ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Rayzon 20 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg vial: Each vial contains 20 mg parecoxib (present as 21.18 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

4.2 Posology and method of administration

The recommended dose is 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. (see section 6.6 for instructions for reconstitution)

Elderly: No dosage adjustment is generally necessary in elderly patients (≥ 65 years). However, for elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of Rayzon and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic Impairment: No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce Rayzon with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10 ), therefore its use is contraindicated in these patients. (see sections 4.3 and 5.2)

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.) or severe (creatinine clearance < 30 ml/min.) renal impairment. However, caution should be observed in patients with renal impairment or patients who may be predisposed to fluid retention. (see sections 4.4 and 5.2)

Children and adolescents: Rayzon has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

Known hypersensitivity to sulphonamides (see sections 4.4 & 4.8).

Active peptic ulceration or gastrointestinal bleeding.
Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10).

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

There is limited clinical experience with Rayzon treatment beyond two days.

Because of the possibility for increased adverse reactions at higher doses parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2)

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for parecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

Rayzon has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Rayzon should be used with caution to treat pain following coronary artery bypass graft surgery as these patients may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m². (see section 4.8)

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because parecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) 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 (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischaemia, coronary bypass graft surgery or peripheral vascular surgery).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib, and cannot be ruled out for parecoxib (the prodrug of valdecoxib) (see section 4.8). Parecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see Section 4.3)
Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib, and cannot be ruled out for parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Rayzon in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Rayzon in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Rayzon.

Rayzon should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)
Rayzon may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Rayzon. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Rayzon.

Caution should be exercised when co-administering Rayzon with warfarin and other oral anticoagulants. (see section 4.5)

The use of Rayzon, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Anticoagulant therapy should be monitored, particularly during the first few days after initiating Rayzon therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed. (see 4.4).

Rayzon had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Rayzon can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see 5.1).

Co-administration of parecoxib sodium and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors or diuretics are co-administered with parecoxib sodium.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when parecoxib sodium and any of these medicinal products are co-administered.

Rayzon may be co-administered with opioid analgesics. When Rayzon was co-administered with morphine, a smaller dose (by 28-36%) of morphine could be used to achieve the same clinical level of analgesia.
**Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)**

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C$_{\text{max}}$) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib sodium should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C$_{\text{max}}$) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

**Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products**

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering Rayzon and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Rayzon with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate intramuscularly, orally administered valdecoxib (40 mg twice daily) did not have a clinically significant effect on the plasma concentrations of methotrexate. However, adequate monitoring of methotrexate-related toxicity should be considered when co-administering these two medicinal products.

Co-administration of valdecoxib and lithium 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 parecoxib sodium therapy in patients receiving lithium.

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

**Injectable anaesthetics:** Coadministration of IV parecoxib sodium 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib sodium 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

**Inhalation anaesthetics:** No formal interaction studies have been done. In surgery studies in which parecoxib sodium was administered pre-operatively, no evidence of pharmacodynamic interaction was
observed in patients receiving parecoxib sodium and the inhalation anaesthetic agents nitrous oxide and isoflurane. (see section 5.1)

4.6 Pregnancy and lactation

Pregnancy:
The use of Rayzon is contraindicated in the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia. (see sections 4.3, 5.1 and 5.3)

Like other medicinal products that inhibit COX-2, Rayzon is not recommended in women attempting to conceive. (see sections 4.4, 5.1 and 5.3)

There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown. Rayzon should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:
Parecoxib, valdecoxib (its active metabolite) and a valdecoxib active metabolite are excreted in the milk of rats. It is not known whether valdecoxib is excreted in human milk. Rayzon should not be administered to women who breast-feed. (see sections 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effect of Rayzon on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving Rayzon should refrain from driving or operating machines.

4.8 Undesirable effects

Of the Rayzon treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Rayzon 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0% for patients receiving Rayzon and 4.3% for patients receiving placebo.

[Very Common (>1/10), Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

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

Psychiatric disorders:
Common: agitation, insomnia

Nervous system disorders
Common: hypoaesthesia, cerebrovascular disorder

**Cardiac disorders**
Uncommon: bradycardia

**Vascular disorders**
Common: hypertension, hypotension
Uncommon: aggravated hypertension

**Respiratory, thoracic and mediastinal disorders**
Common: pharyngitis, respiratory insufficiency

**Gastrointestinal disorders**
Common: alveolar osteitis (dry socket), dyspepsia, flatulence
Uncommon: gastroduodenal ulceration

**Skin and subcutaneous tissue disorders**
Common: pruritus
Uncommon: ecchymosis

**Musculoskeletal and connective tissue disorders**
Common: back pain

**Renal and urinary disorders**
Common: oliguria

**General disorders and administration site conditions**
Common: peripheral oedema

**Investigations**
Common: blood creatinine increased
Uncommon: SGOT increased, SGPT increased, BUN increased

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Rayzon: acute renal failure, congestive heart failure, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered Rayzon may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, myocardial infarction (very rare), erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).
4.9 Overdose

No case of parecoxib overdose has been reported.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

The efficacy of Rayzon was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Rayzon. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

Gastrointestinal studies: In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (≥ 65 years) subjects administered Rayzon (5-21%), although higher than placebo (5-12%), was statistically significantly lower than the incidence observed with NSAIDs (66-90%).

Platelet studies: In a series of small, multiple dose studies in healthy young and elderly subjects, Rayzon 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Rayzon 40 mg twice daily had no clinically significant effect on acetylsalicylic acid -mediated inhibition of platelet function. (see section 4.5)

5.2 Pharmacokinetic properties

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

Absorption

Exposure of valdecoxib following single doses of Rayzon, 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 daily administration is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with twice daily 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. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average C_{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C_{max} of valdecoxib is comparable after IM and IV parecoxib sodium administration.

**Distribution**
The volume of distribution of valdecoxib after its IV administration is approximately 55 liters. 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 and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) 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; 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.

**Elimination**
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib 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:** Rayzon has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. 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. (see section 4.2)

**Renal Impairment:** In patients with varying degrees of renal impairment administered 20 mg IVRayzon, 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 severe renal impairment or in patients undergoing dialysis. (see section 4.2)

**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 score 7-9), treatment should be initiated with half the usual recommended dose of Rayzon 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 Rayzon in patients with severe hepatic impairment is not recommended. (see sections 4.2 and 4.3)

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib.
However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) were approximately 0.8-fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and foetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib on male or female fertilities were found in rats.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal period. Parecoxib sodium administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib sodium has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Dibasic sodium phosphate, heptahydrate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

20 mg vial: When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Rayzon contains approximately 0.22 mEq of sodium per vial.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products other than those mentioned in 6.6.

Rayzon and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 g/l (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is not recommended.

Use of Sterile Water for Injection is not recommended, as the resulting solution is not isotonic.

Injection into an IV line delivering glucose 50 g/l (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 12 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

6.5 Nature and contents of container

Parecoxib sodium vials
20 mg vials: Type I colourless glass vials (2 ml) with a laminated stopper, sealed with a yellow flip-off cap on the aluminium overseal.

Rayzon is available in packs containing 10 vials.

6.6 Instructions for use and handling <and disposal>

Acceptable solvents for reconstitution of Rayzon are:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium). Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the 20 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 20 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

The reconstituted solution is clear and colourless. It should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

The reconstituted product is isotonic.

After reconstitution with acceptable solvents, Rayzon may only be injected IV or IM, or into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

For single use only. Any unused solution, solvent or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/210/001
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22nd March 2002

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Rayzon 20 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg vial: Each vial contains 20 mg parecoxib (present as 21.18 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

4.2 Posology and method of administration

The recommended dose is 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. (see section 6.6 for instructions for reconstitution)

Elderly: No dosage adjustment is generally necessary in elderly patients (≥ 65 years). However, for elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of Rayzon and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic Impairment: No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce Rayzon with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore its use is contraindicated in these patients. (see sections 4.3 and 5.2)

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.) or severe (creatinine clearance < 30 ml/min.) renal impairment. However, caution should be observed in patients with renal impairment or patients who may be predisposed to fluid retention. (see sections 4.4 and 5.2)

Children and adolescents: Rayzon has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

Known hypersensitivity to sulphonamides (see sections 4.4 & 4.8).

Active peptic ulceration or gastrointestinal bleeding.
Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10 ).

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

There is limited clinical experience with Rayzon treatment beyond two days.

Because of the possibility for increased adverse reactions at higher doses parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for parecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

Rayzon has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Rayzon should be used with caution to treat pain following coronary artery bypass graft surgery as these patients may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m². (see section 4.8).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because parecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) 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 (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib, and cannot be ruled out for parecoxib (the prodrug of valdecoxib) (see section 4.8). Parecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see Section 4.3).
Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib, and cannot be ruled out for parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Rayzon in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Rayzon in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Rayzon.

Rayzon should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)

Rayzon may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Rayzon. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Rayzon.

Caution should be exercised when co-administering Rayzon with warfarin and other oral anticoagulants. (see section 4.5)

The use of Rayzon, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

### 4.5 Interaction with other medicinal products and other forms of interaction

**Pharmacodynamic interactions**

Anticoagulant therapy should be monitored, particularly during the first few days after initiating Rayzon therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed. (see 4.4).

Rayzon had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Rayzon can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see 5.1).

Co-administration of parecoxib sodium and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors or diuretics are co-administered with parecoxib sodium.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when parecoxib sodium and any of these medicinal products are co-administered.

Rayzon may be co-administered with opioid analgesics. When Rayzon was co-administered with morphine, a smaller dose (by 28-36%) of morphine could be used to achieve the same clinical level of analgesia.
Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib sodium 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 (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering Rayzon and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Rayzon with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate intramuscularly, orally administered valdecoxib (40 mg twice daily) did not have a clinically significant effect on the plasma concentrations of methotrexate. However, adequate monitoring of methotrexate-related toxicity should be considered when co-administering these two medicinal products.

Co-administration of valdecoxib and lithium 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 parecoxib sodium therapy in patients receiving lithium.

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

Injectable anaesthetics: Coadministration of IV parecoxib sodium 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib sodium 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics: No formal interaction studies have been done. In surgery studies in which parecoxib sodium was administered pre-operatively, no evidence of pharmacodynamic interaction was
observed in patients receiving parecoxib sodium and the inhalation anaesthetic agents nitrous oxide and isoflurane. (see section 5.1)

4.6 Pregnancy and lactation

Pregnancy:
The use of Rayzon is contraindicated in the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia. (see sections 4.3, 5.1 and 5.3)

Like other medicinal products that inhibit COX-2, Rayzon is not recommended in women attempting to conceive. (see sections 4.4, 5.1 and 5.3)

There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown. Rayzon should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:
Parecoxib, valdecoxib (its active metabolite) and a valdecoxib active metabolite are excreted in the milk of rats. It is not known whether valdecoxib is excreted in human milk. Rayzon should not be administered to women who breast-feed. (see sections 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effect of Rayzon on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving Rayzon should refrain from driving or operating machines.

4.8 Undesirable effects

Of the Rayzon treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Rayzon 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0% for patients receiving Rayzon and 4.3% for patients receiving placebo.

[Very Common (>1/10), Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

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

Psychiatric disorders:
Common: agitation, insomnia

Nervous system disorders
Common: hypoaesthesia, cerebrovascular disorder

**Cardiac disorders**
Uncommon: bradycardia

**Vascular disorders**
Common: hypertension, hypotension
Uncommon: aggravated hypertension

**Respiratory, thoracic and mediastinal disorders**
Common: pharyngitis, respiratory insufficiency

**Gastrointestinal disorders**
Common: alveolar osteitis (dry socket), dyspepsia, flatulence
Uncommon: gastroduodenal ulceration

**Skin and subcutaneous tissue disorders**
Common: pruritus
Uncommon: ecchymosis

**Musculoskeletal and connective tissue disorders**
Common: back pain

**Renal and urinary disorders**
Common: oliguria

**General disorders and administration site conditions**
Common: peripheral oedema

**Investigations**
Common: blood creatinine increased
Uncommon: SGOT increased, SGPT increased, BUN increased

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Rayzon: acute renal failure, congestive heart failure, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered Rayzon may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, myocardial infarction (very rare), erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).
4.9 Overdose

No case of parecoxib overdose has been reported.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established."

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

The efficacy of Rayzon was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7-13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Rayzon. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

Gastrointestinal studies: In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (≥ 65 years) subjects administered Rayzon (5-21%), although higher than placebo (5-12%), was statistically significantly lower than the incidence observed with NSAIDs (66-90%).

Platelet studies: In a series of small, multiple dose studies in healthy young and elderly subjects, Rayzon 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Rayzon 40 mg twice daily had no clinically significant effect on acetylsalicylic acid-mediated inhibition of platelet function. (see section 4.5)

5.2 Pharmacokinetic properties

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

Absorption

Exposure of valdecoxib following single doses of Rayzon, 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\text{max} following twice daily administration is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with twice daily dosing.

Following single IV and IM doses of parecoxib sodium 20 mg, C\text{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\text{max} following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average C\text{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C\text{max} of valdecoxib is comparable after IM and IV parecoxib sodium administration.

**Distribution**
The volume of distribution of valdecoxib after its IV administration is approximately 55 liters. 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 and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) 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; 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.

**Elimination**
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib 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\text{p}) for valdecoxib is about 6 l/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life (t\text{1/2}) of valdecoxib is about 8 hours.

**Elderly Subjects:** Rayzon has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. 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. (see section 4.2)

**Renal Impairment:** In patients with varying degrees of renal impairment administered 20 mg IVRayzon, 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 severe renal impairment or in patients undergoing dialysis. (see section 4.2)

**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 score 7-9), treatment should be initiated with half the usual recommended dose of Rayzon 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 Rayzon in patients with severe hepatic impairment is not recommended. (see sections 4.2 and 4.3)

**Preclinical safety data**
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib.
However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) were approximately 0.8-fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and foetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib on male or female fertilities were found in rats.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal period. Parecoxib sodium administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib sodium has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

_Powder_
Dibasic sodium phosphate, heptahydrate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

_Solvent_
Sodium chloride
Hydrochloric acid or sodium hydroxide (for pH adjustment)
Water for injections.

20 mg vial: When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Rayzon contains approximately 0.22 mEq of sodium per vial.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products other than those mentioned in 6.6.

Rayzon and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 g/l (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is not recommended.

Use of Sterile Water for Injection is not recommended, as the resulting solution is not isotonic.

Injection into an IV line delivering glucose 50 g/l (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the
responsibility of the user and would not normally be longer than 12 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

6.5 Nature and contents of container

_Parecoxib sodium vials_

20 mg vials: Type I colourless glass vials (2 ml) with a laminated stopper, sealed with a yellow flip-off cap on the aluminium overseal.

_Solvent ampoules_

2 ml ampoule: colourless neutral glass, Type I.

Rayzon is supplied as a sterile, single unit-of-use vial that is packaged with a 2 ml ampoule with a fill volume of 1 ml sodium chloride 9mg/ml (0.9%) solution (see below for various pack sizes and configurations).

Pack sizes

1 x 1 pack: contains 1 vial with parecoxib 20 mg and 1 ampoule with 1 ml sodium chloride 9 mg/ml (0.9%) solution.

3 x 3 pack: contains 3 vials of parecoxib 20 mg and 3 ampoule with 1 ml sodium chloride 9 mg/ml (0.9%) solution.

5 x 5 pack: contains 5 vials of parecoxib 20 mg and 5 ampoule with 1 ml sodium chloride 9 mg/ml (0.9%) solution.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>

Reconstitute Rayzon 20 mg with 1 ml sodium chloride 9 mg/ml (0.9%) solution using aseptic technique. The only other acceptable solvents for reconstitution are:

- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium). Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the 20 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 20 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

The reconstituted solution is clear and colourless. It should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

The reconstituted product is isotonic.

After reconstitution with acceptable solvents, Rayzon may only be injected IV or IM, or into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
glucose 50 g/l (5%) solution for infusion
sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
Ringer-Lactate solution for injection

For single use only. Any unused solution, solvent or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/210/002-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22nd March 2002

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Rayzon 40 mg powder for solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

40 mg vial: Each vial contains 40 mg parecoxib (present as 42.36 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml.

For excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Powder for solution for injection

White to off-white powder.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

4.2 Posology and method of administration

The recommended dose is 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. (see section 6.6 for instructions for reconstitution)

**Elderly:** No dosage adjustment is generally necessary in elderly patients (≥ 65 years). However, for elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of Rayzon and reduce the maximum daily dose to 40 mg (see section 5.2).

**Hepatic Impairment:** No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce Rayzon with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10 ), therefore its use is contraindicated in these patients. (see sections 4.3 and 5.2)

**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.) or severe (creatinine clearance < 30 ml/min.) renal impairment. However, caution should be observed in patients with renal impairment or patients who may be predisposed to fluid retention. (see sections 4.4 and 5.2)

**Children and adolescents:** Rayzon has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

Known hypersensitivity to sulphonamides (see sections 4.4 & 4.8).

Active peptic ulceration or gastrointestinal bleeding.
Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10).

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

There is limited clinical experience with Rayzon treatment beyond two days.

Because of the possibility for increased adverse reactions at higher doses parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for parecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

Rayzon has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Rayzon should be used with caution to treat pain following coronary artery bypass graft surgery as these patients may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m². (see section 4.8)

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because parecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) 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 (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib, and cannot be ruled out for parecoxib (the prodrug of valdecoxib) (see section 4.8). Parecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see Section 4.3)
Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib, and cannot be ruled out for parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Rayzon in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Rayzon in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Rayzon.

Rayzon should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)
Rayzon may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Rayzon. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Rayzon.

Caution should be exercised when co-administering Rayzon with warfarin and other oral anticoagulants. (see section 4.5)

The use of Rayzon, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Anticoagulant therapy should be monitored, particularly during the first few days after initiating Rayzon therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed. (see 4.4).

Rayzon had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Rayzon can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see 5.1).

Co-administration of parecoxib sodium and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors or diuretics are co-administered with parecoxib sodium.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when parecoxib sodium and any of these medicinal products are co-administered.

Rayzon may be co-administered with opioid analgesics. When Rayzon was co-administered with morphine, a smaller dose (by 28-36%) of morphine could be used to achieve the same clinical level of analgesia.
Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C$_{\text{max}}$) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib sodium should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C$_{\text{max}}$) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering Rayzon and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Rayzon with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate intramuscularly, orally administered valdecoxib (40 mg twice daily) did not have a clinically significant effect on the plasma concentrations of methotrexate. However, adequate monitoring of methotrexate-related toxicity should be considered when co-administering these two medicinal products.

Co-administration of valdecoxib and lithium 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 parecoxib sodium therapy in patients receiving lithium.

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

Injectable anaesthetics:
Coadministration of IV parecoxib sodium 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib sodium 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics: No formal interaction studies have been done. In surgery studies in which parecoxib sodium was administered pre-operatively, no evidence of pharmacodynamic interaction was
observed in patients receiving parecoxib sodium and the inhalation anaesthetic agents nitrous oxide and isoflurane. (see section 5.1)

4.6 Pregnancy and lactation

Pregnancy:
The use of Rayzon is contraindicated in the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia. (see sections 4.3, 5.1 and 5.3)

Like other medicinal products that inhibit COX-2, Rayzon is not recommended in women attempting to conceive. (see sections 4.4, 5.1 and 5.3)

There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown. Rayzon should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:
Parecoxib, valdecoxib (its active metabolite) and a valdecoxib active metabolite are excreted in the milk of rats. It is not known whether valdecoxib is excreted in human milk. Rayzon should not be administered to women who breast-feed. (see sections 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effect of Rayzon on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving Rayzon should refrain from driving or operating machines.

4.8 Undesirable effects

Of the Rayzon treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Rayzon 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0 % for patients receiving Rayzon and 4.3% for patients receiving placebo.

[Very Common (>1/10), Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

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

Psychiatric disorders:
Common: agitation, insomnia

Nervous system disorders
Common: hypoesthesia, cerebrovascular disorder

**Cardiac disorders**  
Uncommon: bradycardia

**Vascular disorders**  
Common: hypertension, hypotension  
Uncommon: aggravated hypertension

**Respiratory, thoracic and mediastinal disorders**  
Common: pharyngitis, respiratory insufficiency

**Gastrointestinal disorders**  
Common: alveolar osteitis (dry socket), dyspepsia, flatulence  
Uncommon: gastroduodenal ulceration

**Skin and subcutaneous tissue disorders**  
Common: pruritus  
Uncommon: ecchymosis

**Musculoskeletal and connective tissue disorders**  
Common: back pain

**Renal and urinary disorders**  
Common: oliguria

**General disorders and administration site conditions**  
Common: peripheral oedema

**Investigations**  
Common: blood creatinine increased  
Uncommon: SGOT increased, SGPT increased, BUN increased

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Rayzon: acute renal failure, congestive heart failure, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered Rayzon may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, myocardial infarction (very rare), erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).
4.9 **Overdose**

No case of parecoxib overdose has been reported.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

The efficacy of Rayzon was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Rayzon. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

**Gastrointestinal studies:** In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (≥ 65 years) subjects administered Rayzon (5-21%), although higher than placebo (5-12%), was statistically significantly lower than the incidence observed with NSAIDs (66-90%).

**Platelet studies:** In a series of small, multiple dose studies in healthy young and elderly subjects, Rayzon 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Rayzon 40 mg twice daily had no clinically significant effect on acetylsalicylic acid -mediated inhibition of platelet function. (see section 4.5)

5.2 **Pharmacokinetic properties**

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

**Absorption**

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

Following single IV and IM doses of parecoxib sodium 20 mg, $C_{\text{max}}$ of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and $C_{\text{max}}$ following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average $C_{\text{max}}$ of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since $C_{\text{max}}$ of valdecoxib is comparable after IM and IV parecoxib sodium administration.

**Distribution**
The volume of distribution of valdecoxib after its IV administration is approximately 55 liters. 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 and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) 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; 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.

**Elimination**
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib 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:** Rayzon has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. 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. (see section 4.2)

**Renal Impairment:** In patients with varying degrees of renal impairment administered 20 mg IVRayzon, 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 severe renal impairment or in patients undergoing dialysis. (see section 4.2)

**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 score 7-9), treatment should be initiated with half the usual recommended dose of Rayzon 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 Rayzon in patients with severe hepatic impairment is not recommended. (see sections 4.2 and 4.3)

**Preclinical safety data**
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib.
However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) were approximately 0.8-fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and foetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib on male or female fertilities were found in rats.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal period. Parecoxib sodium administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib sodium has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Dibasic sodium phosphate, heptahydrate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

40 mg vial: When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Rayzon contains approximately 0.44 mEq of sodium per vial.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products other than those mentioned in 6.6.

Rayzon and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 g/l (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is not recommended.

Use of Sterile Water for Injection is not recommended, as the resulting solution is not isotonic.

Injection into an IV line delivering glucose 50 g/l (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 12 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

6.5 Nature and contents of container

Parecoxib sodium vials
40 mg vials: Type I colourless glass vials (5 ml) with a laminated stopper, sealed with a yellow flip-off cap on the aluminium overseal.

Rayzon is available in packs containing 10 vials.

6.6 Instructions for use and handling <and disposal>

Acceptable solvents for reconstitution of Rayzon are:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium). Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

The reconstituted solution is clear and colourless. It should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

The reconstituted product is isotonic.

After reconstitution with acceptable solvents, Rayzon may only be injected IV or IM, or into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

For single use only. Any unused solution, solvent or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
EU/1/02/210/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22nd March 2002

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Rayzon 40 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

40 mg vial: Each vial contains 40 mg parecoxib (present as 42.36 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain.

4.2 Posology and method of administration

The recommended dose is 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. (see section 6.6 for instructions for reconstitution)

Elderly: No dosage adjustment is generally necessary in elderly patients (≥ 65 years). However, for elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose of Rayzon and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic Impairment: No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Introduce Rayzon with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and reduce the maximum daily dose to 40 mg. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore its use is contraindicated in these patients. (see sections 4.3 and 5.2)

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.) or severe (creatinine clearance < 30 ml/min.) renal impairment. However, caution should be observed in patients with renal impairment or patients who may be predisposed to fluid retention. (see sections 4.4 and 5.2)

Children and adolescents: Rayzon has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

Known hypersensitivity to sulphonamides (see sections 4.4 & 4.8).

Active peptic ulceration or gastrointestinal bleeding.
Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥ 10).

Inflammatory bowel disease.

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

There is limited clinical experience with Rayzon treatment beyond two days.

Because of the possibility for increased adverse reactions at higher doses parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see 4.2).

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is an increased risk of gastrointestinal adverse effects for parecoxib, other COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

Rayzon has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Rayzon should be used with caution to treat pain following coronary artery bypass graft surgery as these patients may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m². (see section 4.8)

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of effect on platelets function. Because parecoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) 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 (prior history of MI, angina, ischaemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery).

Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported through postmarketing surveillance in patients receiving valdecoxib, and cannot be ruled out for parecoxib (the prodrug of valdecoxib) (see section 4.8). Parecoxib should be discontinued at the first appearance of skin rash. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions (see Section 4.3).
Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib, and cannot be ruled out for parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Rayzon in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Rayzon in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Rayzon.

Rayzon should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). (see section 4.2)

Rayzon may mask fever and other signs of inflammation. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Rayzon. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Rayzon.

Caution should be exercised when co-administering Rayzon with warfarin and other oral anticoagulants. (see section 4.5)

The use of Rayzon, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Anticoagulant therapy should be monitored, particularly during the first few days after initiating Rayzon therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed. (see 4.4).

Rayzon had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Rayzon can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see 5.1).

Co-administration of parecoxib sodium and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. As for NSAIDs, the risk of acute renal insufficiency may be increased when ACE inhibitors or diuretics are co-administered with parecoxib sodium.

Co-administration of NSAIDs and cyclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when parecoxib sodium and any of these medicinal products are co-administered.

Rayzon may be co-administered with opioid analgesics. When Rayzon was co-administered with morphine, a smaller dose (by 28-36%) of morphine could be used to achieve the same clinical level of analgesia.
**Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)**

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C\text{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib sodium should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C\text{max}) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

**Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products**

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering Rayzon and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Rayzon with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In interaction studies in rheumatoid arthritis patients receiving weekly methotrexate intramuscularly, orally administered valdecoxib (40 mg twice daily) did not have a clinically significant effect on the plasma concentrations of methotrexate. However, adequate monitoring of methotrexate-related toxicity should be considered when co-administering these two medicinal products.

Co-administration of valdecoxib and lithium 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 parecoxib sodium therapy in patients receiving lithium.

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

**Injectable anaesthetics:** Coadministration of IV parecoxib sodium 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib sodium 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

**Inhalation anaesthetics:** No formal interaction studies have been done. In surgery studies in which parecoxib sodium was administered pre-operatively, no evidence of pharmacodynamic interaction was
observed in patients receiving parecoxib sodium and the inhalation anaesthetic agents nitrous oxide and isoflurane. (see section 5.1)

4.6 Pregnancy and lactation

_Pregnancy:_
The use of Rayzon is contraindicated in the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin synthesis, it may cause premature closure of the ductus arteriosus or uterine inertia. (see sections 4.3, 5.1 and 5.3)

Like other medicinal products that inhibit COX-2, Rayzon is not recommended in women attempting to conceive. (see sections 4.4, 5.1 and 5.3)

There are no adequate data from the use of parecoxib sodium in pregnant women or during labour. Studies in animals have shown reproductive effects (see sections 5.1 and 5.3). The potential risk for humans is unknown. Rayzon should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

_Lactation:_
Parecoxib, valdecoxib (its active metabolite) and a valdecoxib active metabolite are excreted in the milk of rats. It is not known whether valdecoxib is excreted in human milk. Rayzon should not be administered to women who breast-feed. (see sections 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effect of Rayzon on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving Rayzon should refrain from driving or operating machines.

4.8 Undesirable effects

Of the Rayzon treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Rayzon 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0% for patients receiving Rayzon and 4.3% for patients receiving placebo.

[Very Common (>1/10), Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

_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

_Psychiatric disorders:_
Common: agitation, insomnia

_Nervous system disorders_
Common: hypoesthesia, cerebrovascular disorder

*Cardiac disorders*
Uncommon: bradycardia

*Vascular disorders*
Common: hypertension, hypotension
Uncommon: aggravated hypertension

*Respiratory, thoracic and mediastinal disorders*
Common: pharyngitis, respiratory insufficiency

*Gastrointestinal disorders*
Common: alveolar osteitis (dry socket), dyspepsia, flatulence
Uncommon: gastroduodenal ulceration

*Skin and subcutaneous tissue disorders*
Common: pruritus
Uncommon: ecchymosis

*Musculoskeletal and connective tissue disorders*
Common: back pain

*Renal and urinary disorders*
Common: oliguria

*General disorders and administration site conditions*
Common: peripheral oedema

*Investigations*
Common: blood creatinine increased
Uncommon: SGOT increased, SGPT increased, BUN increased

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Rayzon: acute renal failure, congestive heart failure, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered Rayzon may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (see section 4.4).

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, myocardial infarction (very rare), erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4).
4.9 Overdose

No case of parecoxib overdose has been reported.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxib, ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

The efficacy of Rayzon was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Rayzon. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

Gastrointestinal studies: In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (≥ 65 years) subjects administered Rayzon (5-21%), although higher than placebo (5-12%), was statistically significantly lower than the incidence observed with NSAIDs (66-90%).

Platelet studies: In a series of small, multiple dose studies in healthy young and elderly subjects, Rayzon 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Rayzon 40 mg twice daily had no clinically significant effect on acetylsalicylic acid -mediated inhibition of platelet function. (see section 4.5)

5.2 Pharmacokinetic properties

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

Absorption

Exposure of valdecoxib following single doses of Rayzon, 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<sub>max</sub> following twice daily administration is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with twice daily dosing.

Following single IV and IM doses of parecoxib sodium 20 mg, C<sub>max</sub> of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C<sub>max</sub> following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average C<sub>max</sub> of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C<sub>max</sub> of valdecoxib is comparable after IM and IV parecoxib sodium administration.

Distribution
The volume of distribution of valdecoxib after its IV administration is approximately 55 liters. 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 and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) 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; 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.

Elimination
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib 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<sub>p</sub>) for valdecoxib is about 6 l/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life (t<sub>1/2</sub>) of valdecoxib is about 8 hours.

Elderly Subjects:
Rayzon has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. 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. (see section 4.2)

Renal Impairment:
In patients with varying degrees of renal impairment administered 20 mg IVRayzon, 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 severe renal impairment or in patients undergoing dialysis. (see section 4.2)

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 score 7-9), treatment should be initiated with half the usual recommended dose of Rayzon 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 Rayzon in patients with severe hepatic impairment is not recommended. (see sections 4.2 and 4.3)

Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib.

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However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) were approximately 0.8-fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and foetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib on male or female fertilities were found in rats.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal period. Parecoxib sodium administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib sodium has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

*Powder*
Dibasic sodium phosphate, heptahydrate
Phosphoric acid and/or sodium hydroxide (for pH adjustment).

*Solvent*
Sodium chloride
Hydrochloric acid or sodium hydroxide (for pH adjustment)
Water for injections.

40 mg vial: When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Rayzon contains approximately 0.44 mEq of sodium per vial.

6.2 Incompatibilities

This medicinal product must **not** be mixed with other medicinal products other than those mentioned in 6.6.

Rayzon and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 g/l (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is **not** recommended.

Use of Sterile Water for Injection is **not** recommended, as the resulting solution is not isotonic.

Injection into an IV line delivering glucose 50 g/l (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in 6.6, is **not** recommended as this may cause precipitation from solution. Rayzon Rayzon

6.3 Shelf life

3 years.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the aseptically prepared product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the
responsibility of the user and would not normally be longer than 12 hours at 25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 **Special precautions for storage**

No special precautions for storage prior to reconstitution.

Do not refrigerate or freeze reconstituted solutions.

6.5 **Nature and contents of container**

*Parecoxib sodium vials*

40 mg vials: Type I colourless glass vials (5 ml) with a laminated stopper, sealed with a yellow flip-off cap on the aluminium overseal.

Solvent ampoules

2 ml ampoule: colourless neutral glass, Type I.

Rayzon is supplied as a sterile, single unit-of-use vial that is packaged with a 2 ml ampoule with a fill volume of 2 ml sodium chloride 9 mg/ml (0.9%) solution (see below for various pack sizes and configurations)

**Pack Sizes**

- 1 x 1 pack: contains 1 vial with parecoxib 40 mg and 1 ampoule with 2 ml sodium chloride 9 mg/ml (0.9%) solution.
- 3 x 3 pack: contains 3 vials with parecoxib 40 mg and 3 ampoule with 2 ml sodium chloride 9 mg/ml (0.9%) solution.
- 5 x 5 pack: contains 5 vials with parecoxib 40 mg and 5 ampoule with 2 ml sodium chloride 9 mg/ml (0.9%) solution.

Not all pack sizes may be marketed.

6.6 **Instructions for use and handling and disposal**

Reconstitute Rayzon 40 mg with 2 ml sodium chloride 9 mg/ml (0.9%) solution using aseptic technique. The only other acceptable solvents for reconstitution are:

*glucose 50 g/l (5%) solution for infusion*

*sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection*

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).

Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

The reconstituted solution is clear and colourless. It should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

The reconstituted product is isotonic.

After reconstitution with acceptable solvents, Rayzon may only be injected IV or IM, or into IV lines delivering:

*sodium chloride 9 mg/ml (0.9%) solution*
glucose 50 g/l (5%) solution for infusion
sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
Ringer-Lactate solution for injection

For single use only. Any unused solution, solvent or waste material should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/210/006-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22\textsuperscript{nd} March 2002

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pharmacia Ltd.
Whalton Road
Morpeth
Northumberland NE61 3YA
United Kingdom

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription

• OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER CARTON: 20 mg</td>
</tr>
<tr>
<td>PACK SIZE: 10 vials</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Rayzon 20 mg
Powder for solution for injection
Parecoxib (as parecoxib sodium)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 20 mg parecoxib, as 21.18 mg parecoxib sodium. When reconstituted with 1 ml solvent, provides 20 mg/ml of parecoxib.

3. **LIST OF EXCIPIENTS**

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for injection
10 vials

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use. Intravenous or intramuscular use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

There are no special storage precautions.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/210/001

13. MANUFACTURER’S BATCH NUMBER

<Batch>/<Lot>{number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT: 20 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rayzon 20 mg

Powder for solution for injection

Parecoxib (as parecoxib sodium)

IV/IM

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
3. **EXPIRY DATE**

<EXP {MM/YYYY}>

4. **BATCH NUMBER**

<Batch>/<Lot> <BN>

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON: 20 mg
PACK SIZE: 1 vial AND 1 solvent ampoule

1. NAME OF THE MEDICINAL PRODUCT

Rayzon 20 mg
Powder and solvent for solution for injection
Parecoxib (as parecoxib sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg parecoxib, as 21.18 mg parecoxib sodium. When reconstituted with 1 ml solvent, provides 20 mg/ml of parecoxib.

3. LIST OF EXCIPIENTS

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.
1 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial and 1 solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmacia Europe EEIG  
Sandwich  
Kent CT13 9NJ  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/210/002

13. **MANUFACTURER'S BATCH NUMBER**

<Batch>/<Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON TEXT: 20 mg
PACK SIZE: 3 vials and 3 solvent ampoules

1. NAME OF THE MEDICINAL PRODUCT

Rayzon 20 mg

Powder and solvent for solution for injection

Parecoxib (as parecoxib sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg parecoxib, as 21.18 mg parecoxib sodium. When reconstituted with 1 ml solvent, provides 20 mg/ml of parecoxib.

3. LIST OF EXCIPIENTS

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.

1 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

3 vials and 3 solvent ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Intravenous or intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmacia Europe EEIG  
Sandwich  
Kent CT13 9NJ  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/210/003

13. **MANUFACTURER'S BATCH NUMBER**

<Batch> <Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**OUTER CARTON TEXT:** 20 mg  
**PACK SIZE:** 5 vials and 5 solvent ampoules

1. **NAME OF THE MEDICINAL PRODUCT**

Rayzon 20 mg  
Powder and solvent for solution for injection  
Parecoxib (as parecoxib sodium)

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 20 mg parecoxib, as 21.18 mg parecoxib sodium. When reconstituted with 1 ml solvent, provides 20 mg/ml of parecoxib.

3. **LIST OF EXCIPIENTS**

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.  
1 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for injection  
5 vials and 5 solvent ampoules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use. Intravenous or intramuscular use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
8. **EXPIRY DATE**

EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmacia Europe EEIG  
Sandwich  
Kent CT13 9NJ  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/210/004

13. **MANUFACTURER'S BATCH NUMBER**

<Batch>/<Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
## MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**SOLVENT AMPOULE TEXT :** 1 ml

### 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sodium chloride 9 mg/ml (0.9%) solution

### 2. METHOD OF ADMINISTRATION

Solvent for Rayzon 20 mg

Read the package leaflet before use.

### 3. EXPIRY DATE

<EXP {MM/YYYY}>

### 4. BATCH NUMBER

<Batch>/<Lot> {number}

### 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

**OUTER CARTON:** 40 mg  
**PACK SIZE:** 10 vials

| 1. NAME OF THE MEDICINAL PRODUCT | Rayzon 40 mg  
Powder for solution for injection  
Parecoxib (as parecoxib sodium) |
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<th></th>
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<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
</tbody>
</table>
| 4. PHARMACEUTICAL FORM AND CONTENTS | Powder for solution for injection  
10 vials |
| 5. METHOD AND ROUTE(S) OF ADMINISTRATION | Read the package leaflet before use. Intravenous or intramuscular use. |
| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN | Keep out of the reach and sight of children. |
| 7. OTHER SPECIAL WARNING(S), IF NECESSARY | |
| 8. EXPIRY DATE | |
EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage precautions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/210/005

13. MANUFACTURER'S BATCH NUMBER

<Batch>/<Lot> {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only. After reconstitution the product should be used immediately.
1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Rayzon 40 mg

Powder for solution for injection

Parecoxib (as parecoxib sodium)

IV/IM

2. **METHOD OF ADMINISTRATION**

Read the package leaflet before use.

3. **EXPIRY DATE**

<EXP {MM/YYYY}>

4. **BATCH NUMBER**

<Batch>/<Lot> {number}

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON: 40 mg
PACK SIZE: 1 vial and 1 solvent ampoule

1. NAME OF THE MEDICINAL PRODUCT

Rayzon 40 mg
Powder and solvent for solution for injection
Parecoxib (as parecoxib sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. When reconstituted with 2 ml solvent, provides 20 mg/ml of parecoxib.

3. LIST OF EXCIPIENTS

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.

2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
1 vial and 1 solvent ampoule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORITY HOLDER**

Pharmacia Europe EEIG  
Sandwich  
Kent CT13 9NJ  
United Kingdom

12. **MARKETING AUTHORIZATION NUMBER(S)**

EU/1/02/210/006

13. **MANUFACTURER'S BATCH NUMBER**

<Batch>/<Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
1. NAME OF THE MEDICINAL PRODUCT

Rayzon 40 mg

Powder and solvent for solution for injection

Parecoxib (as parecoxib sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. When reconstituted with 2 ml solvent, provides 20 mg/ml of parecoxib.

3. LIST OF EXCIPIENTS

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.

2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

3 vials and 3 solvent ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Intravenous or intramuscular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmacia Europe EEIG
Sandwich
Kent CT13 9NJ
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/210/007

13. **MANUFACTURER'S BATCH NUMBER**

<Batch>/<Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON TEXT: 40 mg
PACK SIZE: 5 vials and 5 solvent ampoules

1. NAME OF THE MEDICINAL PRODUCT

Rayzon 40 mg
Powder and solvent for solution for injection
Parecoxib (as parecoxib sodium)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 40 mg parecoxib, as 42.36 mg parecoxib sodium. When reconstituted with 2 ml solvent, provides 20 mg/ml of parecoxib.

3. LIST OF EXCIPIENTS

Also contains dibasic sodium phosphate heptahydrate, phosphoric acid and sodium hydroxide.
2 ml solvent ampoule contains sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
5 vials and 5 solvent ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Intravenous or intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
9. **SPECIAL STORAGE CONDITIONS**

There are no special storage instructions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pharmacia Europe EEIG  
Sandwich  
Kent CT13 9NJ  
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/02/210/008

13. **MANUFACTURER'S BATCH NUMBER**

<Batch>/<Lot> {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

For single use only. After reconstitution the product should be used immediately.
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**SOLVENT AMPOULE TEXT:** 2 ml

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<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tr>
<td>Sodium chloride 9 mg/ml (0.9%) solution</td>
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</tbody>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent for Rayzon 40 mg</td>
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<tr>
<td>Read the package leaflet before use.</td>
</tr>
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<table>
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<th>3. EXPIRY DATE</th>
</tr>
</thead>
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<td>&lt;EXP {MM/YYYY}&gt;</td>
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<table>
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<th>4. BATCH NUMBER</th>
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<tr>
<td>&lt;Batch&gt;/&lt;Lot&gt; {number}</td>
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<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
</tr>
</tbody>
</table>
ANNEX III

B. PACKAGE LEAFLET
PACKAGE LEAFLET

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

What’s in this leaflet:
1. What Rayzon is and what it’s used for
2. Before you are given Rayzon
3. How the injection is given
4. Possible side effects
5. Storing Rayzon
6. Other information
7. Information for the Health Professional

Rayzon 20 mg powder for solution for injection

The active substance in Rayzon is parecoxib 20 mg/vial (as 21.18 mg parecoxib sodium). After reconstitution the final concentration of parecoxib is 20 mg/ml.

Other ingredients are dibasic sodium phosphate heptahydrate; phosphoric acid and/or sodium hydroxide may have been added for pH adjustment.

Marketing authorisation holder: Pharmacia Europe EEIG, Sandwich, Kent CT13 9NJ, United Kingdom.

Manufacturer: Pharmacia Limited, Whalton Road, Morpeth, Northumberland NE61 3YA, United Kingdom.

1. WHAT Rayzon IS AND WHAT IT’S USED FOR

Rayzon is a powder for solution for injection. It is supplied in cartons containing 10 glass vials.

Rayzon is used to treat pain. The injection is given to you by a doctor or nurse, usually in a hospital or clinic, such as after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for cyclo-oxygenase-2 inhibitors).

Pain and swelling are sometimes caused by substances in the body called prostaglandins. Rayzon works by lowering the amount of these prostaglandins. There are other prostaglandins that protect the stomach lining or cause the blood to clot, and Rayzon does not affect those.

2. BEFORE YOU ARE GIVEN Rayzon

You will not be given Rayzon...
- if you are hypersensitive (allergic) to parecoxib or any of the other ingredients of Rayzon
- if you have had an allergic reaction to a group of medicines called “sulphonamides” (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have severe heart failure

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

**Taking special care with Rayzon**
Some people will need special care from their doctors when they are given Rayzon.

**Make sure your doctor knows,** before you are given Rayzon …
- If you have had an ulcer, bleeding or perforation of the gastrointestinal tract
- If you are taking acetylsalicylic acid or other NSAIDs (e.g. ibuprofen)
- If you have heart failure, ischaemic heart disease, high blood pressure, or if you are about to have heart surgery and have had a stroke
- If you are taking anti-platelet therapies (e.g. acetylsalicylic acid)
- If you have fluid retention (*œdema*)
- If you have liver or kidney disease
- If you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- If you have an infection as it may hide a fever (which is a sign of infection)
- If you use medicines to reduce blood clotting (e.g. warfarin)
- If you are a woman trying to become pregnant

**Pregnant or breast-feeding women**
- If you are pregnant, tell your doctor, as Rayzon may not be right for you. You will not be given Rayzon in the last three months of pregnancy.
- If you are breast-feeding, you must not have Rayzon. Ask your doctor for advice: it may be better to stop breast-feeding altogether to take the injections.

Get advice from a doctor or pharmacist before taking any medicine if you’re pregnant or breast-feeding.

**Driving or using machines**
If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

**Other medicines and Rayzon**
**Tell your doctor or nurse about any other medicines** you are taking or took recently (in the last week) – even medicines you bought yourself without a prescription. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Rayzon or other medicines, or you may need to take a different medicine. It’s especially important to mention:

- Acetylsalicylic acid or other anti-inflammatory drugs
- Fluconazole – used for fungal infections
- ACE inhibitors – used for high blood pressure and heart conditions
- Cyclosporin or Tacrolimus – used after transplants
- Warfarin – or other medicines used to prevent blood clots
- Lithium – used to treat depression.
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Theophylline – used for asthma
- Methotrexate – used for rheumatoid arthritis and cancer
- Antidepressants – used to treat depression
- Neuroleptics – used to treat psychoses

Rayzon can be used in combination with low dose acetylsalicylic acid
3. HOW THE INJECTION IS GIVEN

Rayzon will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. You will only be given Rayzon for short periods, and only for pain relief.

If there are particles in the injection solution or if either the powder or solution is discoloured, the product will not be used.

The usual dose to start with is 40 mg.
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.
You will not be given more than 80 mg in 24 hours.

Some people may be given lower doses:
- People with liver problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

Children and adolescents under the age of 18 will not be given Rayzon. People aged 18 and over will be given the adult dose.

4. POSSIBLE SIDE EFFECTS

Some people given Rayzon can have side effects. If you notice any of these, or any other effects of the injections not mentioned, tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.

More common effects
These could affect between 1 and 10 in every 100 people
- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual.
> If any of these affects you, talk to your doctor or nurse.

Uncommon effects
These could affect less than 1 in every 100 people
- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.
> If any of these affects you, talk to your doctor or nurse.

Rare Effects
These could affect less than 1 in every 1000 people.
- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin.

> If any of these affects you, tell your doctor or nurse immediately.

5. STORING Rayzon

For Section 5
please turn over >

There are no special storage instructions.

Keep out of the reach or sight of children.

The product should not be used after the expiry date stated on the label.

Your doctor will use Rayzon as soon as possible after it is mixed with solvent.

If there are particles in the injection solution or if either the powder or solution is discoloured, the solution will not be used.
6. OTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Deutschland
Pfizer GmbH
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Eesti
Pfizer H.C.P. Corporation Eesti
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Magyarország
Pfizer Kft.
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Malta
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Nederland
Pfizer bv
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Norge
Pfizer AS
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Österreich
Pfizer Corporation Austria Ges.m.b.H.
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Portugal
Laboratórios Pfizer, Lda.
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Pfizer Polska Sp. z o.o.
Tel.: +48 22 549 38 00

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Laboratórios Pfizer, Lda.
Tel: 351 21 423 5500

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Slovenská republika
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Latvija
Pfizer H.C.P. Corporation
Tel: +371 70 35 775

United Kingdom
Pfizer Limited
Tel: +44 (0)1737 331111

Lietuva
Pfizer H.C.P. Corporation Representation Office in Lithuania
Tel: +3705 2514000

This leaflet was last approved on {date}
Administration is by intramuscular (IM) or intravenous (IV) injection. The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. Rayzon

This medicinal product must not be mixed with other medicinal products and is to be reconstituted only with:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).

20 mg vial: Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the parecoxib 20 mg vial. Withdraw with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 20 mg vial.

Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use.

The entire contents of the vial should be withdrawn for a single administration.

After reconstitution with acceptable solvents, Rayzon may only be injected into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

The reconstituted solution must not be used if discoloured or cloudy or if particulate matter is observed.

The solution is for single use only and must not be stored in a refrigerator or freezer.
READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU ARE GIVEN THIS MEDICINE.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

WHAT’S IN THIS LEAFLET:
1. What Rayzon is and what it’s used for
2. Before you are given Rayzon
3. How the injection is given
4. Possible side effects
5. Storing Rayzon
6. Other information
7. Information for the Health Professional

Rayzon 20 mg powder and solvent for solution for injection

The active substance in Rayzon is parecoxib 20 mg/vial (as 21.18 mg parecoxib sodium). After reconstitution the final concentration of parecoxib is 20 mg/ml.

Other ingredients are dibasic sodium phosphate heptahydrate; phosphoric acid and/or sodium hydroxide may have been added for pH adjustment.

The liquid solvent to dissolve the powder contains sodium chloride and water for injections. Small amounts of hydrochloric aid or sodium hydroxide may have been added for pH-adjustment.

Marketing authorisation holder: Pharmacia Europe EEIG, Sandwich, Kent CT13 9NJ, United Kingdom.

Manufacturer: Pharmacia Limited, Whalton Road, Morpeth, Northumberland NE61 3YA, United Kingdom.

1. WHAT Rayzon IS AND WHAT IT’S USED FOR

Rayzon is a powder for solution for injection. It is supplied in cartons containing 1, 3 or 5 vials that also contain 1,3 or 5 glass ampoules of a solvent for dissolving the contents of the vials.

Rayzon is used to treat pain. The injection is given to you by a doctor or nurse, usually in a hospital or clinic, such as after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for cyclo-oxygenase-2 inhibitors).

Pain and swelling are sometimes caused by substances in the body called prostaglandins. Rayzon works by lowering the amount of these prostaglandins. There are other prostaglandins that protect the stomach lining or cause the blood to clot, and Rayzon does not affect those.

2. BEFORE YOU ARE GIVEN Rayzon

You will not be given Rayzon…
- if you are hypersensitive (allergic) to parecoxib or any of the other ingredients of Rayzon
- if you have had an allergic reaction to a group of medicines called “sulphonamides” (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly
blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have severe heart failure

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

**Taking special care with Rayzon**

Some people will need special care from their doctors when they are given Rayzon. **Make sure your doctor knows, before you are given Rayzon …**

- If you have had an ulcer, bleeding or perforation of the gastrointestinal tract
- If you are taking acetylsalicylic acid or other NSAIDs (e.g. ibuprofen)
- If you have heart failure, ischaemic heart disease, high blood pressure, or if you are about to have heart surgery and have had a stroke
- If you are taking anti-platelet therapies (e.g. acetylsalicylic acid)
- If you have fluid retention (oedema)
- If you have liver or kidney disease
- If you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- If you have an infection as it may hide a fever (which is a sign of infection)
- If you use medicines to reduce blood clotting (e.g. warfarin)
- If you are a woman trying to become pregnant

**Pregnant or breast-feeding women**

- If you are pregnant, tell your doctor, as Rayzon may not be right for you. You will not be given Rayzon in the last three months of pregnancy.
- If you are breast-feeding, you must not have Rayzon. Ask your doctor for advice: it may be better to stop breast-feeding altogether to take the injections.

Get advice from a doctor or pharmacist before taking any medicine if you’re pregnant or breast-feeding.

**Driving or using machines**

If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

**Other medicines and Rayzon**

**Tell your doctor or nurse about any other medicines** you are taking or took recently (in the last week) – even medicines you bought yourself without a prescription. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Rayzon or other medicines, or you may need to take a different medicine. It’s especially important to mention:

- Acetylsalicylic acid or other anti-inflammatory drugs
- Fluconazole – used for fungal infections
- ACE inhibitors – used for high blood pressure and heart conditions
- Cyclosporin or Tacrolimus – used after transplants
- Warfarin – or other medicines used to prevent blood clots
- Lithium – used to treat depression.
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Theophylline – used for asthma
- Methotrexate – used for rheumatoid arthritis and cancer
- Antidepressants – used to treat depression
- Neuroleptics – used to treat psychoses

Rayzon can be used in combination with low dose acetylsalicylic acid

3. HOW THE INJECTION IS GIVEN

Rayzon will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. You will only be given Rayzon for short periods, and only for pain relief.

If there are particles in the injection solution or if either the powder or solution is discoloured, the product will not be used.

The usual dose to start with is 40 mg.
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.
You will not be given more than 80 mg in 24 hours.

Some people may be given lower doses:
- People with liver problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

Children and adolescents under the age of 18 will not be given Rayzon. People aged 18 and over will be given the adult dose.

4. POSSIBLE SIDE EFFECTS

Some people given Rayzon can have side effects. If you notice any of these, or any other effects of the injections not mentioned, tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.

More common effects
These could affect between 1 and 10 in every 100 people
- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual.
> If any of these affects you, talk to your doctor or nurse.

Uncommon effects
These could affect less than 1 in every 100 people
- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.
If any of these affects you, talk to your doctor or nurse.

**Rare Effects**

These could affect less than 1 in every 1000 people.

- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin.

> If any of these affects you, tell your doctor or nurse immediately.

5. **STORING Rayzon**

For Section 5

Please turn over >

There are no special storage instructions.

Keep out of the reach or sight of children.

The product should not be used after the expiry date stated on the label.

Your doctor will use Rayzon as soon as possible after it is mixed with solvent. **If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.
6. OTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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7. INFORMATION FOR THE HEALTH PROFESSIONAL

**Administration is by intramuscular (IM) or intravenous (IV) injection.** The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line.

**This medicinal product must not be mixed** with other medicinal products and is to be reconstituted only with:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

**Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).**

20 mg vial: Remove the yellow flip-off cap to expose the central portion of the rubber stopper of the parecoxib 20 mg vial. Withdraw with a sterile needle and syringe, 1 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 20 mg vial.

**Dissolve the powder completely** using a gentle swirling motion and inspect the reconstituted product before use.

**The entire contents of the vial should be withdrawn for a single administration.**

**After reconstitution** with acceptable solvents, Rayzon may only be injected into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

**The reconstituted solution must not be used** if discoloured or cloudy or if particulate matter is observed.

**The solution is for single use only and must not be stored in a refrigerator or freezer.**
Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

What’s in this leaflet:
1. What Rayzon is and what it’s used for
2. Before you are given Rayzon
3. How the injection is given
4. Possible side effects
5. Storing Rayzon
6. Other information
7. Information for the Health Professional

Rayzon 40 mg powder for solution for injection

The active substance in Rayzon is parecoxib 40 mg/vial (as 42.36 mg parecoxib sodium). After reconstitution the final concentration of parecoxib is 20 mg/ml.

Other ingredients are dibasic sodium phosphate heptahydrate; phosphoric acid and/or sodium hydroxide may have been added for pH adjustment.

Marketing authorisation holder: Pharmacia Europe EEIG, Sandwich, Kent CT13 9NJ, United Kingdom.

Manufacturer: Pharmacia Limited, Whalton Road, Morpeth, Northumberland NE61 3YA, United Kingdom.

1. WHAT Rayzon IS AND WHAT IT’S USED FOR

Rayzon is a powder for solution for injection. It is supplied in cartons containing 10 glass vials.

Rayzon is used to treat pain. The injection is given to you by a doctor or nurse, usually in a hospital or clinic, such as after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for cyclo-oxygenase-2 inhibitors).

Pain and swelling are sometimes caused by substances in the body called prostaglandins. Rayzon works by lowering the amount of these prostaglandins. There are other prostaglandins that protect the stomach lining or cause the blood to clot, and Rayzon does not affect those.

2. BEFORE YOU ARE GIVEN Rayzon

You will not be given Rayzon...
- if you are hypersensitive (allergic) to parecoxib or any of the other ingredients of Rayzon
- if you have had an allergic reaction to a group of medicines called “sulphonamides” (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have severe heart failure

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

**Taking special care with Rayzon**
Some people will need special care from their doctors when they are given Rayzon.

- **Make sure your doctor knows**, before you are given Rayzon …
- **If you have had an ulcer, bleeding or perforation of the gastrointestinal tract**
- **If you are taking acetylsalicylic acid or other NSAIDs** (e.g. ibuprofen)
- **If you have heart failure, ischaemic heart disease, high blood pressure, or if you are about to have heart surgery and have had a stroke**
- **If you are taking anti-platelet therapies** (e.g. acetylsalicylic acid)
- **If you have fluid retention** (*oedema*)
- **If you have liver or kidney disease**
- **If you might be dehydrated** – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- **If you have an infection** as it may hide a fever (which is a sign of infection)
- **If you use medicines to reduce blood clotting** (e.g. warfarin)
- **If you are a woman trying to become pregnant**

**Pregnant or breast-feeding women**

- **If you are pregnant**, tell your doctor, as Rayzon may not be right for you. You will not be given Rayzon in the last three months of pregnancy.
- **If you are breast-feeding**, you must not have Rayzon. Ask your doctor for advice: it may be better to stop breast-feeding altogether to take the injections.

Get advice from a doctor or pharmacist before taking any medicine if you’re pregnant or breast-feeding.

**Driving or using machines**
If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

**Other medicines and Rayzon**
Tell your doctor or nurse about any other medicines you are taking or took recently (in the last week) – even medicines you bought yourself without a prescription. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Rayzon or other medicines, or you may need to take a different medicine. It’s especially important to mention:

- Acetylsalicylic acid or other anti-inflammatory drugs
- Fluconazole – used for fungal infections
- ACE inhibitors – used for high blood pressure and heart conditions
- Cyclosporin or Tacrolimus – used after transplants
- Warfarin – or other medicines used to prevent blood clots
- Lithium – used to treat depression.
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Theophylline – used for asthma
- Methotrexate – used for rheumatoid arthritis and cancer
- Antidepressants – used to treat depression
- Neuroleptics – used to treat psychoses

Rayzon can be used in combination with low dose acetylsalicylic acid
3. HOW THE INJECTION IS GIVEN

Rayzon will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. You will only be given Rayzon for short periods, and only for pain relief.

If there are particles in the injection solution or if either the powder or solution is discoloured, the product will not be used.

The usual dose to start with is 40 mg.
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.
You will not be given more than 80 mg in 24 hours.

Some people may be given lower doses:
- People with liver problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

Children and adolescents under the age of 18 will not be given Rayzon. People aged 18 and over will be given the adult dose.

4. POSSIBLE SIDE EFFECTS

Some people given Rayzon can have side effects. If you notice any of these, or any other effects of the injections not mentioned, tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.

More common effects
These could affect between 1 and 10 in every 100 people
- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual.
> If any of these affects you, talk to your doctor or nurse.

Uncommon effects
These could affect less than 1 in every 100 people
- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.
> If any of these affects you, talk to your doctor or nurse.

Rare Effects
These could affect less than 1 in every 1000 people.
- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin.
> If any of these affects you, tell your doctor or nurse immediately.

5. **STORING Rayzon**

*For Section 5*
please turn over >

There are no special storage instructions.

Keep out of the reach or sight of children.

The product should not be used after the expiry date stated on the label.

Your doctor will use Rayzon as soon as possible after it is mixed with solvent. **If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.
6. OTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}
Administration is by intramuscular (IM) or intravenous (IV) injection. The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. Rayzon

**This medicinal product must not be mixed** with other medicinal products and is to be reconstituted only with:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

**Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).**

40 mg vial: Remove the purple flip-off cap to expose the central portion of the rubber stopper of the 40 mg vial. Withdraw with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 40 mg vial.

Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use.

**The entire contents of the vial should be withdrawn for a single administration.**

After reconstitution with acceptable solvents, Rayzon may only be injected into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

The reconstituted solution must not be used if discoloured or cloudy or if particulate matter is observed.

The solution is for single use only and must not be stored in a refrigerator or freezer.
1. WHAT Rayzon IS AND WHAT IT’S USED FOR

Rayzon is a powder for solution for injection. It is supplied in cartons containing 1, 3 or 5 vials that also contain 1,3 or 5 glass ampoules of a solvent for dissolving the contents of the vials.

Rayzon is used to treat pain. The injection is given to you by a doctor or nurse, usually in a hospital or clinic, such as after an operation. It is one of a family of medicines called COX-2 inhibitors (this is short for cyclo-oxygenase-2 inhibitors).

Pain and swelling are sometimes caused by substances in the body called prostaglandins. Rayzon works by lowering the amount of these prostaglandins. There are other prostaglandins that protect the stomach lining or cause the blood to clot, and Rayzon does not affect those.

2. BEFORE YOU ARE GIVEN Rayzon

You will not be given Rayzon…
- if you are hypersensitive (allergic) to parecoxib or any of the other ingredients of Rayzon
- if you have had an allergic reaction to a group of medicines called “sulphonamides” (e.g. some antibiotics used to treat infections)
- if you have a gastric or intestinal ulcer or gastrointestinal bleeding
- if you have had an allergic reaction to acetylsalicylic acid (aspirin) or to other NSAIDs (e.g. ibuprofen) or to COX-2 inhibitors. Reactions might include wheezing (bronchospasm), badly
blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines
- if you are more than 6 months pregnant
- if you are breastfeeding
- if you have severe liver disease
- if you have inflammation of the intestines (ulcerative colitis or Crohn’s disease)
- if you have severe heart failure

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

**Taking special care with Rayzon**
Some people will need special care from their doctors when they are given Rayzon. **Make sure your doctor knows,** before you are given Rayzon …

- **If you have had an ulcer, bleeding or perforation of the gastrointestinal tract**
- **If you are taking acetylsalicylic acid or other NSAIDs** (e.g. ibuprofen)
- **If you have heart failure, ischaemic heart disease, high blood pressure, or if you are about to have heart surgery and have had a stroke**
- **If you are taking anti-platelet therapies** (e.g. acetylsalicylic acid)
- **If you have fluid retention** *(oedema)*
- **If you have liver or kidney disease**
- **If you might be dehydrated** – this may happen if you have had diarrhoea or have been vomiting (being sick) or unable to drink fluids
- **If you have an infection** as it may hide a fever (which is a sign of infection)
- **If you use medicines to reduce blood clotting** (e.g. warfarin)
- **If you are a woman trying to become pregnant**

**Pregnant or breast-feeding women**

- **If you are pregnant,** tell your doctor, as Rayzon may not be right for you. You will not be given Rayzon in the last three months of pregnancy.
- **If you are breast-feeding,** you must not have Rayzon. Ask your doctor for advice: it may be better to stop breast-feeding altogether to take the injections.

Get advice from a doctor or pharmacist before taking any medicine if you’re pregnant or breast-feeding.

**Driving or using machines**
If the injection makes you feel dizzy or tired, do not drive or use machines until you feel better again.

**Other medicines and Rayzon**
**Tell your doctor or nurse about any other medicines** you are taking or took recently (in the last week) – even medicines you bought yourself without a prescription. Medicines can sometimes interfere with each other. Your doctor may reduce the dose of Rayzon or other medicines, or you may need to take a different medicine. It’s especially important to mention:

- Acetylsalicylic acid or other anti-inflammatory drugs
- Fluconazole – used for fungal infections
- ACE inhibitors – used for high blood pressure and heart conditions
- Cyclosporin or Tacrolimus – used after transplants
- Warfarin – or other medicines used to prevent blood clots
- Lithium – used to treat depression.
- Rifampicin – used for bacterial infections
- Antiarrhythmics – used to treat an irregular heartbeat
- Phenytoin or Carbamazepine – used for epilepsy
- Theophylline – used for asthma
- Methotrexate – used for rheumatoid arthritis and cancer
- Antidepressants – used to treat depression
- Neuroleptics – used to treat psychoses

Rayzon can be used in combination with low dose acetylsalicylic acid

3. **HOW THE INJECTION IS GIVEN**

Rayzon will be given to you by a doctor or nurse. They will dissolve the powder before giving you the injection, and will inject the solution into a vein or a muscle. You will only be given Rayzon for short periods, and only for pain relief.

**If there are particles** in the injection solution or if either the powder or solution is discoloured, the product will not be used.

**The usual dose to start with is 40 mg.**
You may be given another dose – either 20 mg or 40 mg – 6 to 12 hours after the first one.
**You will not be given more than 80 mg in 24 hours.**

**Some people may be given lower doses:**
- People with liver problems
- Patients over 65 who weigh less than 50 kg
- People taking fluconazole.

**Children and adolescents under the age of 18 will not be given** Rayzon. People aged 18 and over will be given the adult dose.

4. **POSSIBLE SIDE EFFECTS**

Some people given Rayzon can have side effects. If you notice any of these, or any other effects of the injections not mentioned, **tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.**

**More common effects**  
*These could affect between 1 and 10 in every 100 people*
- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual.

>*If any of these affects you, talk to your doctor or nurse.*

**Uncommon effects**  
*These could affect less than 1 in every 100 people*
- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.
> If any of these affects you, talk to your doctor or nurse.

**Rare Effects**
*These could affect less than 1 in every 1000 people.*
- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin.

> If any of these affects you, tell your doctor or nurse immediately.

5. **STORING Rayzon**

For Section 5
please turn over >

There are no special storage instructions.

Keep out of the reach or sight of children.

The product should not be used after the expiry date stated on the label.

Your doctor will use Rayzon as soon as possible after it is mixed with solvent.
**If there are particles** in the injection solution or if either the powder or solution is discoloured, the solution will not be used.
6. OTHER INFORMATION

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This leaflet was last approved on {date}
7. INFORMATION FOR THE HEALTH PROFESSIONAL

**Administration is by intramuscular (IM) or intravenous (IV) injection.** The IM injection is to be given slowly and deeply into the muscle and the IV bolus injection may be given rapidly and directly into a vein or into an existing IV line.

**This medicinal product must not be mixed** with other medicinal products and is to be reconstituted only with:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection

**Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib sodium).**

**40 mg vial:** Remove the purple flip-off cap to expose the central portion of the rubber stopper of the 40 mg vial. Withdraw with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the parecoxib 40 mg vial.

**Dissolve the powder completely** using a gentle swirling motion and inspect the reconstituted product before use.

**The entire contents of the vial should be withdrawn for a single administration.**

**After reconstitution** with acceptable solvents, Rayzon may only be injected into IV lines delivering:

- sodium chloride 9 mg/ml (0.9%) solution
- glucose 50 g/l (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 g/l (5%) solution for injection
- Ringer-Lactate solution for injection

**The reconstituted solution must not be used** if discoloured or cloudy or if particulate matter is observed.

**The solution is for single use only and must not be stored in a refrigerator or freezer.**