in which RAYZON Injection was administered preoperatively, no evidence of medicine interaction was observed in patients receiving RAYZON Injection and the inhalation anaesthetic agents nitrous oxide and isoflurane.

PREGNANCY AND LACTATION:

Safety of RAYZON has not been demonstrated in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

RAYZON is only indicated for patients with a need for parenteral therapy and for whom a similar benefit could not be obtained from alternative oral therapy. It is recommended that patients be transitioned to alternative oral therapy as soon as clinically indicated.

As the cardiovascular risk of RAYZON may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. However, the relevance of these findings for the short-term use of RAYZON in the post-operative setting has not been evaluated.

Management of post-operative pain:

The usual recommended dose is a single or initial 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line.

The IM injection should be given slowly and deeply into the muscle. When given at the recommended doses for management of acute pain, the onset of analgesia was 7 – 14 minutes and reached a peak effect within 2 hours. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 7 to greater than 24 hours.

Concomitant use with opioid analgesia:

Opioid analgesia can be used concurrently with RAYZON dosing as described in the paragraph above, for the management of post-operative pain for up to 48 hours. In a hip replacement surgery trial, the daily requirements for opioid were significantly reduced (20 – 40 %) when co-administered with RAYZON. An optimal effect is achieved when RAYZON is given at the end of hip replacement surgery, prior to opioid administration. In all clinical assessments RAYZON was administered at a fixed time interval (i.e. 12 hourly), whereas the opioids were administered when needed (PRN basis).

Elderly:

Dosage adjustment in the elderly is not generally necessary, however, for elderly female patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of RAYZON Injection and reduce the maximum daily dose to 40 mg.

Hepatic impairment:

No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh scale 5 – 6). Introduce RAYZON Injection with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh scale 7 – 9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh scale > 9); therefore its use is not recommended in these patients (see CONTRAINDICATIONS).

Renal impairment:

On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate (creatinine clearance of 30 – 80 ml/min) renal impairment. In patients with severe (creatinine clearance < 30 ml/min) renal impairment or patients who may be predisposed to fluid retention, RAYZON should not be used (see CONTRAINDICATIONS).

Children:

RAYZON Injection has not been studied in patients under 18 years old. Therefore, its use is not recommended in these patients.

INSTRUCTIONS FOR USE/HANDLING:

Reconstitute RAYZON Injection with 1 ml (20 mg vials) or 2 ml (40 mg vials) sodium chloride solution (0,9 % w/v) using aseptic technique. The **only** other acceptable solvents for reconstitution are 5 % Glucose Intravenous Infusion, 0,45 % Sodium Chloride and 5 % Glucose Injection.

Use of Sterile Water for Injection is **not recommended**, as the resulting solution is not isotonic. Use of Lactated Ringer's or 5 % Glucose in Lactated Ringers for reconstitution will cause the active substance to precipitate from solution and therefore is not recommended.

After reconstitution, RAYZON Injection should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

SIDE EFFECTS:

The following side effects have been reported in patients on RAYZON treatment. Incidence rates are categorized as follows: Common (≥ 1/100 and < 1/10) (≥ 1 % and < 10 %) and Uncommon (≥ 1/1 000 and < 1/100) (≥ 0,1 % and < 1 %)

System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Uncommon	Abnormal sternal serous wound drainage Wound infection
Blood and lymphatic system disorders	Common	Post-operative anaemia
	Uncommon	Thrombocytopenia
Metabolism and nutrition disorders	Common	Hypokalaemia
	Uncommon	Hyperglycaemia
Psychiatric disorders	Common	Agitation Insomnia
Nervous system disorders	Common	Hypoaesthesia Dizziness
	Uncommon	Cerebrovascular disorder Dry mouth
Cardiac disorders	Uncommon	Bradycardia Peripheral oedema

		Aggravated hypertension Dysrhythmia Hypertension Palpitations Tachycardia Congestive cardiac failure Myocardial infarction Cardiovascular thrombotic events
Neurologic disorders	Uncommon	Cerebrovascular incidents (strokes)
Vascular disorders	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Pharyngitis Respiratory insufficiency
Gastrointestinal disorders	Common	Alveolar osteitis Dyspepsia Flatulence Constipation
Skin and subcutaneous tissue disorders	Common	Pruritus Increased sweating
	Uncommon	Ecchymosis Rash Skin post-operative complications
Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Arthralgia
Renal and urinary disorders	Common	Oliguria
General disorders and administration site conditions	Uncommon	Injection site pain Asthenia Earache
Investigations	Common	Increase creatinine
	Uncommon	Increased AST

		Increased ALT Increased blood urea

Post-marketing surveillance:

In post-marketing experience, the following serious adverse events have been reported in association with the use of RAYZON:

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal failure, acute renal failure and hypersensitivity reactions including anaphylaxis and angioedema.

Gastrointestinal disorders:

Nausea, vomiting.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No symptoms of overdose have been observed with single IV doses of up to 200 mg of RAYZON Injection in healthy subjects. RAYZON Injection doses of 50 mg BID IV for 7 days did not result in any signs of toxicity.

In case of overdose, patients should be managed by symptomatic and supportive care.

IDENTIFICATION:

Powder for Solution for Injection: White to off-white lyophilized powder in a stoppered 5 ml (40 mg) clear glass vial.

Solvent for Solution for Injection: 2 ml solvent ampoules with a fill volume of 2 ml Sodium Chloride Intravenous Infusion (0,9 % w/v) BP.

Reconstituted solution is clear and colourless.

PRESENTATION:

RAYZON Injection is supplied as a sterile, single unit-of-use vial, sealed with a purple flip-off cap on the aluminium overseal, that may be packaged with a 2 ml ampoule with a fill volume of 2 ml sodium chloride solution (0,9 % w/v), respectively.

Pack sizes available: Sets of either 1, 3, 5 or 10 vials containing parecoxib 40 mg (as parecoxib sodium), together with 2 ml ampoules containing 2 ml sodium chloride injection (0,9 % w/v), packed into an outer carton. Some RAYZON Injection packs do not include solvent.

STORAGE INSTRUCTIONS:

Store below 30 °C in the outer container in order to protect from light.

Keep out of reach of children.

Reconstituted solution should be used within 24 hours and should not be stored in a refrigerator or freezer.

REGISTRATION NUMBERS:

RAYZON 40 mg IV/IM: 36/2.9/0120

RAYZON 2 ml SOLVENT: 36/34/0122

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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NAMIBIA: S2

RAYZON 40 mg IV/IM – Reg. No.: 05/2.9/0348

RAYZON 2 ml SOLVENT – Reg. No.: 05/34/0350