SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

RAYZON® 40 mg IV/IM Powder

2. QUALITATIVE AND QUANTITATIVE 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.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

RAYZON 40 mg IV/IM: White to off-white lyophilised powder in a stoppered 5 mL (40 mg) clear glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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. Patients should be transferred to alternative oral therapy as soon as clinically indicated.

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

4.2 Posology and method of administration

Posology

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 reduced by 20 to 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).

Special populations

Elderly population

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. Patients with severe hepatic impairment (Child-Pugh scale > 9) should not be given RAYZON (see section 4.3).

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 section 4.3).

Paediatric population

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

Method of administration

For intravenous or intramuscular injection.

For instructions on RAYZON reconstitution, before administration of injection and RAYZON diluent incompatibilities, refer to sections 6.2 and 6.6.

4.3 Contraindications

- hypersensitivity to parecoxib or to any of the excipients of RAYZON (listed in section 6.1)

- 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)
- heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease
- history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including RAYZON
- active or history of recurrent ulcer/haemorrhage/perforations
- concomitant therapy with lithium or digoxin
- porphyria
- pregnancy and lactation (see section 4.6)
- children younger than 18 years of age

4.4 Special warnings and precautions for use

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

Administration other than IV or IM

Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.

Cardiovascular effects

RAYZON has been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long-term. The 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. This risk is associated with higher doses and prolonged duration of treatment (see section 4.3).

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

Hypertension

RAYZON can lead to the onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including RAYZON, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with RAYZON and throughout the course of therapy.

Gastrointestinal (GI) effects

Upper gastrointestinal (GI) complications including perforations, ulcers, or bleedings (PUBs), some of them resulting in fatal outcome, have occurred in patients treated with RAYZON. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with RAYZON: the elderly, patients with cardiovascular disease, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, selective serotonin reuptake inhibitors or patients with a prior history of gastrointestinal disease, such as ulceration, GI bleeding, or inflammatory conditions. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when RAYZON is taken concomitantly with acetylsalicylic acid (aspirin) (even at low doses).

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 aggregation effects, RAYZON is not a substitute for aspirin for prophylaxis of cardiovascular disease.

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

Renal effects

RAYZON injection should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or severe hepatic impairment (Child-Pugh scale ≥ 9) (see section 4.3).

Caution should be used when initiating treatment with RAYZON injection in patients with moderate hepatic impairment (Child-Pugh scale 7 – 9), and 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, pre-existing oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolaemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored (see section 4.3).

Anaphylactoid reactions

Hypersensitivity reactions such as anaphylaxis and angioedema have been reported in post-marketing experience with RAYZON injection. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides.

Severe hypotension

Cases of severe hypotension shortly following RAYZON administration have been reported. Some of these cases have occurred without other signs of anaphylaxis. The practitioner should be prepared to treat severe hypotension.

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.

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

The concomitant use of RAYZON injection with other non-specific NSAIDs should be avoided.

4.5 Interaction with other medicines and other forms of interaction

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 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 aggregation effects, RAYZON injection is not a substitute for aspirin for prophylaxis of cardiovascular disease. 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 prostaglandins 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.

In patients who are elderly, volume-depleted (including those on diuretic therapy) or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors such as RAYZON, with ACE inhibitors, may result in deterioration of renal function, including possible acute renal failure. These effects may be reversible.

Ciclosporin or tacrolimus

Co-administration of RAYZON and ciclosporin or tacrolimus may 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 increases (62 % and 19 %, respectively) when co-administered with fluconazole. The dose of RAYZON injection should be reduced in patients 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 may not be necessary for patients receiving ketoconazole.

Lithium

RAYZON produces significant decreases in lithium serum clearance (25 %) and renal clearance (30 %) with a 34 % higher serum exposure compared to lithium alone (see section 4.3).

Warfarin or similar medicines

Anticoagulant therapy should be more frequently monitored, particularly during the first few days after initiating RAYZON injection therapy in patients receiving warfarin or similar medicines, 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.

RAYZON may be co-administered with opioid analgesics.

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 medicines nitrous oxide and isoflurane.

4.6 Fertility, pregnancy and lactation

Safety of RAYZON has not been demonstrated in pregnancy and lactation. RAYZON is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

Cases of adverse reactions in the foetus or newborn have been reported with exposure to the NSAID class of medicine during pregnancy and/or during lactation, including:

- foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation of the NSAID treatment
- premature closure of the foetal ductus arteriosus *in utero* with regular use of NSAID treatment
- possibly, persistent pulmonary hypertension of the newborn with regular use of NSAID treatment during pregnancy
- the onset of labour may be delayed and its duration increased

Breastfeeding

Women breastfeeding their infants should not be given RAYZON.

Fertility

Based on the mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including RAYZON, should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence after receiving RAYZON should refrain from driving or operating machines.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following side effects have been reported in patients on RAYZON treatment. Incidence rates are categorised as follows: Common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100).

System organ class	Frequency	Undesirable effects
Infections and infestations	Common	Alveolar osteitis (dry socket)
	Uncommon	Abnormal sternal serous wound drainage, wound infection, pharyngitis
Blood and lymphatic system disorders	Common	Post-operative anaemia
	Uncommon	Thrombocytopenia
Immune system disorders	Uncommon	Anaphylactoid reaction
Metabolism and nutrition disorders	Common	Hypokalaemia
	Uncommon	Hyperglycaemia, anorexia
Psychiatric disorders	Common	Insomnia
	Uncommon	Agitation
Nervous system disorders	Common	Hypoaesthesia, dizziness
	Uncommon	Cerebrovascular disorder
Ear and labyrinth disorders	Uncommon	Earache
Cardiac disorders	Uncommon	Bradycardia, dysrhythmia, palpitations, tachycardia, congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events

Neurologic disorders	Uncommon	Cerebrovascular incidents (strokes)
Vascular disorders	Common	Hypotension
	Uncommon	Hypertension, aggravated hypertension, postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory insufficiency
	Uncommon	Pulmonary embolism
Gastrointestinal disorders	Common	Dyspepsia, constipation, nausea, abdominal pain, vomiting
	Uncommon	Dry mouth, flatulence, oesophagitis, gastroesophageal reflux, hypoactive bowel sounds, pancreatitis, perioral swelling
Skin and subcutaneous tissue disorders	Common	Pruritus, increased sweating
	Uncommon	Ecchymosis, rash, urticaria
Injury, poisoning and procedural complications	Uncommon	Skin post-operative complications
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, back pain
Renal and urinary disorders	Common	Oliguria
	Uncommon	Acute renal failure
General disorders and administration site conditions	Common	Peripheral oedema
	Uncommon	Injection site pain, injection site reaction, asthenia

Investigations	Uncommon	Increased creatinine, increased creatine phosphokinase, increased LDH, increased BUN

Post-marketing surveillance

In post-marketing experience, the following serious adverse events have been reported in association with the use of RAYZON: Circulatory collapse, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal failure, acute renal failure and hypersensitivity reactions including anaphylaxis and angioedema.

Gastrointestinal disorders: Nausea, vomiting

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics

Parecoxib sodium, a COX-2 selective non-steroidal anti-inflammatory drug (NSAID), is an inactive prodrug of 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.

5.2 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 in 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. 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.

Biotransformation

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

In healthy elderly subjects, the apparent clearance of valdecoxib after oral intake 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. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Dibasic sodium phosphate heptahydrate

Phosphoric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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 Ringer's for reconstitution will cause the active substance to precipitate from solution and therefore is not recommended.

6.3 Shelf life

36 months.

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

RAYZON injection is supplied as a sterile, single unit-of-use vial, sealed with a purple flip-off cap on the aluminium overseal.

Pack sizes available: Sets of either 1, 3, 5 or 10 vials containing parecoxib 40 mg (as parecoxib sodium) packed into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitute RAYZON injection with 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.

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.

Reconstituted solution is clear and colourless.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

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

9. DATE OF FIRST AUTHORISATION

25 April 2003

10. DATE OF REVISION OF THE TEXT

15 June 2021

NAMIBIA: S2

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

RAYZON 2 mL Solvent – Reg. No.: 05/34/0350