RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	Parecoxib sodium
Pharmaco-therapeutic group (ATC Code):	M01AH04
Name of Marketing Authorisation Holder or Applicant:	Pfizer Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Dynastat®

Data lock point for current RMP	31 March 2014	Version number	4.1
Date of final sign off	17 March 2015		

1. PART I: PRODUCT(S) OVERVIEW

Administrative Information on the RMP

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	*Version Number of RMP When Last Submitted/or Not Applicable
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	18 June 2014	4.0
	SII Non-clinical part of the safety specification	18 June 2014	4.0
	SIII Clinical trial exposure	18 June 2014	4.0
	SIV Populations not studied in clinical trials	18 June 2014	4.0
	SV Post-authorisation experience	18 June 2014	4.0
	SVI Additional EU requirements for the safety specification	18 June 2014	4.0
	SVII Identified and potential risks	18 June 2014	4.0
	SVIII Summary of the safety concerns	18 June 2014	4.0
Part III Pharmacovigilance Plan		18 June 2014	4.0
Part IV Plan for Post-Authorisation Efficacy Studies		18 June 2014	4.0
Part V Risk Minimisation Measures		18 June 2014	4.0
Part VI Summary of RMP		17 March 2015	4.1
Part VII Annexes	**ANNEX 2** Current or proposed SmPC/PIL	18 June 2014	4.0
	ANNEX 3 Worldwide marketing status by country	18 June 2014	4.0
	ANNEX 4 Synopsis of clinical trial programme	18 June 2014	4.0
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	18 June 2014	4.0
	ANNEX 6 Protocols for proposed and ongoing studies in Part III	NA	NA
	ANNEX 7 Specific adverse event follow-up forms	NA	NA
	ANNEX 8 Protocols for studies in Part IV	NA	NA

Part	Module/Annex	Date Last Updated for Submission (Sign Off Date)	*Version Number of RMP When Last Submitted/or Not Applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	NA	NA
	ANNEX 10 Details of proposed additional risk minimisation activities	NA	NA
	ANNEX 11 Mock up examples	NA	NA
	ANNEX 12 Other supporting data	18 June 2014	4.0

QPPV name	MariaGrazia Zurlo, MD
QPPV signature	[redacted]
Contact person for this RMP	
E-mail address or telephone number of contact person	

Overview of Versions

Version number of last agreed RMP:

Version number	4.0
Agreed within	Centralized Procedure EMEA/H/C/000381

Current RMP Versions Under Evaluation

RMP Version Number	Submitted on	Submitted Within
Not applicable	Not applicable	Not applicable

Invented name(s) in the European Economic Area (EEA)	Dynastat®
Authorisation procedure	Centralised EMEA/H/C/000381
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Parecoxib is a non-steroidal anti-inflammatory drug (NSAID) developed for the management of acute pain. Parecoxib is a prodrug of valdecoxib, a selective inhibitor of cyclooxygenase-2 (COX-2), the cyclooxygenase isoform that has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever.
Indication(s) in the EEA	Parecoxib is indicated in Europe for the short-term treatment of postoperative pain in adults.
Posology and route of administration in the EEA	**Posology:** The recommended dose is 40 mg administered intravenous (IV) or intramuscular (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. **Concomitant Use With Opioid Analgesics:** Opioid analgesics can be used concurrently with parecoxib, dosing as described above.
Pharmaceutical form(s) and strengths	**Forms:** Powder for solution for injection Powder and solvent for solution for injection **Strengths:** 40-mg vial: Each vial contains 40 mg parecoxib (present as 42.36 mg parecoxib sodium) for reconstitution with 2 mL of solvent. After reconstitution, the final concentration of parecoxib is 20 mg/mL.

Country and date of first authorisation worldwide

Mexico	19 May 2001

Country and date of first launch worldwide	Mexico	19 May 2001

Country and date of first authorisation in the EEA	Europe	22 March 2002

Is the product subject to additional monitoring in the EU? Yes [ ] No [X]

LIST OF ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AUC	Area Under the Plasma Concentration–Time Curve
BID	bis in die, Twice Daily
BSE	Bovine Spongiform Encephalopathy
CABG	Coronary Artery Bypass Graft
CDS	Core Data Sheet
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
COX	Cyclooxygenase
CV	Cardiovascular
DVT	Deep Vein Thrombosis
EA	Epidural Analgesia
ED	Exfoliative Dermatitis
EM	Erythema Multiforme
EMA	European Medicines Agency (current)
EMEA	European Agency for the Evaluation of Medicinal Products (prior to late 2009)
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration (United States)
GI	Gastrointestinal
HCP	Health Care Professional
HLGT	High Level Group Terms
ICD	International Classification of Diseases
IM	Intramuscular
IMS	Intercontinental Marketing Services
INR	International Normalised Ratio
IV	Intravenous
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial Infarction
mL	Milliliter
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSAS	National Survey of Ambulatory Surgery
PE	Pulmonary Embolism
PIL	Package Information Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	quaque die, Once Daily
RMP	Risk Management Plan
RTU	Ready to Use

SAE	Serious Adverse Event
SCAR	Severe Cutaneous Adverse Reaction
SJS	Stevens-Johnson Syndrome
SmPC or SPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SSI	Surgical Site Infection
TEN	Toxic Epidermal Necrolysis
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
UK	United Kingdom
US	United States
VTE	Venous Thromboembolism

2. PART II: SAFETY SPECIFICATION

2.1. Part II: Module SI—Epidemiology of the Indication(s) and Target Population

Indication

In Europe, parecoxib is indicated for the short-term treatment of postoperative pain in adults.

Worldwide, parecoxib is indicated for management of acute pain; preoperatively to prevent or reduce postoperative pain (pre-emptive analgesia); or concomitantly with opioid analgesics to reduce opioid requirements.

2.1.1. Epidemiology of the Disease

2.1.1.1. Incidence and Prevalence

Incidence

Annual incidence of surgery in the European Union (EU)

It has been estimated that in developed countries 5% to 10% of the general population undergo surgery each year. Using the 2003-2004 data from the United Kingdom (UK) Hospital Episode Statistics database,[1] Decision Resources[2] estimated the total number and incidence rates of select surgical procedures typically associated with moderate-to-severe post-operative pain in 5 European countries (France, Germany, Italy, Spain and the UK). The estimates for the year 2004 are shown below.[2]

Surgery Type	Annual Incidence	
	Count	Rate per 10,000*
Orthopaedic procedures		
Replacement (hip, knee)	723,200	27.4-31.5
Other orthopaedic procedures	2,741,800	104.0-119.6
Appendectomy (excluding incidental)	125,500	5.0-5.3
Cholecystectomy	264,100	10.6-11.0
Coronary artery bypass graft	125,400	4.8-5.5
Debridement of wound, burn, or infection	314,600	12.8-13.0
Partial colectomy	104,800	4.1-4.5
Lysis of peritoneal adhesions	109,400	4.4-4.6
Laminectomy/Excision of intervertebral disk	215,200	8.7-8.9
Caesarean section	617,800	47.0-50.8 (Females)
Hysterectomy	246,700	19.4-19.5 (Females)
Mastectomy	138,200	10.8-11.1 (Females)
Oöphorectomy	136,000	10.5-11.0 (Females)
Prostatectomy	172,800	13.7-15.8 (Males)

* Ranges reflect projected variation of rates across European countries.

Oral surgery

The incidence of secondary care oral surgery services can be estimated using the data from the UK hospital episode statistics database.[1] According to HES, there were 60,904 in-hospital oral surgeries performed during the period 1989–1994 in the population served by the West Midlands Regional Health Authority (approximately 5.5 million people).[3,4] Using

these data, the annual incidence of hospital oral surgery can be estimated roughly at 22.2 per 10,000.

Experience of post-operative pain by surgery patients

Despite the development of new standards for pain management, many patients continue to experience intense pain after surgery. For example, in a study of 250 adults who had recently undergone surgery in the US and were administered telephone questionnaires, approximately 80% experienced acute pain after surgery.[5] Of those patients, 86% had moderate, severe, or extreme pain.

Prevalence

Due to the nature of the indication (short-term treatment of postoperative pain), prevalence data are not applicable.

2.1.1.2. Demographics of the Target Population – Age, Sex, Race/Ethnic Origin

The demographic profile of patients experiencing postoperative pain varies greatly. The data for the populations of orthopaedic surgery and oral surgery patients are summarized below.

2.1.1.2.1. Demographic profile of orthopaedic surgery patients

Age

The majority of patients undergoing hip or knee replacement surgery are over the age of 60 to 65. For example, in a study of total hip replacement patients in the Netherlands and Sweden (17,401 and 10,015 patients in 1997, respectively), over 70% were aged 65 years or older.[6] Similarly, in a study of patients admitted for elective orthopaedic surgery in Finland in 1981 to 1990, almost 79% of those who had undergone hip or knee replacement procedures were aged older than 60 years.[7] Patients undergoing arthroscopy and vertebral procedures tend to be younger than hip or knee replacement patients. In the same study of elective orthopaedic surgery in Finland, 75.5% of lumbar disc herniation patients and 84.9% of knee arthroscopy patients were younger than 50 years of age.[7]

Gender

The literature suggests that women account for over 60% of major orthopaedic surgeries. For instance, in a recent study of 715 elective major orthopaedic surgery patients in a single institution in Spain, 67.6% were females.[8] Of 41,223 primary knee arthroplasties recorded in the Swedish Knee Arthroplasty Registry (1988-1997), 67% were done in female patients.[9]

2.1.1.2.2. Demographic profile of oral surgery patients

In a study of 5,877 patients undergoing ambulatory oral surgery in 3 oral surgery centers in Madrid, Spain, most of the patients (59.2%) were 21 to 40 years of age, followed by those under the age of 20 (31.7%), those 41 to 64 years of age (7.1%), and those over the age of 65 (1.9%).[10] Females predominated over males (62% vs. 38%, respectively).

2.1.1.3. Risk Factors for the Disease

Due to the nature of the indication (short-term treatment of postoperative pain), "risk factors for the disease" are not directly applicable. Procedures commonly requiring postoperative pain management include but are not limited to oral surgery, orthopaedic procedures, caesarean sections, hysterectomy, prostatectomy, cholecystectomy and debridement of wound, burn or infection[2] and risk factors are generally procedure specific although increasing age, pre-operative impairment of activities of daily living, emergency operation, and high American Society of Anesthesiology classification grade predict mortality following surgical procedure for all age groups.[11]

2.1.1.4. Main Treatment Options

The parenteral administration of analgesic medication is necessary in certain acutely painful postsurgical conditions to provide rapid onset of analgesia, especially in patients who are unable to ingest or tolerate oral medications. Opioids and conventional non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used parenteral analgesics for the management of acute postsurgical pain; however, the use of these agents may be limited by a spectrum of adverse events. Parenteral opioids are associated with respiratory depression, nausea, vomiting, urinary retention, constipation and decreased gastrointestinal (GI) motility. Parenteral NSAIDs may cause upper GI ulceration and bleeding, reduced renal function and for some agents haemostatic impairment, characterized by decreased platelet aggregation and increased bleeding time.

2.1.1.5. Mortality and Morbidity (Natural History)

Mortality among patients being treated for postoperative pain can be expected to vary greatly depending on the type of surgery the patient has undergone as well as a number of other factors including age and comorbidity. Since orthopaedic surgery is the most frequent type of surgery that requires subsequent pain management, the following summary focuses on mortality data for this patient population.[12]

2.1.1.5.1. Acute inpatient mortality following orthopaedic surgery

Using discharge survey data from 43,215 inpatient orthopaedic operations in the US, Bhattacharyya et al. observed 397 deaths, corresponding to an overall mortality rate of 0.92% (95% CI, 0.89%-0.95%).[12] Of all deaths, 77% occurred among patients older than 70 years of age and 50% occurred after hip fracture operations. The mortality rates varied by procedure type. The estimates for the 3 most common orthopaedic surgical procedures are shown below.[12]

Procedure Category	Mortality
Adult reconstruction	0.29%
Trauma	0.83%
Hip fracture	3.07%

Liu et al reported a similar estimate (0.32%) for in-hospital mortality among patients undergoing total hip arthroplasty (THA)[13] between 1990 and 2004. In the study time periods

1990-94, 1995-99, and 2000-04 the mortality rates among patients undergoing THA were 0.33%, 0.33%, and 0.30%, respectively.[14]

2.1.2. Concomitant Medication(s) in the Target Population

Because parecoxib is indicated in adults for the management of acute pain as pre-emptive analgesia or concomitantly with opioids to reduce opioid requirements, nearly all approved medications for adults might be expected to be used concurrently, as most patients would likely resume their daily medication regimen after surgery.

In the surgical setting, local and general anesthetics, opioids and paracetamol would be among the most likely candidates for concomitant use.

2.1.3. Important Co-Morbidities Found in the Target Population

Depending on the type of surgery undergone by patients who require short-term treatment for postoperative pain, the co-morbidity burden varies greatly. In this section, data on the co-morbidities among patients undergoing orthopaedic surgery are summarised.

Table 1. Co-morbidity and Complications in the Population of Orthopaedic Surgery Patients

<table>
<tr><th>Co-morbidity</th><th>Incidence/Prevalence and mortality in target population and main co-prescribed medications</th></tr>
<tr><td>Co-morbid cardiovascular disease and risk factors</td><td>Due to the demographic profile of orthopaedic surgery patients, this population has a substantial cardiovascular co-morbidity burden.

<u>Prevalence</u>
The data on the prevalence of cardiovascular disease and risk factors among 953,130 primary hip arthroplasties conducted in the US in 2000 to 2004 are summarised in the following table.[14]

<table>
<tr><th>Co-morbidity</th><th>Prevalence</th></tr>
<tr><td>Hypertension</td><td>45.17%</td></tr>
<tr><td>Hypercholesterolaemia</td><td>6.49%</td></tr>
<tr><td>Cerebrovascular disease</td><td>0.67%</td></tr>
<tr><td>Peripheral vascular disease</td><td>0.84%</td></tr>
<tr><td>Coronary artery disease</td><td>11.28%</td></tr>
</table>

<u>Mortality</u>
No published data on cardiovascular mortality in the population of orthopaedic surgery patients were identified.

<u>Medications</u>
Polypharmacy is the standard of care for people with cardiovascular disease and those at high risk. For the treatment of hypertension, clinicians commonly prescribe diuretics, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Statins are most popular for the treatment of dyslipidaemia. Patients with overt symptoms (ie, angina) commonly use nitrates for symptomatic relief.</td></tr>
</table>

Table 1. Co-morbidity and Complications in the Population of Orthopaedic Surgery Patients

Co-morbid diabetes mellitus	Prevalence The prevalence of diabetes among 953,130 primary hip arthroplasties conducted in the US between 2000 and 2004 was 11.05%. [14] Mortality No published data on diabetes mortality in the population of orthopaedic surgery patients were identified. Medications Most commonly, persons with diabetes take oral antihyperglycemics (eg, metformin) or insulin. Other medications commonly taken by patients with diabetes include HMG CoA-reductase inhibitors (statins), anti-platelets, and anti-hypertensives, especially angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.
Post-surgical complications: Venous thromboembolic events	Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cardiovascular complication of major orthopaedic surgery and can be fatal. Undergoing total hip or knee arthroplasty is associated with both an immediate and a prolonged hypercoagulable state, and blood flow in the legs is reduced, placing patients at risk of VTE.[15] Incidence The reported incidence of DVT among orthopaedic surgery patients who do not receive thromboprophylaxis varies widely, from 30% to 88%.[16,17] This wide range can be partially explained by the different types of procedures as well as underlying demographic factors. Among patients undergoing hip replacement, the reported incidence of DVT is around 50%.[18,19] In contrast, patients who do receive anti-thrombotic treatment have a much lower incidence of VTE. As summarised by Douketis and colleagues, 4 prospective studies of VTE among 6,089 hip and knee replacement patients within the first 3 months after surgery report an overall frequency of 3.2%.[20] Similarly, retrospective studies using hospital records for 20,000 hip and 24,000 knee replacement patients reported the incidence of VTE to be 2.4%.[21]. Mortality In the absence of thromboprophylaxis, fatal PE has been estimated to occur in ~0.2% of total hip arthroplasty patients, 0.2% to 0.7% of total knee arthroplasty patients, and 1.4% to 7% of hip fracture surgery patients.[19] The frequency of fatal PE is lower in patients receiving thromboprophylaxis, but is still not negligible. For example, in a study by Douketis et al (2002), 6 out of 6,089 (0.1%) hip and knee replacement patients developed fatal PE. Medications Thrombosis and embolism may be prevented with anticoagulants in those deemed at risk. Although specific recommendations vary by type of surgery, low-molecular-weight heparin, fondaparinux, warfarin, and sometimes low-dose unfractionated heparin are effective alone or with mechanical prophylaxis. Anti-coagulant therapy is a mainstay not only of prophylaxis of PE events, but of their treatment as well.

Table 1. Co-morbidity and Complications in the Population of Orthopaedic Surgery Patients

Post-surgical complications: Bleeding	Patients who receive anti-thrombotic medication as prophylaxis against VTE during surgery are at higher risk of bleeding. Incidence Meta-analyses of studies of hip replacement patients taking anti-thrombotic medications estimated pooled rates of major bleeding at 3.3% for oral anti-coagulants and 5.3% for enoxaparin.[22,23,24] Lower rates have been reported among patients undergoing knee replacements taking warfarin (0.9%) and low-molecular-weight heparin (2.8%).[25] A large database study of 23,518 patients undergoing orthopaedic surgery between 1998 and 2000, reported major bleeding in 2.6% of the patients. The incidence was slightly higher among patients who had hip-related procedures (total hip replacement, 4.9%; and hip fracture repair, 2.8%) than among those who had major knee surgery (1.3%).[25] Mortality In a database study of 23,518 patients undergoing orthopaedic surgery, 0.1% (n = 21) died due to fatal bleeding.[25] Medications Pharmacological interventions that may be used in prophylaxis and therapeutically to stop bleeding include aprotinin, tranexamic acid, desmopressin and, increasingly, recombinant Factor VIIa.
Post-surgical complications: Surgical site infections	Orthopaedic surgery patients are at risk of surgical site infections (SSIs), including prosthetic joint infections, osteomyelitis, and infections related to arthroscopy. Incidence According to the data generated on over 5,400 orthopaedic procedures by a multi-site SSI surveillance in the UK, the crude SSI incidence was 2.4%.[1] In a surveillance study following 3,249 orthopaedic surgeries in a single private medical center in Turkey between 1999 and 2003, 1.85% of the patients developed SSIs.[26] According to a recently published review of the literature, total knee or hip replacements are associated with SSI incidence rates below 3%, and arthroscopy is perceived as having a low risk of SSIs (0.01%-0.48%).[27] Mortality In their review of the literature, Saadatian-Elahi et al (2008)[27] report a range of mortality due to SSIs following orthopaedic surgery, from 0.0% to 1.8%. Medications While surgical therapy remains the treatment of choice for SSIs, deep incisional and organ/space SSIs often require adjunctive anti-microbial therapy for optimal outcomes.

2.2. Part II: Module SII—Non-Clinical Part of the Safety Specification

The non-clinical safety program included (1) repeated dose toxicology studies for durations of up to 4 weeks in the rat and the dog, (2) genetic toxicity studies; (3) reproductive toxicity studies in male and female rats and female rabbits that collectively addressed mating, early pregnancy, and fetal organogenesis; and (4) additional studies that evaluated the acute lethal, hemolytic, and parenteral irritation potential and the potential adverse pharmacological effects (safety pharmacology) of parecoxib sodium.

All of the findings seen in animals treated with parecoxib sodium are consistent with the known pharmacological action of valdecoxib, the active moiety, (ie, inhibition of prostaglandin synthesis). These included dose-limiting GI toxicity in rats, dose-limiting septic skin sores in dogs, renal effects in rats and dogs, and post-implantation embryonal loss in rats and rabbits[28].

Table 2. Key Safety Findings and Relevance to Human Usage

Findings (From Non-clinical Studies)	Relevance to Human Usage
Toxicity including: • Repeat-dose toxicity In repeat-dose toxicity studies gastrointestinal injury in rats was characterized by small intestinal ulceration and perforation, and secondary peritonitis similar to that seen with conventional NSAIDs. These effects occurred at systemic exposures, based on the area under the plasma concentration-time curve 24 (AUC24) of parecoxib, valdecoxib, and SC-66905, an inactive metabolite, that are approximately 8-, 6-, and 13-fold greater than those in humans given 80 mg/day. With the exception of focal erosions in the small intestinal mucosa of a single dog in an exploratory study, no parecoxib sodium-related gastrointestinal toxicity was observed in dogs in studies up to 4 weeks in duration.	Dynastat is contraindicated for patients with active peptic ulceration or GI bleeding.
• Reproductive Increased postimplantation loss was observed in early embryonic development study in rats at systemic exposures of parecoxib, valdecoxib, and SC-66905 that are, respectively, 3, 2 and 6 times greater than those in humans given 80 mg/day. Evidence of implantation loss was also noted in the rabbit in embryo-fetal development studies. These effects are considered pharmacologically mediated and reversible.	During the first and second trimester of pregnancy, Dynastat should not be given unless clearly necessary.

Table 2. Key Safety Findings and Relevance to Human Usage

Findings (From Non-clinical Studies)	Relevance to Human Usage
• Developmental toxicity Parecoxib sodium was not teratogenic in rats at dosages up to those that produced maternal death (exposure margins of 10-, 9-, and 9-fold for parecoxib, valdecoxib, and SC-66905, respectively for the 30 mg clinical dose), or in rabbits at dosages that produced significant fetal loss (exposure margins of 141-, 5-, and 23-fold for parecoxib, valdecoxib, and SC-66905, respectively for the 80 mg/day clinical dose).	
Other toxicity-related information or data • Lactation Both parecoxib and valdecoxib have been detected in the milk of the dam at levels generally lower than those of maternal plasma.	Dynastat should not be used by mothers who are breast-feeding their infants.

2.2.1. Conclusions on Non-Clinical Data

Non-clinical safety findings observed during the development program for parecoxib sodium have been adequately evaluated and addressed in the extensive clinical development program and in the post-marketing experience.

A need for additional non-clinical data has not been identified.

Table 3. Safety Concerns

Important identified risks (confirmed by clinical data)	Gastrointestinal ulceration-related events Use during pregnancy, lactation, or in wormen attempting to conceive
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	None

2.3. Part II: Module SIII—Clinical Trial Exposure

2.3.1. Brief Overview of Development

Parecoxib is a non-steroidal anti-inflammatory drug (NSAID) developed for the management of acute pain. Parecoxib is a prodrug of the COX-2 inhibitor valdecoxib. Following parenteral administration, parecoxib is rapidly and completely converted into the pharmacologically active moiety, valdecoxib, by enzymatic hydrolysis in the liver. The active moiety acts through inhibition of prostaglandin synthesis, primarily by selective inhibition of the COX-2 isoenzyme.

Parecoxib, which can be administered either by intravenous (IV) or intramuscular (IM) injection, is indicated globally as follows (not all indications are approved in all countries):

- For the management of acute pain
- Pre-operative (preemptive) analgesia, to prevent or reduce post-operative pain
- Concomitantly with opioid analgesics, to reduce opioid requirements

The specific indication approved in Europe is the short-term treatment of postoperative pain in adults.

Parecoxib is supplied as 40 mg powder vials and solvent for solution for injection. The maximum recommended daily dose of parecoxib in adult patients is 80 mg; for elderly patients or patients with hepatic impairment, the daily dose should not exceed 40 mg. Parecoxib has not been approved for use in children or adolescents.

Since the last update of the pharmacovigilance plan, 1 clinical trial (A3481066) was completed and analyzed with clinical study report available. This study evaluated the morphine-sparing efficacy and safety of parecoxib 40 mg IV followed by 20 mg IV every 12 hours in the treatment of pain following radical prostatectomy. Parecoxib 40/20 mg was safe and well tolerated in this patient population.

2.3.2. Clinical Trial Exposure

Exposure was calculated from all completed clinical studies conducted by the MAH for which a completed clinical database was available as of 31 March 2014. Exposure is presented by age group, race, and gender for all studies phases 1 through 4, in all indications and includes healthy volunteers (Table 4). A total of 7814 subjects were exposed to parecoxib in the clinical trial program (5381 received parecoxib and 2433 received parecoxib in combination with other drugs). Exposure from blinded, randomized studies for the indication of postoperative pain are presented by duration of exposure (Table 5), dose (Table 7), number of administrations (Table 9), by age group and gender (Table 11), by ethnic or racial origin (Table 13), and in subjects with a medical history of congestive heart failure (Table 15). Exposure from all clinical trial populations for the indication of postoperative pain are also presented by duration of exposure (Table 6), dose (Table 8), number of administrations (Table 10), by age group and gender (Table 12), by ethnic or

racial origin (Table 14), and in subjects with a medical history of congestive heart failure (Table 16).

Table 17 presents exposure from a single Phase 2, open-label, non-comparative, pharmacokinetic study in subjects with hepatic impairment. Table 18 presents exposure by age group and gender from blinded, randomized studies for the indication of acute pain. A total population table was not included for this indication because only blinded, randomized studies were conducted by the MAH for this indication.

Table 4. Exposure by Age Group, Race, and Gender in Phase 1, 2, 3, and 4 All Indications*

	Parecoxib	Parecoxib /Heparin	Parecoxib /Morphine	Parecoxib /Placebo	Parecoxib /Pro-pacetamol	Parecoxib /Valecoxib	Parecoxib /Valdecoxib /Placebo
Treated Patients	5381	18	51	734	72	1509	49
Age (Years)							
≤17	1	0	0	0	0	0	0
18 – 30	1709	7	1	132	1	80	27
31 – 50	1921	11	21	385	7	355	22
51 – 64	983	0	11	124	20	620	0
65 – 74	532	0	13	60	25	384	0
≥75	234	0	5	33	19	70	0
Unspecified	1	0	0	0	0	0	0
Race							
White	3750	7	35	443	71	1391	45
Black	389	10	9	36	1	49	0
Asian	363	0	0	44	0	26	1
Hispanic	331	1	7	9	0	6	3
Other	160	0	0	1	0	26	0
Unspecified	388	0	0	201	0	11	0
Gender							
Male	1920	18	15	128	29	965	24
Female	3461	0	36	606	43	544	25
Unspecified	0	0	0	0	0	0	0

*Of the total 7814 persons who received parecoxib, 611 were healthy volunteers.
Includes studies:124-IFL-0505-001,124-IFL-0505-003,124-IFL-0505-004,124-IFL-0505-005,124-IFL-0505-006,A3481004,A3481053, A3481065,A3481066,E93-01-02-067,E93-99-02-033,I93-01-02-049,I93-01-02-069,I93-99-02-035,N93-00-02-032,N93-00-02-044,N93-01-02-047,N93-01-02-065,N93-01-02-068,N93-97-02-001,N93-97-02-002,N93-97-02-003, N93-97-02-004,N93-97-02-005,N93-97-02-006,N93-97-02-008,N93-97-02-009,N93-97-02-010,N93-97-02-011, N93-97-02-012,N93-97-02-013,N93-97-02-014,N93-97-02-015,N93-97-02-016,N93-97-02-017,N93-98-02-018, N93-98-02-019,N93-98-02-020,N93-98-02-021,N93-98-02-022,N93-98-02-024,N93-98-02-025,N93-98-02-026,N93-98-02-027,N93-98-02-030,N93-99-02-028,N93-99-02-029,N93-99-02-031,N93-99-02-037,N93-99-02-038, N93-99-02-039,N93-99-02-040,PARA-0505-071,PARA-0505-072,PARA-0505-073,PARA-0505-074,PARA-0505-075, PARA-0505-076,PARA-0505-077,PARA-0505-078,PARA-0505-079,PARA-0505-080,PARA-0505-081,PARA-0505-086,PARA-0505-087,PARA-0505-088,PARA-0505-089

Table 5. Duration of Exposure (Indication: Postoperative Pain) - Blinded Randomized Population*

Duration of Exposure	Persons (N = 5917)	Person Time (Days)
Cumulative up to 3 days	5278	8717
Cumulative up to 7 days	5917	11352
Cumulative up to any exposure	5917	11352

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.

Table 6. Duration of Exposure (Indication: Postoperative Pain) - Total Population*

Duration of Exposure	Persons (N = 5959)	Person Time (Days)
Cumulative up to 3 days	5320	8792
Cumulative up to 7 days	5959	11427
Cumulative up to any exposure	5959	11427

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.

Table 7. Exposure by Dose (Indication: Postoperative Pain) - Blinded Randomized Population*

Dose of Exposure	Persons	Person Time (Days)
1 mg IM	51	51
1 mg IV	51	51
2 mg IM	50	50
2 mg IV	51	51
5 mg IM	51	51
5 mg IV	51	51
10 mg IM	50	50
10 mg IV	51	51
20 mg IM	152	152
20 mg IV	751	1189
40 mg IM	112	112
40 mg IV	3105	6564
50 mg IV	51	51
60 mg IM (RTU formulation)†	118	131
60 mg IV	127	135

Table 7. Exposure by Dose (Indication: Postoperative Pain) - Blinded Randomized Population*

Dose of Exposure	Persons	Person Time (Days)
60 mg IV (RTU formulation)†	119	135
80 mg IV	896	2339
100 mg IV	51	51
400 mg IV+	29	87

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.
†Details contained in the protocol PARA-0505-089.
+These subjects are all from site 1002 in study A3481066. They were erroneously recorded as having been dosed 200mg initially followed by 200mg bid, when they were actually dosed 40mg initially followed by 20mg bid, for a total daily dose of 40mg.

Table 8. Exposure by Dose (Indication: Postoperative Pain) - Total Population*

Dose of Exposure	Persons	Person Time (Days)
1 mg IM	51	51
1 mg IV	51	51
2 mg IM	50	50
2 mg IV	51	51
5 mg IM	51	51
5 mg IV	51	51
10 mg IM	50	50
10 mg IV	51	51
20 mg IM	152	152
20 mg IV	751	1189
40 mg IM	112	112
40 mg IV	3147	6639
50 mg IV	51	51
60 mg IM (RTU formulation)†	118	131
60 mg IV	127	135
60 mg IV (RTU formulation)†	119	135
80 mg IV	896	2339
100 mg IV	51	51
400 mg IV+	29	87

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.
†Details contained in the protocol PARA-0505-089.
+These subjects are all from site 1002 in study A3481066. They were erroneously recorded as having been dosed 200mg initially followed by 200mg bid, when they were actually dosed 40mg initially followed by 20mg bid, for a total daily dose of 40mg.

Table 9. Clinical Trial Exposure by Number of Administrations (Indication: Postoperative Pain) - Blinded Randomized Population*

Number of Administrations	Number of Persons (N = 5917)
1	2491
2	567
3	291
4	190
5	365
6	1486
7	253
8	120
9	6
10	148

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.

Table 10. Clinical Trial Exposure by Number of Administrations (Indication: Postoperative Pain) - Total Population*

Number of Administrations	Number of Persons (N = 5959)
1	2500
2	570
3	321
4	190
5	365
6	1486
7	253
8	120
9	6
10	148

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.

Table 11. Exposure by Age Group and Gender (Indication: Postoperative Pain) - Blinded Randomized Population*

Age Group (Years)	Persons		Person Time (Days)	
	Male	Female	Male	Female
Missing†	1	0	1	0
≤ 18	49	77	52	85
19 - 30	460	893	536	1048
31 - 50	520	1357	1034	2324
51 - 64	730	691	1981	1451
65 - 80	575	515	1614	1135
≥81	16	33	28	63

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.
†In cases where age is missing the following calculation for age is used: age = (colldate – DOB)/365.25

Table 12. Exposure by Age Group and Gender (Indication: Postoperative Pain) - Total Population*

Age Group (Years)	Persons		Person Time (Days)	
	Male	Female	Male	Female
Missing†	1	0	1	0
≤ 18	49	77	52	85
19 - 30	461	899	538	1060
31 - 50	527	1370	1048	2348
51 - 64	734	693	1989	1455
65 - 80	581	518	1621	1139
≥81	16	33	28	63

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.
†In cases where age is missing the following calculation for age is used: age = (colldate – DOB)/365.25

Table 13. Exposure by Ethnic or Racial Origin (Indication: Postoperative Pain) - Blinded Randomized Population*

Ethnic/racial Origin	Persons	Person Time (Days)
Asian	303	468
Black	350	544
Caucasian	4431	9206
Hispanic	264	293
Native American	2	2
Not listed	433	681
Other	134	158

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.

Table 14. Exposure by Ethnic or Racial Origin (Indication: Postoperative Pain) - Total Population*

Ethnic/racial Origin	Persons	Person Time (Days)
Asian	333	528
Black	350	544
Caucasian	4431	9206
Hispanic	264	293
Native American	2	2
Not listed	445	696
Other	134	158

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.

Table 15. Subjects With Medical History of Congestive Heart Failure: Clinical Trial Exposure by Age Group and Gender (Indication: Postoperative Pain) - Blinded Randomized Population*

	Persons		Person Time (Days)	
Age Group (Years)	**Male**	**Female**	**Male**	**Female**
31 – 50	2	2	5	2
51 – 64	15	4	42	10
65 – 80	18	16	46	39
≥81	1	3	2	4

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, A3481004, and A3481066.
In cases where age is missing the following calculation for age is used: age = (colldate – DOB)/365.25

Table 16. Subjects With Medical History of Congestive Heart Failure: Clinical Trial Exposure by Age Group and Gender (Indication: Postoperative pain) - Total Population*

	Persons		Person Time (Days)	
Age Group (Years)	**Male**	**Female**	**Male**	**Female**
31 – 50	2	2	5	2
51 – 64	15	4	42	10
65 – 80	19	16	48	39
≥81	1	3	2	4

*Includes studies N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, PARA-0505-089, 124-IFL-0505-001, 124-IFL-0505-003, 124-IFL-0505-006, I93-01-02-049, PARA-0505-079, A3481004, and A3481066.
In cases where age is missing the following calculation for age is used: age = (colldate – DOB)/365.25

Table 17. Subjects With Hepatic Impairment by Age Group and Gender*

	Persons		Person Time (Days)	
Age Group (Years)	**Male**	**Female**	**Male**	**Female**
31 – 50	20	10	151	80
51 – 64	12	6	96	48
65 – 80	2	0	16	0

*Includes study N-93-97-02-012, the only study in the clinical program in which subjects with hepatic impairment were enrolled. This was an open-label pharmacokinetic study.

Table 18. Exposure by Age Group and Gender (Indication: Non-Surgical Acute Pain) - Blinded Randomized Population*

	Persons		Person Time (Days)	
Age Group (Years)	**Male**	**Female**	**Male**	**Female**
≤ 18	1	0	1	0
19 – 30	22	24	22	24
31 – 50	95	42	95	42
51 – 64	21	16	21	16
65 – 80	1	2	1	2

*Includes studies 124-IFL-0505-004, 124-IFL-0505-005, N93-01-02-065, and A3481065.

2.4. Part II: Module SIV—Populations Not Studied in Clinical Trials

2.4.1. Limitations of ADR Detection Common to Clinical Trial Development Programmes

Table 19. Limitations of ADR Detection

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare (1 in 1000)	Events which occur less than 1 in 10,000 may escape detection as 5402 patients were studied.	With 5402 patients, it would be possible to detect rare events which occur with a frequency of 1 in 1000. Events which occur less frequently may not have been detected in the clinical trial program.
Due to prolonged exposure	Parecoxib studies have been limited to a duration of 7 days.	Clinical trial data cannot be used to determine events with prolonged exposure. Parecoxib is indicated only for short term use.
Due to cumulative effects	Parecoxib studies have been limited to a duration of 7 days.	Clinical trial data cannot be used to determine cumulative events as there are no studies of chronic duration. Parecoxib is indicated only for short term use.
Which have a long latency	Parecoxib studies have been limited to a duration of 7 days.	Events which have a long latency were not measured in our trial programme, given the relatively short duration of exposure to parecoxib.

2.4.2. Effect of Exclusion Criteria in the Clinical Trial Development Plan

Inclusion and exclusion criteria were applied to clinical studies to assist in the appropriate evaluation of safety and efficacy for the specific indications. All studies included general exclusion criteria for subjects who had

- been diagnosed or had treatment initiated for GI bleeding, oesophageal, gastric, pyloric channel or duodenal ulceration within the 30 days prior to receiving study medication;
- significant GI complaints as determined by the investigator;
- been diagnosed with, treated for, or were in remission from cancer other than basal cell carcinoma (Phase 3b studies update to be within 6 months) within the 2 years preceeding screening;
- a history of hypersensitivity to any NSAID, other cyclooxygenase inhibitor, opioid, or any agent that has a cross-sensitivity to the medications used in this study;

- known alcohol, analgesic, or narcotic substance abuse within 90 days prior to screening; and

- volume depletion in the opinion of the investigator.

All studies also excluded users of the following medications: intrathecal opioids, long-acting NSAIDs (such as piroxicam and oxaprozin) within 5 days prior to study medication administration, or short-acting NSAIDs (such as ibuprofen) within 75 hours prior to study medication administration. Also excluded were subjects who used any antidepressants, narcotic analgesics, antihistamines, anxiolytics, hypnotics, sedatives, NSAIDs, corticosteroids or other similar agents during the 24 hours preceding administration of study medication—with the exception of routine preoperative medication or long-acting NSAIDs, including, but not limited to, oxaprozin, piroxicam and/or full-dose aspirin within 5 days.

The subject population in the clinical program (per the inclusion/exclusion criteria) included subjects from 18 to 96 years of age. Excluded from the clinical program were children below the age of 18 years, women who were pregnant or lactating, or women of childbearing potential who might become pregnant.

Studies were conducted in oral surgery subjects and general surgery subjects. Subjects with clinically significant renal, hepatic or cardiac impairment were selectively excluded from clinical trials.

Table 20. Exclusion Criteria That Will Remain as Contraindications

Criteria	Implications for Target Population
Hypersensitivity to the active substance or to any of the excipients	Contraindication as stated, no known risk factors for hypersensitivity to parecoxib
History of previous serious allergic reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, toxic epidurmal nercolysis, erythema multiforme or patients with known hypersensitivity to sulphonamides	Contraindication as stated. As stated in the current SmPC, patients with a history of sulphonamide allergy may be at greater risk of skin reactions with parecoxib.
Active peptic ulceration or GI bleeding	Contraindication as stated. As stated in the current SmPC: Caution is advised in the treatment of patients most at risk of developing a GI complication with NSAIDs.
Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicyclic acid or NSAIDs including COX-2 inhibitors	Contraindication as stated.
The third trimester of pregnancy and breast feeding	Contraindication as stated. As with with other medicinal products known to inhibit prostaglandin, parecoxib may cause premature closure of the ductus arteriosus or uterine inertia. As currently stated in the SmPC: During the first and second trimester of pregnancy, parecoxib should not be given unless clearly necessary.

Table 20. Exclusion Criteria That Will Remain as Contraindications

Criteria	Implications for Target Population
Severe hepatic impairment	Parecoxib is contraindicated in patients with severe hepatic impairment as these patients were not studied in the clinical trials. As stated in the current SmPC: No dosage adjustment is generally required in mild hepatic impairment. Parecoxib should be introduced with caution in patients with moderate hepatic impairment at half the recommended dose and the maximum daily dose should not exceed 40mg.
Inflammatory bowel disease	Contraindication as stated.
Congestive heart failure (NYHA II-IV)	Contraindication as stated. As stated in the current SmPC: As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib.
Treatment of post-operative pain following coronary artery bypass graft (CABG) surgery	Contraindication as stated. CABG is a risk factor for a cardiovascular (CV) thrombotic event with parecoxib.[29]
Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease	Contraindication as stated. As stated in the current SmPC: Patients with significant risk factors for cardiovascular events should only be treated with parecoxib after careful consideration.

Table 21. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criteria	Reason for Being an Exclusion Criterion	Justification for not Being a Contraindication
History of significant GI complaints	Determination of etiology of GI complaints beyond the scope of the parecoxib clinical trial programme.	Parecoxib is currently contraindicated for patients with active GI bleeds. As stated in the current SmPC: Caution is advised in the treatment of patients most at risk of developing a GI complication with NSAIDs.
Been diagnosed with, treated for, or were in remission from cancer other than basal cell carcinoma within 6 months to 2 years	Subjects excluded because of increased risks of surgical complications in a clinical trial setting, and because consequences of underlying malignancy may confound the assessment of the profile of the study drug.	Subjects with cancer were excluded primarily because of clinical trial considerations; however, there is no justification for their exclusion in a general surgical setting.
Known alcohol, analgesic or narcotic abuse with 90 days	Subjects may increase opioid usage during period of study and introduce uncontrolled variability into study measurements.	Parecoxib may decrease need for opioid usage post-operatively, no contraindication clinically warranted in this group of patients.

Table 21. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Volume depletion	NSAIDs have been associated with acute renal failure.	Patients are routinely hydrated prior to surgery, SmPC currently states: Caution should be used when initiating treatment with parecoxib in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with parecoxib.
Excluded medications from the clinical trial program 1) long acting NSAIDs within 5 days and short acting NSAIDs within 75 hours 2) antidepressants, narcotic analgesics, antihistamines, hypnotics, sedatives, corticosteroids within 24 hours	1) These medications were excluded using these specific temporal parameters because of clinical trial considerations. 2) These medications could not be taken by patients 24 hours before enrollment because of clinical trial considerations.	1) While there is no justification for applying these temporal parameters to the general population, the concurrent use of other NSAIDs and parecoxib should be avoided. As stated in the current SmPC, caution is advised in the treatment of patients using any other NSAID. 2) There is no justification for applying these temporal exclusions to the general surgical population.

2.4.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

2.4.3.1. Children

The safety and efficacy of parecoxib in children under 18 years old have not been established. No clinical trial data are available. Therefore, parecoxib is not recommended in these patients.

2.4.3.2. Pregnant or Breast Feeding Women

There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. During the first and second trimesters of pregnancy, parecoxib should not be given unless clearly necessary.

Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Despite the relatively low exposure to the infant, parecoxib must not be administered to women who breast-feed.

2.4.3.3. Patients with Hepatic Impairment

Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid in vivo. Elimination of valdecoxib is by extensive hepatic metabolism. There is no clinical trial experience in patients with severe hepatic impairment (Child-Pugh score ≥ 10), therefore parecoxib use is contraindicated in these patients. No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5–6). Parecoxib should be introduced with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7–9) and the maximum daily dose should not exceed 40 mg.

2.4.3.4. Patients with Renal Impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose (20 mg) and the patient's kidney function should be closely monitored. On the basis of pharmacokinetics, no dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min).

2.4.3.5. Patients with Other Relevant Co-Morbidity

Use with Warfarin or Similar Agents: Coadministration of parecoxib with warfarin caused a small increase in the AUC of warfarin, and also in the prothrombin time (measured by International Normalized Ratio [INR]). While mean INR values were only slightly increased, the day-to-day variability in individual INR values was increased. Anticoagulant activity should be monitored, particularly during the first few days after initiating parecoxib, in patients receiving warfarin or similar agents. Note that this scenario is unlikely when parecoxib is administered peri-operatively, as patients administered warfarin as part of their medical regimen are taken off warfarin peri-operatively.

Hypertension: As with all NSAIDs, parecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension. Blood pressure should be monitored closely during the initiation and course of parecoxib therapy.

2.4.3.6. Patients with a Disease Severity Different From the Inclusion Criteria in the Clinical Trial Population

Not applicable.

2.4.3.7. Sub-Populations Carrying Known and Relevant Polymorphisms

None known.

2.4.3.8. Patients of Different Racial and/or Ethnic Origin

Most subjects enrolled in clinical studies have been Caucasian in origin but these studies have also enrolled subjects of other origins, including black, Asian and Hispanic patients. No difference in response to parecoxib in different races has been identified. Large global clinical studies conducted in populations in all parts of the world have not shown any observed differences in efficacy or safety based on race or ethnic origin. Therefore, there are no known obvious safety or tolerability differences with regard to race and/or ethnic origin.

2.4.4. Conclusions on the Populations Not Studied and Other Limitations of the Clinical Trial Development Programme

Missing information

Table 22. Safety Concerns Due to Limitations of the Clinical Trial Programme

Safety Concern	Comment	Outstanding Concern?
Use in children and adolescents aged ≤17 years	There is no clinical trial experience with parecoxib therapy in paediatric populations; therefore, its use is not recommended in children and adolescents. Assessment of missing information is ongoing.	Yes
Use in long-term treatment (>7 days)	There is limited clinical experience with parecoxib treatment extending beyond 3 days. Clinical studies were conducted for up to 7 days of treatment. Assessment of missing information is ongoing.	Yes
Use during pregnancy/lactation	There are no adequate well-controlled studies of parecoxib in pregnant women. Assessment of identified risk is ongoing.	Yes, use during pregnancy or lactation is an important identified risk. See section 2.7.3.
Renal failure and impairment	Clinical experience in such patients is limited. Based on pharmacokinetic data, no dose adjustment is needed in patients with mild to moderate renal impairment. Assessment of identified risk is ongoing.	Yes, renal failure and impairment is an important identified risk. See section 2.7.3.
Use in patients with hepatic impairment	Parecoxib is contraindicated in patients with severe hepatic impairment as these patients were not studied in the clinical trials. No dosage adjustment is generally required in mild hepatic impairment. Parecoxib should be introduced with caution in patients with moderate hepatic impairment at half the recommened dose and the maximum daily dose should not exceed 40mg. Assessment of identified risk is ongoing.	Yes, use in patients with hepatic impairment is an important identified risk. See section 2.7.3.

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2.5. Part II: Module SV—Post-Authorisation Experience

2.5.1. Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

Table 23 and Table 24 summarize all regulatory actions taken in relation to the safety of parecoxib.

Table 23. Detailed Description of Actions Taken Since Last Update to This Module (01 April 2011 through 31 March 2014)

Safety Issue 1 – Severe hypotension and circulatory collapse	
Background to issue	Based on cumulative reviews, Pfizer determined that additions to the product labeling were warranted, and the core data sheet (CDS) was revised accordingly. The revisions included the addition of two statements to CDS Section 4.4 "Special warnings and precautions for use." The first statement was a warning against the administration of parecoxib by any mode other than IV or IM injection. The second statement was a caution that cases of severe hypotension not associated with other signs of anaphylaxis have been reported in association with parecoxib administration and that practitioners should be prepared to treat such an event. In addition, the reaction "circulatory collapse" was added to CDS Section 4.8 "Undesirable effects." The SmPC was updated to align with the CDS revisions.
Evidence source	Type II Variation EMEA/H/C/381/II /046
Action taken	Update to SmPC
Countries affected	European Union
Date(s) of action	Submitted 27 Jul 2011, Approved 22 Nov 2011
Evidence source	Type II Variation EMEA/H/C/381/II/0052
Action taken	Update to SmPC
Countries affected	European Union
Date(s) of action	Submitted 21 Sept 2012, Approved 16 Apr 2013

Table 24. Cumulative List of Regulatory Actions Taken

Country(ies)	**Action Taken**	**Comment**	**Date(s)**
Safety Concern 1 – Severe Cutaneous Adverse Reaction (SCAR) and other hypersensitivity-type reactions with valdecoxib and potential impact on parecoxib			
EU	Type II Variation EMEA/H/C/381/II/003. Urgent Safety Restrictions; Dear Doctor Letter; Update to the SmPC Sections 4.3, 4.4, 4.8, and the package information leaflet (PIL).		Submitted on: 21 Nov 2002 Approved on: 09 Apr 2003
Safety Concern 2 - Warnings in CV disease, Caution in CABG surgery, and GI warnings			
EU	Type II Variation EMEA/H/C/381/II/011. Update to the SmPC Sections 4.3, 4.4, 4.5, 4.8, 5.1 and the PIL.	Article 31 Referral procedure [Directive 2001/82/EC] initiated during 2002 by the EMEA on all COX-2 drugs resulted in recommendations for label changes to harmonise parecoxib, valdecoxib, and celecoxib labels.	Submitted on: 23 Jan 2004 Approved on: 22 Apr 2004

Table 24. Cumulative List of Regulatory Actions Taken

Country(ies)	Action Taken	Comment	Date(s)
Safety Concern 3 – Hypersensitivity/skin reactions and acute renal failure			
EU	Type II Variation EMEA/H/C/381/II/013. Update to the SmPC Sections 4.4, 4.8, 6.2, 6.6 and the PIL.	Spontaneous reports of hypersensitivity/skin reactions and acute renal failure (Periodic Safety Update Report (PSUR) 2-3).	Submitted on: 16 Jul 2004 Approved on: 06 Dec 2004
Safety Concern 4 - Contraindications for the treatment of postoperative pain following CABG surgery.			
EU	Type II Variation EMEA/H/C/381/II/016. Update to the SmPC Sections 4.3, 4.4, 4.8, 5.1 and the PIL.	Serious adverse events (SAEs) have been reported in association with the use of parecoxib: acute renal failure, congestive heart failure, and hypersensitivity reactions including anaphylaxis and angioedema.	Submitted on: 12 Nov 2004 Approved on: 26 Jan 2005
Safety Concern 5 - SCAR			
EU	Type II Variation EMEA/H/C/381/II/017. Update to the SmPC Sections 4.4, 4.8 and the PIL.	Additional warnings regarding SCARs associated with valdecoxib, which cannot be ruled out for parecoxib. Rare spontaneous reports of erythema multiforme.	Submitted on: 12 Nov 2004 Approved on: 26 Jan 2005
Safety Concern 6 - Contraindication in patients with established ischaemic heart disease and/or cerebrovascular disease			
EU	Type II Variation EMEA/H/C/381/II/019. Urgent Safety Restrictions; Dear Doctor Letter; Update to the SmPC Sections 4.1, 4.3, 4.4 and the PIL.	Contraindication in patients with established ischaemic heart disease and/or cerebrovascular disease; a recommendation to prescribe a selective COX-2 inhibitor based on an assessment of the individual patient's overall risks; and warning for patients with risk factors for CV events or peripheral arterial disease.	Submitted on: 03 Mar 2005 Approved on: 10 Jun 2005
Safety Concern 7 – Multiple dose safety and efficacy of parecoxib 20 and 40 mg up to 4 times a day			
US	None at this time.	Non-approval letter from the US FDA for Pfizer's submission dated 11 Sep 2001. The multiple dose safety and efficacy of parecoxib 20 and 40 mg up to 4 times a day have not been adequately demonstrated.	FDA Response letter dated: 12 Jul 2001
Safety Concern 8 – Contraindication in patients with a history of previous serious allergic drug reaction			
EU	Referral under Article 18 of Council Regulation (EEC) No 2309/93. EMEA-H-A-18-633. Update to the SmPC Sections 4.3, 4.4, 4.8 and PIL.	Contraindication in patients with a history of previous serious allergic drug reaction of any type, especially SCAR such as erythema multiforme (EM), Stevens-Johnson Syndrome (SJS), or toxic epidermal necrolysis (TEN).	Submitted on: 18 Nov 2004 Approved on: 05 Oct 2005

Table 24. Cumulative List of Regulatory Actions Taken

Country(ies)	Action Taken	Comment	Date(s)
Safety Concern 9 – Cardiovascular and thrombotic adverse events (AEs), SCAR, pregnancy warning			
EU	Type II Variation EMEA/H/C/381/II/025. Update to the SmPC Sections 4.4 and 4.8.	Warning associated with increased risk of COX-2 products with cardiovascular and thrombotic AEs when taken long term. Warning on SCAR was further clarified. Pregnancy warning and contraindication for use in the last trimester of pregnancy. AEs: Myocardial infarction and SJS. (PSUR 6).	Submitted on: 30 Nov 2006 Approved on: 29 Mar 2007
Safety Concern 10 - SCAR			
EU	Type II Variation EMEA/H/C/381/II/036. Update to SmPC Section 4.4.	Based on the Assessment Report for PSUR No. 8, information relating to serious skin reactions was updated in section 4.4 of SmPC.	Submitted on: 07 Apr 2009 Approved on: 23 Jul 2009
Safety Concern 11 - Cardiac function, pre-existing oedema, hypertension, and concomitant use with other non-aspirin NSAIDs.			
EU	Type II Variation EMEA/H/C/381/II/041. Update to the SmPC Section 4.4.	Precaution for patients with compromised cardiac function, pre-existing oedema, or other conditions predisposing to, or worsened by, fluid retention. Precaution concerning the onset of new hypertension or worsening of pre-existing hypertension. Warning to avoid concomitant use with other non-aspirin NSAIDs.	Submitted on: 18 Apr 2010. Commission Decision: 30 Jul 2010
Safety Concern 12 – Severe hypotension and circulatory collapse			
EU	Type II Variation EMEA/H/C/381/II /046. Update to the SmPC Section 4.4 and 4.8.	SmPC update to Section 4.4 for severe hypotension and correct mode of administration, update to Section 4.8 to add circulatory collapse.	Submitted on 27 Jul 2011 Approved on 22 Nov 2011

AE = adverse event; CABG = coronary artery bypass graft; COX = cyclooxygenase; CV = cardiovascular; EM = erythema multiforme; EMEA or EMA = European Medicines Agency; EU = European Union; GI = gastrointestinal; MAH = Marketing Authorisation Holder; NSAID = non-steroidal anti-inflammatory drug; PIL = Package Information Leaflet; PSUR = Periodic Safety Update Report; SAE = serious adverse event; SCAR = severe cutaneous adverse reaction; SJS = Stevens Johnson syndrome; SmPC = Summary of Product Characteristics; TEN = toxic epidermal necrolysis.

2.5.2. Non-Study Post-Authorisation Exposure

Parecoxib received first regulatory approval on 19 May 2001 in Mexico. The compound was subsequently approved in the EU on 22 March 2002 via the centralized procedure. Parecoxib is approved in 83 countries and is currently marketed in 66 countries.

2.5.2.1. Method Used to Calculate Exposure

The estimated worldwide market experience for parecoxib is based on standard units (vials or ampoules) sold from the first quarter of 2002 through the fourth quarter of 2013 as provided by IMS MIDAS and projected through the first quarter 2014 using a linear fit trend line based on historical quarterly sales. Using this method, it is estimated that 69,567,300 standard units of parecoxib were sold. Since the sales for the 20 mg product have been negligible and this formulation has been withdrawn in Europe, the data provided is almost entirely for the 40 mg product.

2.5.2.2. Exposure

Cumulative estimated commercial exposure to parecoxib by gender, age group, indication, and region based on data provided by IMS Health Prescribing Insights Medical for the period from the first quarter 2002 through the fourth quarter 2013 and extrapolated through the first quarter 2014 is provided in Table 25 and Table 26. Please note that the indications presented below are based on the International Statistical Classification of Disease and Related Health Problems, Tenth Edition (ICD-10). This nomenclature system includes very few surgical procedure-related terms; therefore, the specific surgical procedures for which parecoxib was prescribed for postoperative pain are captured under disease codes that were appropriate for the underlying disease state for which the surgical procedures were performed.

Table 25. Cumulative Estimated Exposure by Gender and Age Group (Standard Units Sold)*

Indication	Gender		Age (Years)	
	Male	Female	17 - 65	>65
Dorsalgia	16,697.7	13,384.3	26,799.0	3,282.9
Gonarthrosis (Knee)	3,352.7	20.8	3,352.7	20.8
Other Intervertebral Disc Disease	1,629.0	405.6	484.3	1,550.4
Unspecified Renal Colic	451.2	1,425.4	1,876.6	0.0
Other Joint Disorders Not Elsewhere Classified	1,618.1	18.1	1,618.1	18.1
Unspecified Multiple Injuries	1,279.3	207.0	1,382.5	103.8
Other Dorsopathies Not Elsewhere Classified	0.0	1,442.9	0.0	1,442.9
Total Others	14,756.8	12,878.5	16,447.3	11,187.9

* Reported in thousands.

Table 26. Cumulative Estimated Exposure by Indication and Region (Standard Units Sold)*

Indication	Region		Total
	Europe	ROW	
Dorsalgia	22,238.2	7,843.7	30,082.0
Gonarthrosis (Knee)	937.7	2,435.8	3,373.5
Other Intervertebral Disc Disease	1,636.6	398.1	2,034.6
Unspecified Renal Colic	968.2	908.4	1,876.6
Other Joint Disorders Not Elsewhere Classified	342.8	1,293.4	1,636.2
Unspecified Multiple Injuries	0.0	1,486.3	1,486.3
Other Dorsopathies Not Elsewhere Classified	1,442.9	0.0	1,442.9
Total Others	5,973.8	21,661.4	27,635.2

*Reported in thousands.

2.5.3. Post-Authorisation Use in Populations Not Studied in Clinical Trials

Commercial patient exposure is presented in section 2.5.2.2. Commercial exposure in paediatric patients was negligible and exposure in pregnant or breast feeding women could not be determined as there is no ICD-9 code for this (as this is not a diagnosis). In patients with hepatic or renal impairment, it is unclear if this information would be accurately captured as the IMS database only captures co-diagnoses made at the time of the visit. The MAHs cumulative post-marketing safety database of 990 cases was searched for cases involving use of parecoxib in paediatric patients, pregnant or lactacting women, or in patients with hepatic or renal impairment. These results are presented below.

Table 27. Paediatric Use

Estimated Use	Number of cases	Comment on Any Variation in Benefit or Risk From Overall Target Population
<18 years old	16	The safety and efficacy of parecoxib in children under 18 years old have not been established. Cumulatively, there have been 16 spontaneously reported cases involving paediatric patients (age range 8-17, mean = 15, N=16). The most frequently reported AEs involved skin and subcutaneous tissue disorders and encoded to the MedDRA preferred terms (PTs) Rash (3), Dermatitis allergic, Swelling face, Rash erythematous, and Urticaria (1 each). Two cases reported events with a fatal outcome (PTs Anaphylactic shock and Death). Based on the review of the data, there appears to be no difference between the risks seen in the paediatric patients and adults treated with parecoxib.
Data source	Post-marketing safety database	
Method of calculation	Searched all cases age range less than or equal to 17 years	

Table 28. Pregnant or Breast Feeding Women*

Estimated Use	Number	Comment on Any Variation in Benefit or Risk From Overall Target Population
Pregnant	18	There are no studies in pregnant women. Cumulatively, there have been 18 spontaneously reported cases, involving 15 distinct pregnancies involving parecoxib exposure. The most frequently reported events (>1) encoded to the PTs Foetal exposure during pregnancy (10), Normal newborn (3), and Maternal exposure timing unspecified (2), The time of exposure was reported for 7 of the 15 pregnancies and occurred in the first trimester. Pregnancy outcomes included 4 normal births, 1 spontaneous abortion, and 1 abortion due to an accident. The only other reported pregnancy related event in a mother was encoded to the PT Postpartum haemorrhage. Use in pregnancy and use during lactation are important identified risks (see section 2.7.3).
Breast feeding	No patients identifed	
Data source	Post-marketing safety database	
Method of calculation	Database searched for all cases meeting pregnancy condition criteria	

* Pregnancy and lactation related cases in the MAH's database are identified as cases that meet one of the following criteria: where the Patient Pregnant Flag is "Yes"; if there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly; if Delivery Notes are available; or if a case includes a PT with primary allocation to either the SOC Pregnancy, puererium and perinatal concitions; the HLT Exposures associated with pregnancy, delivery and lactation; or includes the PTs Drug exposure during pregnancy, Exposure via body fluid, Exposure via partner, Intoxication by breast feeding, Maternal drugs affecting foetus, or Paternal drugs affecting foetus. Cases are excluded if the case is reported to involve an adult male patient.

Table 29. Hepatic Impairment*

Estimated Use	Number	Comment on Any Variation in Benefit or Risk From Overall Target Population
Mild Moderate Severe	1 (severity data not available)	Cumulatively, there has been 1 spontaneously reported case involving a patient with underlying hepatic impairment. Due to limited data, it is not feasible to draw a meaningful conclusion, however review of the single case received does not suggest any difference in risk for patients with a medical history of hepatic impairment. Use in patients with hepatic impairment is an important identified risk (see 2.7.3).
Data source	Post-marketing safety database	
Method of calculation	Database searched for all cases meeting hepatic impairment condition criteria	

* Medical history of hepatic impairment was defined as cases reporting medical history encoded to a MedDRA Preferred Term (PT) in the Hepatic Failure and Associated Disorders or Hepatic Fibrosis and Cirrhosis High Level Term or encoded to PTs Adenoviral Hepatitis,Chronic Hepatitis,Congenital Hepatitis B Infection, Chronic hepatitis B, Chronic hepatitis C,Cytomegalovirus Hepatitis,Gianotti-Crosti Syndrome,Hepatic Atrophy,Hepatic Necrosis,Hepatitis B,Hepatitis C ,Hepatitis D,Hepatitis E,Hepatitis F,Hepatitis G,Hepatitis H ,Hepatitis Chronic Active,Hepatitis Chronic Persistent,Hepatitis Fulminant,Hepatitis Non-A Non-B,Hepatitis Non-A Non-B Non- C,Hepatitis Post Transfusion,Hepatitis Viral,Herpes Simplex Hepatitis,Liver And Pancreas Transplant Rejection,Liver Transplant Rejection,Drug-Induced Liver Injury,Chronic Graft Versus Host Disease In Liver or reporting a Lower Level Term Fulminant Hepatitis B.

Table 30. Renal Impairment*

Estimated Use	Number	Comment on Any Variation in Benefit or Risk From Overall Target Population
Mild Moderate Severe	6 (severity data not available)	Cumulatively, there have been 6 spontaneously reported cases involving patients with underlying renal impairment. Of the 6 patients with underlying renal impairment, 3 experienced renal AEs encoded to the PTs Renal failure, Renal failure acute, and Renal impairment (1 each). Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering parecoxib in patients with impaired renal function.
Data source	Post-marketing safety database	
Method of calculation	Database searched for all cases meeting renal impairment condition criteria	

*Medical history of renal impairment was defined as cases reporting medical history encoded to a MedDRA Preferred Term (PT) in the Renal failure and impairment High Level Term or encoded to PTs Acute Phosphate Nephropathy, Chronic Autoimmune Glomerulonephritis, Complications Of Transplanted Kidney, Glomerulonephritis Chronic, Glomerulonephritis Membranoproliferative, Glomerulonephritis Proliferative, Glomerulonephritis Rapidly Progressive, Ischaemic Nephropathy, Kidney Fibrosis, Kidney Transplant Rejection, Removal Of Renal Transplant, Renal And Pancreas Transplant Rejection, Renal Graft Loss.

2.5.4. Post-Authorisation Off-Label Use

In Europe, parecoxib is indicated for the short-term treatment of postoperative pain in adults. Off-label use of parecoxib in the European Union is summarized in this section.

In the EU, 6 cases reported the MedDRA preferred term Off-label use. In 5 of the 6 cases, the off-label use involved an unapproved indication (e.g., arthralgia, pain, migraine, general anaesthesia, tendonitis). Five of the 6 cases were non-serious. The countries where the events occurred were Greece (4) and Germany (2). In addition, cumulatively there were 16 cases reporting use of parecoxib in the pediatric population, 4 of these cases were from the EU (Greece, Spain, Bulgaria,United Kingdom). Based on the review of these cases, there appears to be no difference between the risks seen in the paediatric patients and adults treated with parecoxib.

There were 337 post-marketing cases from the EU in the safety database. In 112 cases the indication was not provided. Upon review of the remaining 225 cases, 111 cases were categorized as arising from operative use and 114 cases from non-operative use. A review of these cases did not identify a safety signal related to off-label use of parecoxib.

2.5.5. Epidemiological Study Exposure

To date, a single epidemiology study with parecoxib has been conducted in Germany (PARA-0505-091).

Table 31. Epidemiology Study Exposure

Study Title and Study Type	Objectives	Population Studied (Data Source and Country)	Duration (Study Period)	Number of Persons in Each Treatment Group (N = 13,698) and Person-Time (if Appropriate)	Comments
Pain Exit Study (PARA-0505-091) Observational study	Pain Exit was an online application study. The goal of the study was to obtain data from treating physicians on the efficacy, safety and tolerability of the use of parecoxib and comparators under standard-of-care conditions.	General population Germany	6 months	9475 (Parecoxib) 993 (Metamizol) 1634 (Diclofenac) 109 (Lysine-acetyl salicylate) 918 (Tramadol) 64 (Paracetamol) 16 (Tolypyrin) 83 (Ketoprofen) 43 (Glucocorticoids) 160 (Piroxicam) 26 (Meloxicam) 20 (Nefopam) 14 (Phenylbutazone) 18 (Local anesthetic) 80 (Opioids) 45 (Other) Person-time not collected.	Study completed 31 Aug 2003

N = number of subjects at risk.

2.6. Part II: Module SVI—Additional EU Requirements for the Safety Specification

2.6.1. Potential for Harm from Overdose

Clinical experience of overdose is rare. Single IV doses of up to 200 mg parecoxib have been administered to healthy subjects without clinically significant adverse effects. Parecoxib doses of 50 mg IV twice daily (100 mg/day) for 7 days did not result in any signs of toxicity.

The label provides appropriate guidance to ensure that patients receive the correct dose of parecoxib. Given the clinical context in which parecoxib is administered, the potential for overdose is expected to be low (see also Section 2.6.4, Potential for Medication Errors). Parecoxib is administered intravenously or intramuscularly by a health care professional in a monitored setting. The only postmarketing case report of Overdose turned out, upon review, to be a case of medication error in [redacted] the physician accidentally gave an elderly female patient twice as much as the usual dose. In [redacted] the approved dose level of parecoxib is only 20 mg, and the physician administered 40 mg. Since in a number of other countries where parecoxib is marketed the approved dose levels are both 20 mg and 40 mg, with 40 mg being very commonly prescribed, the total exposure received by the patient was not out of the ordinary in relation to worldwide practice. Adverse events associated with the medication error and overdose in this case encoded to the PTs Renal impairment, Pulmonary oedema, and Cardiac failure congestive.

2.6.2. Potential for Transmission of Infectious Agents

Parecoxib sodium for injection, manufactured by the Marketing Authorisation Holder (MAH) in Kalamazoo, Michigan, USA, contains no excipients of animal origin and does not present a risk of transmission of bovine spongiform encephalopathy (BSE). Parecoxib sterile powder for injection, all strengths, is in compliance with EMEA/410/01.

2.6.3. Potential for Misuse for Illegal Purposes

The MAH is not aware of reported illegal use of parecoxib in the EU that would indicate any public health hazard. Nor does the MAH's analysis of the postmarketing pharmacovigilance database disclose such illegal use.

2.6.4. Potential for Medication Errors

The potential for medication errors with parecoxib is low. The drug name has been agreed by the EMA/CHMP naming review group. Physicians, pharmacists, and other health care professionals are unlikely to confuse parecoxib with another medication for the labeled indication. As an additional precaution, Section 4.4, Special warnings and precautions for use, of the CDS and the SmPC, state that "modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used".

In post-marketing experience with parecoxib, periodic reviews of medication error via routine pharmacovigilance activities have not identified a systemic problem.

2.6.4.1. Medication Errors During the Clinical Trial Programme

There were no medication errors reported to the safety database during the parecoxib clinical program. There are no ongoing or planned trials with parecoxib.

2.6.4.2. Preventive Measures for the Final Product(s) Being Marketed

Instructions that explain how to prepare and inject parecoxib are provided in the parecoxib package leaflet (see Annex 2). Users are instructed to read all of the leaflet carefully before starting to use the medicine.

2.6.4.3. Effect of Device Failure

Not applicable.

2.6.4.4. Reports of Medication Errors with the Marketed Product

Review of the Pfizer safety database through 31 March 2014 identified 34 cases which described events potentially indicative of prescription/medication errors related to parecoxib. Upon review, 1 case involved off-label use and is not further discussed in this section. The remaining 33 cases represent 2.1 % of the total number of 1588 cases received for parecoxib. A total of 33 medication error events were reported in these cases (see Table 32) and the majority of the cases (30) were non-serious. Most of these cases (25) described medication error events with no other associated adverse events.

Table 32. Reports of Medication Errors with the Marketed Product

Description of Error (PT)	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Circumstance or information capable of leading to medication error	10	Mostly involved mixing parecoxib with other medicinal products or prescribing to patients with risk factors for cardiovascular events.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Medication error	8	Mostly involved reconstitution errors. Other singular reports included prescribing to a patient in whom the drug was contraindicated, mixing parecoxib with other medicinal products, and incorrect dosing.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Drug administration error	5	Involved incorrect route of administration, incorrect administration, and reconstitution error.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Drug prescribing error	2	Involved prescribing to patient in whom the drug was contraindicated, and mixing parecoxib with other medicinal products.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Expired drug administered	2	Expired drug administered.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Incorrect route of drug administration	2	Involved intra-arterial and intra-articular injections.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Wrong technique in drug usage process	2	Involved reconstitution with wrong diluents and mixing parecoxib with another medicinal product.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Accidental exposure to product	1	During injection, patient got some solution in eye.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required
Incorrect dose administered	1	Accidentally received twice a day instead of daily.	Maintenance of accurate labeling	MAH will continue to monitor and update labels as required

Irrespective of the encoded PT, the most commonly reported medication errors involved mixing parecoxib with another medication, reconstitution errors, or prescribing parecoxib to a patient in whom it is contraindicated. Review of these 34 cases did not identify significant

new safety information and did not provide evidence that these errors were a result of the product label.

2.6.5. Potential for Off-Label Use

In the EU, parecoxib is approved for use for the short-term treatment of post-operative pain. Marketing data, as presented in every PSUR, as well as the Pain Exit (PARA-0505-091) postmarketing observational study show that parecoxib is used for pain outside the context of surgery. We note that the MAH's policy prohibits the endorsement, promotion or marketing of such off-label use of parecoxib in Europe.

The MAH has reviewed the Pain Exit results (Study PARA-0505-091) and examined the postmarketing AEs from both approved and off-label use in Pfizer's safety database. First, in Pain Exit, only 5 of 54 AEs with parecoxib occurred following administration in non-operative settings. None were serious, and all were similar to events occurring following administration in operative and post-operative settings. Second, upon review of the reported AEs in the MAH's safety database, we consider that there is no significant difference in the occurrence of AEs reported between patients receiving parecoxib for the approved European indication and those receiving the drug for off-label use worldwide.

Although there is evidence of off-label use of parecoxib, the data do not show it constitutes an actual risk to patients. Off-label use will continue to be monitored as part of routine pharmacovigilance.

2.6.6. Specific Paediatric Issues

2.6.6.1. Issues Identified in Paediatric Investigation Plans

Parecoxib is not recommended in children under 18 years old. No clinical studies were conducted in the paediatric population.

2.6.6.2. Potential for Paediatric Off-Label Use

In the EU, parecoxib is approved for the short-term treatment of postoperative pain in adults. A cumulative review of the safety database only identified 16 cases that involved the use of parecoxib in children.The MAH acknowledges that there is potential for off-label use in paediatric patients.

2.6.7. Conclusions

The safety of parecoxib has been well characterized based on clinical trials and post-marketing surveillance. The safety concern from this module is listed in Table 33.

Table 33. Safety Concerns From This Module

Missing Information	Comment
Off-label use	The MAH will monitor through routine pharmacovigilance.

2.7. Part II: Module SVII—Identified and Potential Risks: Non-ATMP Version

2.7.1. Newly Identified Safety Concerns (Since this Module was Last Submitted)

Since the previous RMP for parecoxib (version 3.0) was submitted on 26 May 2011, no new identified or potential risks were identified. Off-label use has been added as missing information, and the previous missing information of "failure to monitor and manage AEs or lack of efficacy, especially after dose increase" has been rephrased to "safety profile after dose increase" for increased clarity.

In addition, prior missing information of "driving or operating machines while experiencing dizziness, vertigo or somnolence from parecoxib use" is proposed to be deleted. The reason the MAH is proposing this is because parecoxib is indicated for short-term treatment of post-operative pain most likely in the hospital setting or under healthcare provider monitoring via IV or IM administration, which does not implicate a scenario where the patient would drive or operate a machine after administration of the medication. From a pharmacological perspective, parecoxib is not a central nervous system (CNS) drug, nor does it have significant CNS side effects. A cumulative review of the MAH's postmarking safety database identified no cases with AEs that encoded to the PTs Impaired driving ability, Impaired work ability, Accident at home, Accident at work, or Road traffic accident. Based upon these rationale and facts, driving or operating machines while experiencing dizziness, vertigo or somnolence from parecoxib use is not considered as missing information for parecoxib in the submission.

2.7.2. Recent Study Reports with Implications for Safety Concerns

There are no recent study reports with implications for safety concerns.

2.7.3. Details of Important Identified and Potential Risks from Clinical Development and Post-Authorisation Experience (Including Newly Identified)

Important identified risks for parecoxib include severe cutaneous adverse reactions, CV thrombotic events, GI ulceration-related events, renal failure and impairment, hypersensitivity reactions, use in patients with congestive heart failure (CHF), use in patients with hepatic impairment, severe hypotension, use during pregnancy, lactation, or in women attempting to conceive, masking of signs of inflammation, and discontinuation of antiplatelet therapies. An important potential risk is administration other than IV or IM.

The identified and potential risks for parecoxib are characterized based on pooled safety data from 5402 patients in 28 relevant completed randomized, blinded clinical trials of parecoxib in patients undergoing general surgery including orthopaedic, obstetric, inguinal hernia, prostectomy surgery and CABG procedures and patients undergoing oral surgery, (clinical trials include; N93-97-02-003, N93-97-02-004, N93-97-02-014, N93-98-02-018, N93-98-02-019, N93-98-02-020, N93-98-02-021, N93-98-02-022, N93-98-02-025, N93-99-02-028, N93-99-02-029, E93-99-02-033, I93-99-02-035, N93-99-02-037, N-93-00-02-044, N93-01-02-047, E93-01-02-067, N93-01-02-068, I93-01-02-069, PARA-0505-071, PARA-0505-076, PARA-0505-077, PARA-0505-078, PARA-0505-080, PARA-0505-081, PARA-0505-086, PARA-0505-088, and PARA-0505-089). The frequency is provided as the incidence risk/incidence rate with 95% CIs.

Table 34. Important Identified Risk: Severe Cutaneous Adverse Reactions

Frequency with 95% CI	Severe cutaneous adverse reactions (SCAR) SMQ Narrow Parecoxib: 0.0% Placebo: 0.0% RR (95% CI): N/A
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 17 Serious = 17 Case Outcome: Recovered = 9, Recovering = 1, Not recovered = 2, Unknown = 3, Fatal = 2 Non-medically confirmed cases: 3 Serious = 3 Case Outcome: Recovering = 1, Unknown = 1, Fatal = 1
Severity and nature of risk	Graded severity not available. By nature, all of these events are severe, or have the potential to be severe.
Background incidence/prevalence	Severe cutaneous adverse reactions[30] encompass a series of related severe cutaneous adverse drug reactions, believed to be T-cell–mediated delayed hypersensitivity reactions. Internationally, there is now close agreement among authors on the conditions that are covered by this term: Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis,[6] also known as Lyell's syndrome. However, there is still no consistent agreement on differential diagnoses among these 3 conditions; in particular, differentiation between TEN and SJS or between SJS and EM is problematic. For this reason, there has never been a fully uniform terminology to describe these conditions; and furthermore, it should be noted that Exfoliative dermatitis (ED) is often incorrectly included in this classification. The most widely used classification of SCAR, developed by Bastuji-Garin, differentiates among the various conditions according to the degree of epidermal detachment and the type and body distribution of lesions. This classification was used to define SCAR in this document.[31] Incidence No data were found specifically for orthopaedic surgery patients, and therefore the summary below describes all hospitalised patients. Severe cutaneous adverse reactions[30] are extremely rare, occurring with a rate ranging from 0.4 to 7.4 cases per million persons per year in the general population, and are primarily drug induced[32]. The incidence among hospitalized patients ranges from 2% to 5%, and approximately 1 in 1,000 hospitalized patients suffers from life-threatening SCAR.[33] Duration of exposure plays an important role in the development of severe cutaneous reactions with all drugs, as the majority of reactions occur within the first 8 weeks of treatment. A large study using discharge data collected at Peking University Third Hospital reported an overall incidence of SCAR of 1.8 per million persons per year and specific incidence rates for SJS, 0.8; ED, 0.6; and TEN, 0.05 cases per million persons per year.[33] Different patterns of clinical types have been observed in different countries; for example, in France the most common type of SCAR was SJS at 55%, whereas 40% of SCAR cases in Italy were EM.[33]
Risk groups or risk factors	Drugs are implicated in over 95% of toxic epidermal necrolysis (TEN) cases, and about 50% of SJS cases. NSAIDs are included in the drug classes recognized as imparting the greatest risk of TEN and SJS.[34] Among those treated with selective COX-2–inhibiting NSAIDs, the occurrence of these reactions appears unpredictable,[35] and no risk factors for SCAR events that are specific to parecoxib have been identified.

Table 34. Important Identified Risk: Severe Cutaneous Adverse Reactions

Potential mechanisms	SCAR is an immune-mediated reaction. In certain individuals, reactive metabolites of a drug combine with healthy tissue and incite a pathoimmunologic response. In SCAR, this eventually leads to autoimmune attack on the skin, with epidermal necrosis.
Preventability	Patients who experience SCAR related to any drug should avoid further use of that drug. Currently, there is no reliable way to predict or prevent SCAR as a reaction to a particular drug in a patient who has not previously experienced SCAR with that drug. Patients appear at highest risk early during therapy, and therapy should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and supportive therapy.
Potential public health impact of safety concern	Due to the rarity of severe cutaneous adverse reactions reported from clinical trial and post-marketing spontaneous sources, as well as the relatively limited use of the product (in the hospital/clinic setting under medical supervision and short duration of use), the risk should have minimal impact on public health.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify severe cutaneous adverse reactions in postmarketing surveillance included preferred terms within the narrow SMQ category of Severe Cutaneous Adverse Reactions (SCAR).

Table 35. Important Identified Risk: Cardiovascular Thrombotic Events

Frequency with 95% CI	Embolic and thrombotic events, arterial SMQ (all indications) Parecoxib: 0.3% Placebo: 0.2% RR (95% CI): 1.438 (0.647–3.198) Embolic and thrombotic events, venous SMQ (all indications) Parecoxib: 0.2% Placebo: 0.1% RR (95% CI): 1.438 (0.492–4.205) Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous SMQ (all indications) Parecoxib: 0.2% Placebo: 0.2% RR (95% CI): 1.438 (0.540–3.829)
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 66 Serious = 64, Non-serious = 2 Outcome: Recovered = 20, Recovering = 4, Recovered with sequelae = 2, Not recovered = 2, Unknown = 18, Fatal = 20 Non-medically confirmed cases: 1 Serious = 1 Outcome: Fatal = 1
Severity and nature of risk	Graded severity not available. By nature, these events are severe, or have the potential to be severe.

Table 35. Important Identified Risk: Cardiovascular Thrombotic Events

Background incidence/prevalence	The risk of cardiovascular events can be expected to vary depending on type of surgery. In this section, data pertaining to patients undergoing orthopaedic surgery (the most frequent type of surgery that requires subsequent pain management) are summarised. In general, according to the American College of Cardiology/American Heart Association, the risk of cardiac morbidity among the orthopaedic patient population is considered intermediate (1%-5%).[36] Data for myocardial infarction (MI) and stroke are presented separately below. **Myocardial infarction** Incidence In a large prospective database study of 10,244 patients undergoing primary hip or knee arthroplasty at the Mayo Clinic (Rochester, Minnesota, USA), the frequency of clinically relevant MI within 30 days of surgery was 0.4%. For patients aged 60-69, 70-79, and 80 years of age or older, the corresponding frequencies of MI were 0.1%, 0.4% and 1.3% for female patients and 0.4%, 0.7% and 2.2% for male patients, respectively.[37] In a study of 23,136 total hip replacement patients identified from the 5% random sample of 1994-1999 US Medicare claims data, the 7-day incidence of acute MI was 0.79% (95% CI, 0.67%-0.91%) in patients who had post-operative epidural analgesia (EA) and 0.85% (95% CI, 0.50%-1.20%) in those who did not have EA.[38] The incidence of in-hospital MI was 0.27% in a large US study of 15,383 hip and knee arthroplasties performed in 13,517 patients in 2000-2006.[39] Another study of 3,471 total joint arthroplasty patients reported that 1.8% (95% CI, 1.4%-2.4%) suffered a clinically relevant post-operative MI occurring at a mean of 3 days post surgery.[40] **Stroke** The risk of ischaemic stroke increases after surgery and is estimated to occur in 2.9% of all patients who undergo general surgery.[41] While postoperative stroke is usually due to co-morbid conditions rather than surgical complications, immobility may also increase the risk of stroke, particularly among patients who have undergone orthopaedic surgery.[41] Incidence Using data collected from 13,517 total joint arthroplasty patients, Pulido et al (2008)[39] estimated incidence of in-hospital stroke at 0.14%. **Venous thromboembolic events** For the data on occurrence of VTEs post orthopaedic surgery and related mortality, see Section 2.1.3 of this RMP.
Risk groups or risk factors	CABG is a risk factor for a CV thrombotic event with parecoxib.[29] Outside the post-CABG setting, several major risk factors for CV thrombotic events are well established, including age >75 years, hypertension, smoking, hyperlipidemia, use of low-dose aspirin, diabetes, and previous history of CV disease.[29] These are risk factors for CV events regardless of parecoxib exposure, and their interaction with parecoxib has not been studied.

Table 35. Important Identified Risk: Cardiovascular Thrombotic Events

Potential mechanisms	Possible overlapping mechanisms that may help explain the CV effects of COX-2 selective and nonselective NSAIDs include increased blood pressure, inhibition of renal function, and reduced production of vasculoprotective prostacyclin in the arterial endothelium, as well as alteration of the prostacyclin/thromboxane balance. There is a lack of clinical evidence, however, to distinguish among these various hypotheses.[42] The mechanism of CV thromboembolic events after CABG surgery is not known, and may be different from the mechanism of thrombotic events in other context of NSAID use.[43] Because the cardiovascular risks observed in CABG surgery patients reflect the unique and highly dynamic prothrombotic and inflammatory syndrome that immediately follows cardiopulmonary bypass, the effects of parecoxib sodium in this population may not represent the effects of parecoxib sodium in surgical settings other than CABG surgery.
Preventability	Parecoxib should not be used following CABG surgery. Except for CABG, there are no data to predict or prevent CV thromboembolic events in patients receiving parecoxib.
Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and in some instances therapeutic intervention.
Potential public health impact of safety concern	Due to the rarity of these events, as well as the relatively limited use of the product (in the hospital/clinic setting under medical supervision and short duration of use), the risk is expected to have minimal impact on public health.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify cardiovascular thrombotic events in postmarketing surveillance included preferred terms in the narrow SMQs: Cerebrovascular disorders, Embolic and thrombotic events, and Ischaemic heart disease.

Table 36. Important Identified Risk: Gastrointestinal Ulceration-Related Events

Frequency with 95% CI	Gastrointestinal haemorrhage SMQ Parecoxib: 0.2% Placebo: 0.2% RR = 0.925; 95% CI (0.345–2.481) Gastrointestinal perforation SMQ Parecoxib: 0.0% Placebo: <0.1% RR (95% CI): N/A Gastrointestinal ulceration SMQ Parecoxib: 0.1% Placebo: <0.1% RR = 2.877; 95% CI (0.611 to 13.54)
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 35 Serious = 35 Outcome: Recovered = 12, Recovering = 3, Not recovered = 4, Unknown = 12, Fatal = 4 Non-medically confirmed cases: None
Severity and nature of risk	Graded severity not available. By nature, these events are severe, or have the potential to be severe.

Table 36. Important Identified Risk: Gastrointestinal Ulceration-Related Events

Background incidence/prevalence	**Ileus/Perforation** Incidence Following total hip or knee arthroplasty, the most common gastrointestinal complication is post-operative ileus. Post-operative ileus, the partial or complete blockage of the bowel, has found to be correlated with the method and type of anaesthesia, and post-operative narcotics as well as previous surgeries or postoperative feeding.[44] After total joint arthroplasty, the incidence of ileus has been reported to range from 0.7% to 4.0% and to occur more frequently in younger males.[44] In a study of 23,136 total hip replacement patients identified from the 5% random sample of 1994-1999 US Medicare claims data, the 7-day incidence of paralytic ileus was 1.09% (95% CI, 0.95%-1.23%) in patients who had post-operative epidural analgesia (EA) and 0.73% (95% CI, 0.40%-1.06%) in those who did not have EA.[38] Another large US study of 15,383 hip and knee arthroplasties performed in 13,517 patients in 2000 to 2006, estimated in-hospital incidence of small bowel obstruction at 0.02% and the incidence of ileus at 0.23%.[39] Although rare, post-operative ileus, if left untreated, has been linked to serious GI dysfunction, including perforation of the colon, which has an estimated mortality of 46%.[44] **Bleeding** Incidence Within the orthopaedic population, the incidence of acute GI hemorrhage has been reported to range from 0.39% to 14%.[45,46,47] This wide range can be explained by the varied types of procedures falling under the term orthopaedic surgery as well as the underlying demographic factors of such a diverse population. One study using prospectively collected data from a single high-volume site on 13,517 total joint arthroplasties reported only 3 cases of gastrointestinal bleeding (0.02%).[39] Another study compared the incidence of peri-operative complications among bilateral and unilateral total knee arthroplasty patients. From this sample of bilateral (255) and unilateral procedures (514), the authors reported 5 (2.0%) and 7 (1.4%) cases of GI bleeding, respectively.[48] The rates were not significantly different between the 2 procedure groups.
Risk groups or risk factors	With NSAIDs in general, patients most at risk of developing GI ulcer-related events are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, patients with positive *Helicobacter pylori* status; patients with a history of, or active, GI disease, such as ulceration, bleeding, dyspepsia or inflammatory conditions; patients prescribed NSAIDs; patients using multiple NSAIDs; or patients using concomitant prescription drugs, such as corticosteroids and anticoagulants.[49,50] The risk factors for GI-ulceration events and their interaction with parecoxib have not been studied.
Potential mechanisms	The most important mechanism by which NSAIDs cause ulcers is by indirectly decreasing prostaglandin production via the inhibition of COX-1. Prostaglandins are important in maintaining mucosal integrity by producing mucus, stimulating bicarbonate production, decreasing acid production, and maintaining mucosal blood flow.[49]
Preventability	Parecoxib should be used with caution in patients who are elderly, are using concomitant aspirin or other NSAID, or have a history of, or active, GI disease, such as ulceration or bleeding.
Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and in some instances therapeutic intervention.

Table 36. Important Identified Risk: Gastrointestinal Ulceration-Related Events

Potential public health impact of safety concern	The frequency of gastrointestinal haemorrhage, perforation and ulceration events are comparable between the parecoxib and placebo groups in the pooled safety data from clinical trial data source. In addition, the use of parecoxib is limited to short-term with medical supervision. Therefore it should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify gastrointestinal ulceration-related events in postmarketing surveillance included preferred terms in the narrow SMQs Gastrointestinal haemorrhage, Gastrointestinal perforation , and Gastrointestinal ulceration.

Table 37. Important Identified Risk: Renal Failure and Impairment

Frequency with 95% CI	Renal failure and impairment (HLT) Parecoxib: 1.1% Placebo: 1.0% RR = 1.108; 95% CI (0.734-1.672)
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 77 Serious = 68, Non-serious = 9 Outcome: Recovered = 32, Recovering = 9, Recovered with sequelae = 1, Not recovered = 8, Unknown = 21, Fatal = 6 Non-medically confirmed cases: 2 Serious = 2 Outcome: Recovered = 2
Severity and nature of risk	Graded severity not available. By nature, these events are severe, or have the potential to be severe.
Background incidence/prevalence	Population-level data are not available in the literature for the incidence and prevalence of renal impairment among patients who have undergone orthopaedic surgery. A few hospital-based studies, however, have been conducted to evaluate post-surgical complications and fatalities within this population and, where mentioned, renal events are described below. Incidence/Prevalence One study evaluated the systemic and local complications associated with unilateral lower-extremity arthroplasties. Among the 1636 patients who underwent surgery for primary total hip replacement (THR) or total knee replacement (TKR), 14 events of acute renal failure occurred within 4 days of the surgical procedure.[51]
Risk groups or risk factors	Patients with a history of renal impairment.
Potential mechanisms	Both COX-1 and COX-2 are active (in different structures in the kidney) in regulating renal processes, which include salt and water retention or elimination and electrolyte balance. Parecoxib may also reduce the effectiveness of diuretics, including the thiazides and furosemide.

Table 37. Important Identified Risk: Renal Failure and Impairment

Preventability	Renal function should be closely monitored in patients with advanced renal disease who are administered parecoxib. In patients with creatinine clearance <30 mL/min or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose and the patient's kidney function closely monitored. Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with parecoxib.[52,53]
Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and therapeutic intervention.
Potential public health impact of safety concern	The frequency of renal failure and impairment is comparable between the parecoxib and placebo groups based on the pooled safety data from clinical trial data source. In addition, the use of parecoxib is limited to short-term with medical supervision. Therefore it should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify renal failure and impairment in postmarketing surveillance included preferred terms with a primary allocation to the HLT Renal failure and impairment.

Table 38. Important Identified Risk: Hypersensitivity Reactions

Frequency with 95% CI	Anaphylactic reaction (SMQ) - Narrow Parecoxib: 8.7% Placebo: 8.6% RR (95% CI): 1.010 (0.884-1.155) Angioedema (SMQ) - Narrow Parecoxib: 2.6% Placebo: 3.0% RR (95% CI): 0.888 (0.697-1.132) Allergic conditions (HLGT) Parecoxib: <1.0% Placebo: 1.0% RR (95% CI): 0.575 (0.155-2.141)
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 190 Serious = 98, Non-serious = 92 Outcome: Recovered = 125, Recovering = 15, Recovered with sequelae = 1, Not recovered = 8, Unknown = 34, Fatal = 7 Non-medically confirmed cases: 34 Serious = 18, Non-serious = 16 Outcome: Recovered = 10, Recovering = 5, Not recovered = 9, Unknown = 9, Fatal = 1
Severity and nature of risk	Graded severity not available. These events have the potential to be severe, depending on a number of factors in addition to the drug administered.
Background incidence/prevalence	Hypersensitivity reactions during and after orthopaedic surgery can arise from a number of causes—an implant, anaesthesia, as well as peri-operative analgesic or antibiotic treatments. At this time, however, epidemiologic or population-based data are not available for hypersensitivity reactions among either the postoperative pain or the orthopaedic surgery populations. One multi-center epidemiologic study, however, was conducted in France to better understand the incidence of anaphylactic shock in the general patient population undergoing anaesthesia. From data collected from 1,585 patients at 21 French sites, the authors reported an incidence of anaphylaxis due to anaesthesia ranging from 1:1500 to 1:5000.[54,55] A similar study of 71,063 surgical interventions was conducted in Spain; 48 interventions resulted in a peri-anaesthetic hypersensitivity reaction, yielding an incidence rate of 1/1480 interventions. In the 2 studies, approximately half of the hypersensitivity reactions were immune mediated, 52% in France and 56% in the Spanish study.[56] The 2 studies reported varying causes for these hypersensitivity reactions, including antibiotics (3%, 44%), muscle relaxants (70.3%, 37%) and latex (12.6%, 7%), respectively. Since these studies were of such differing sample sizes with such a wide range of procedures, it is impossible to extrapolate these data to the post-operative pain or post-orthopaedic surgery populations. Nevertheless, these data do provide an overall background incidence of hypersensitivity among patients undergoing surgery that requires anaesthesia.

Table 38. Important Identified Risk: Hypersensitivity Reactions

Risk groups or risk factors	It is not possible to anticipate every case in which a patient might be at risk of experiencing a hypersensitivity reaction. A number of patients, however, will fall into identifiable risk groups: they may have a medical history of general hypersensitivity to other substances (pollen, animal hair or dander, latex, household chemicals, etc), and/or to other drugs; or they may have experienced an anaphylactic reaction, angioedema, etc., previously.
Potential mechanisms	Different immunologic mechanisms, or a combination of mechanisms, could be responsible for a particular episode or an individual patient's reaction patterns.
Preventability	The health care professional (HCP) should inquire about a patient's medical history; conversely, the patient should alert health care professionals about any history of anaphylaxis, angioedema, or allergic reactions to medications, especially those containing sulfonamides. If the HCP, such as a physician or an anesthesiologist, has any reason to suspect a possible hypersensitivity response, the patient should be monitored closely in the hours after receiving parecoxib, preferably in a clinical environment offering appropriate medications, equipment and trained personnel for emergency treatment if required.
Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and therapeutic intervention for symptomatic relief.
Potential public health impact of safety concern	The frequency of anaphylactic reaction, angioedema and allergic conditions is comparable between the parecoxib and placebo groups in the pooled safety data from clinical trial data source. The risk is expected to have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify hypersensitivity reactions in postmarketing surveillance included preferred terms within the narrow SMQ category of Hypersensitivity.

Table 39. Important Identified Risk: Use in Patients with Congestive Heart Failure

Frequency with 95% CI	Not available.
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Non-medically confirmed cases: 1 Non-serious = 1 Outcome: Recovering = 1
Severity and nature of risk	Worsening of congestive heart failure in the postoperative stage is severe by nature.
Background incidence/prevalence	Population-based epidemiologic data are not available for the incidence of congestive heart failure among patients undergoing orthopaedic surgery.
Risk groups or risk factors	Major risk factors for CHF include hypertension, hyperlipidaemia, diabetes mellitus, smoking, and age >70 years.
Potential mechanisms	COX-2 is constitutive as well as inducible upon injury, and is present in a number of tissues, including heart, brain, lungs, and kidney. Also, COX-2 inhibition can interfere with renal function, including promoting fluid retention, and may contribute to pre-existing CHF.
Preventability	The risks of NSAID use in patients with heart failure can be reduced by observing contraindications or warnings in local prescribing information and, in the case of treatment, monitoring such patients' conditions.
Impact on individual patient	CHF has the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and in some instances therapeutic intervention.
Potential public health impact of safety concern	Administration of the product is limited to the hospital/clinic setting with medical supervision, therefore the risk should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify use in CHF in postmarketing surveillance included patient medical history coded to a PT with a primary allocation to the MedDRA HLGT Heart failures.

The MAH is planning to re-assess this risk and its classification, in consideration of the lack of evidence of an actual effect of worsening of preexisting CHF in the 12 years of post-marketing experience cumulated so far.

Table 40. Important Identified Risk: Use in Patients With Hepatic Impairment

Frequency with 95% CI	In the single pharmacokinetic study of subjects with mild and moderate hepatic impairment, AEs were reported for 58% of the subjects with normal hepatic function, 58% of the subjects with mild hepatic impairment, and 64% of the subjects with moderate hepatic impairment. There were no deaths or serious AEs. Adverse events reported by more than 2 subjects in a given group were headache in the normal group, headache and fever in the mild impairment group, and headache and pruritus in the moderate impairment group. The majority of the AEs were of uncertain relationship to the study medication. Although the overall exposure among subjects with moderate impairment was greater than that among subjects with normal hepatic function, the study medication appeared to be equally well tolerated among the subject groups.
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 1 Serious = 1 Outcome: Recovered = 1 Non-medically confirmed cases: None
Severity and nature of risk	In the single pharmacokinetic study of patients with hepatic impairment, the majority of AEs were graded mild in severity, and only 1 AE (non-serious headache) was graded severe.
Background incidence/prevalence	Population-based epidemiologic data are not available for the incidence and prevalence of hepatic impairment among patients undergoing orthopaedic surgery.
Risk groups or risk factors	Patients with a medical history of hepatic impairment from any cause.
Potential mechanisms	Parecoxib is metabolised primarily by the liver; thus hepatic dysfunction may impair clearance and result in higher exposure with increased risk of toxicity.
Preventability	Parecoxib is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C: serum albumin less than 25 g/L or Child-Pugh score, ≥10), and no studies have been performed in this class of patient. Patients with moderate hepatic impairment (Child-Pugh Class B: score, 7-9) should be initially administered a reduced dosage—half the usual level—with a daily maximum dosage of 40 mg, and be monitored for any adverse effects. Patients with mild hepatic impairment (Child-Pugh score, 5-6) generally do not require dosage adjustment. Likewise, any patient receiving parecoxib who has symptoms or signs of hepatic dysfunction, or abnormal results on 1 or more liver function tests, should be monitored carefully for any evidence of developing liver injury or dysfunction.
Impact on individual patient	Hepatic dysfunction may result in higher exposure to parecoxib and an increased risk of toxicity. Management may include discontinuation of therapy and in some instances therapeutic intervention.
Potential public health impact of safety concern	The use of parecoxib in patients with severe hepatic impairment is contraindicated, and the use of the product is limited to the hospital/clinic setting with medical supervision, therefore the risk should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.

Table 40. Important Identified Risk: Use in Patients With Hepatic Impairment

MedDRA terms	The search strategy used to identify use in patients with hepatic impairment in postmarketing surveillance included cases with a medical history of hepatic impairment defined as cases reporting medical history encoded to a MedDRA Preferred Term (PT) in the Hepatic Failure and Associated Disorders or Hepatic Fibrosis and Cirrhosis High Level Term or encoded to PTs Adenoviral Hepatitis,Chronic Hepatitis,Congenital Hepatitis B Infection, Chronic hepatitis B, Chronic hepatitis C,Cytomegalovirus Hepatitis,Gianotti-Crosti Syndrome,Hepatic Atrophy,Hepatic Necrosis,Hepatitis B,Hepatitis C ,Hepatitis D,Hepatitis E,Hepatitis F,Hepatitis G,Hepatitis H ,Hepatitis Chronic Active,Hepatitis Chronic Persistent,Hepatitis Fulminant,Hepatitis Non-A Non-B,Hepatitis Non-A Non-B Non- C,Hepatitis Post Transfusion,Hepatitis Viral,Herpes Simplex Hepatitis,Liver And Pancreas Transplant Rejection,Liver Transplant Rejection,Drug-Induced Liver Injury,Chronic Graft Versus Host Disease In Liver or reporting a Lower Level Term Fulminant Hepatitis B.

The MAH is planning to re-assess this risk and its classification, based on the 12 years of post-marketing experience cumulated so far.

Table 41. Important Identified Risk: Severe Hypotension

Frequency with 95% CI	Shock-associated circulatory or cardiac conditions (excl. torsade de pointes) SMQ (Narrow) Parecoxib: ≤0.1% Placebo: 0.2% RR = 0.103; 95% CI (0.013-0.135) Hypotension events (Hypotension and related PTs combined) Parecoxib: 2.7% Placebo: 2.1% RR = 1.261; 95% CI (0.963-1.651)
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 32 Serious = 25, Non-serious = 7 Outcome: Recovered = 20, Recovering = 3, Unknown = 6, Fatal = 3 Non-medically confirmed cases: 2 Serious = 2 Outcome: Recovered = 1, Not recovered = 1
Severity and nature of risk	Hypotension (PT) - Severity Parecoxib, 2.6%; Placebo, 2.1%; RR = 1.261; 95% CI (0.963-1.651) Mild - Parecoxib: 1.3%; Placebo = 1.1%; RR = 1.137; 95% CI (0.778-1.662) Moderate - Parecoxib: 1.2%; Placebo: 0.8%; RR = 1.1416; 95% CI (0.927-2.162) Severe - Parecoxib: 0.2%; Placebo: 0.2%; RR = 1.1312; 95% CI (0.488-3.562) Blood pressure decreased - Severity Mild - Parecoxib: <0.1%; Placebo: <0.1%; RR = N/A Moderate - Parecoxib: <0.1%; Placebo: <0.1%; RR = 1.438; 95% CI (0.130-15.86) Blood pressure systolic decreased - Severity Parecoxib: <0.1%; Placebo: 0.0%; RR = N/A Mild - Parecoxib: <0.1%; Placebo: 0.0%; RR = NA Blood pressure diastolic decreased - Severity N/A (no cases reported).
Background incidence/prevalence	Population-based epidemiologic data are not available at this time for the incidence and prevalence of hypotension among patients undergoing orthopaedic surgery.
Risk groups or risk factors	The parecoxib SmPC includes a warning of possible sudden hypotension after administration of parecoxib. Caution should be used when treating patients with a medical history of any of the events comprising this composite risk or elderly patients with low blood pressure or CV or circulatory problems.
Potential mechanisms	Severe hypotension can occur with parecoxib injection as part of an anaphylactic or anaphylactoid reaction, in which case hypotension results from the sudden release of relatively large amounts of vasoactive substances, such as histamine, from cells involved in acute hypersensitivity. Severe hypotension may also occur in the absence of other signs of hypersensitivity, in which case the mechanism is unclear.
Preventability	The risks of administering parecoxib in patients with possible risk factors of severe hypotension can be reduced by observing contraindications or warnings in local prescribing information and, in the case of treatment, monitoring such patients' condition carefully.

Table 41. Important Identified Risk: Severe Hypotension

Impact on individual patient	Such events have the potential to be life-threatening and may require medical intervention. Management may include discontinuation of therapy and therapeutic intervention.
Potential public health impact of safety concern	The frequency of severe hypotension events is comparable between the parecoxib and placebo groups in the pooled safety data from clinical trial data source. The risk is expected to have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify severe hypotension in postmarketing surveillance included cases with an AE that encodes to a PT with a primary allocation to the HLTs Circulatory collapse and shock or Vascular hypotensive disorders.

Table 42. Important Identified Risk: Use During Pregnancy, Lactation or in Women Attempting to Conceive

Frequency with 95% CI	In the clinical trial database of 3566 female subjects, 4 subjects (0.11%) reported drug exposure during pregnancy. Three of the 4 subjects believed during the conduct of the trial that they were not pregnant, and found out later that they had been pregnant in their first trimester during the trial. The 4th subject became pregnant within 30 days from discontinuation of the study medication. All 4 subjects gave birth to live, healthy, full-term infants. In addition, a single subject in the trial programme reported an ectopic pregnancy- a non-serious event judged by the investigator and the trial's Ressearch and Development Safety Monitor not to be associated with the study medication. She had a medical abortion after approximately 4 weeks of the pregnancy; there are no data regarding the outcome. There were no cases of use during lactation among subjects in clinical trials.
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Use during pregnancy: Medically confirmed cases: 11 involving 10 distinct pregnancies Serious = 2, Non-serious = 9 Fetal Outcome: Normal newborn = 4; Abortion due to accident = 1; Not available at time of reporting or not reported = 5 Non-medically confirmed cases: 7 involving 5 distinct pregnancies Serious = 1, Non-serious = 6 Fetal Outcome: Intrauterine death/Spontaneous abortion = 1; Not available at time of reporting = 4 Use during lactation: There were no cases identified in the postmarketing safety database for this risk.
Severity and nature of risk	Graded severity not available. By nature, these events have the potential to be severe.
Background incidence/prevalence	As pregnant women rarely undergo surgical procedures not related to their pregnancy, population-based epidemiologic data are not available for the incidence and prevalence of pregnancy among patients undergoing orthopaedic surgery. Population-based epidemiologic data are not available for the incidence and prevalence of lactation among patients undergoing orthopaedic surgery. Similarly, population-based epidemiologic data are not available surrounding women attempting to conceive who undergo orthopaedic surgery.
Risk groups or risk factors	Women of childbearing age who should be aware and informed of possible side effects of their medications in case they wish to conceive or are pregnant, and infants who are breastfed.

Table 42. Important Identified Risk: Use During Pregnancy, Lactation or in Women Attempting to Conceive

Potential mechanisms	Parecoxib is suspected to cause serious birth defects when administered during the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin, it may cause premature closure of the ductus arteriosus or uterine inertia. There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal. Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). A single 40 mg IV dose of parecoxib administered to lactating women after cesarean delivery is unlikely to cause adverse effects in breastfed infants.[57] Based on the mechanism of action, the use of NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.
Preventability	Preventable through physician and patient knowledge. Women who learn they are pregnant should inform their physician immediately if they are receiving parecoxib so that their treatment regimen can be adjusted in a timely and medically appropriate manner. Parecoxib is contraindication in the last trimester of pregnancy and should be used during the first 2 trimesters of pregnancy only if clearly necessary (SmPC, Section 4.6). A nursing mother who is found to require treatment with parecoxib should discontinue breastfeeding her infant. Withdrawal of parecoxib should be considered in women who have difficulties conceiving or who are undergoing investigation of infertility.
Impact on individual patient	Parecoxib may cause serious birth defects, increase the risks of miscarriage, or impact a womans ability to conceive. In addition, parecoxib and its active metabolite valdecoxib may be excreted in human milk.
Potential public health impact of safety concern	Due to the rarity of the events relevant to pregnancy, lactation, or in women attempting to conceive, no finding of serious birth defects reported from either clinical trial data or post-marketing spontaneous sources, and because the drug is limited to short term use in a hospital/clinic setting with medical supervision, it should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.

Table 42. Important Identified Risk: Use During Pregnancy, Lactation or in Women Attempting to Conceive

MedDRA terms	The search strategy used to identify use during pregnancy in postmarketing surveillance included cases that meet one of the following criteria: where the Patient Pregnant Flag is "Yes"; if there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly; if Delivery Notes are available; or if a case includes a PT with primary allocation to either the SOC Pregnancy, puererium and perinatal concitions; the HLT Exposures associated with pregnancy, delivery and lactation; or includes the PTs Drug exposure during pregnancy, Exposure via body fluid, Exposure via partner, Intoxication by breast feeding, Maternal drugs affecting foetus, or Paternal drugs affecting foetus. Cases are excluded if the case is reported to involve an adult male patient. The search strategy used to identify use during lactation in postmarketing surveillance included cases with an AE that encodes to the PT Exposure via breast milk. The search strategy used to identify use in women attempting to conceive in postmarketing surveillance included cases with an AE that encodes to the PTs Infertility or Infertility female.

Table 43. Important Identified Risk: Masking of Signs of Inflammation

Frequency with 95% CI	The frequency of infections in the clinical studies was: Skin structures and soft tissue infections HLT Parecoxib: 0% Placebo: <0.1% RR (95% CI): N/A Incision site infection PT Parecoxib: <0.1% Placebo: 0% RR (95% CI): N/A
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 18 Serious = 18 Outcome: Recovered = 7, Recovering = 1, Not recovered = 3, Unknown = 3, Fatal = 4 Non-medically confirmed cases: 4 Serious = 4 Outcome: Recovered = 1, Not recovered = 2, Unknown = 1 On review, only 1 case was found that was relevant to the concept of masking signs of inflammation. This medically confirmed case involved an elderly patient who died, and the physician stated afterward that parecoxib might have masked fever.
Severity and nature of risk	Graded severity not available. Parecoxib, as an NSAID, may mask fever and other signs of inflammation. In isolated cases an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in non-clinical studies with parecoxib.
Background incidence/prevalence	Data surrounding the treatment or masking of inflammation among patients undergoing orthopaedic surgery were not found in the epidemiologic literature at this time.
Risk groups or risk factors	Postoperative patients will experience inflammation while healing from incisions and invasive procedures that allow entry of pathogens.
Potential mechanisms	By reducing pain, fever and swelling from inflammation, COX-2 inhibitors (and also NSAIDs) may delay recognition, by patient as well as HCP, of a nascent infection capitalizing on the trauma of surgical incision.
Preventability	Close monitoring of the patient's postoperative condition, including vital signs and laboratory tests, may be the most effective approach to preventing health care professionals from overlooking signs of inflammatory processes after surgery.
Impact on individual patient	By reducing inflammation, parecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections; therefore, an infection may be undiagnosed.
Potential public health impact of safety concern	Due to the rarity of the relevant events reported, as no virulent pathogen has been observed so far, and because patients are usually in a hospital/clinic setting with medical supervision, the risk should have minimal publich health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify masking signs of inflammation in postmarketing surveillance included cases with an AE that encodes to a PT with a primary allocation to the SOC Infections and infestations where the infection-related AE was serious.

Table 44. Important Identified Risk: Discontinuation of Antiplatelet Therapies

Frequency with 95% CI	Not applicable.
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): There were no cases identified for the Important Identified Risk Cardiovascular thromboembolic events, where the patients dicontinued antiplatelet therapy after starting parecoxib therapy and prior to AE onset.
Severity and nature of risk	Graded severity not available. The nature of this risk is an incorrect substitution of any NSAID for aspirin, in aspirin's role as a thrombotic prophylactic. Such a substitution could arise from a misunderstanding of the similarities between aspirin and other NSAIDs, which include many effects on inflammation and pain, but do not include effects on thrombotic events. This kind of misunderstanding was probably more common in the early days of NSAIDs use.
Background incidence/prevalence	Since all patients undergoing orthopaedic surgery discontinue antiplatelet therapy prior to the procedure, population-based epidemiologic data are not available in the literature at this time for the discontinuation of antiplatelet therapies within this population.
Risk groups or risk factors	Patients with medical history of CV disease, stroke, hypertension.
Potential mechanisms	COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacycline without affecting platelet thromboxane. Parecoxib, like other COX-2 inhibitors, are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Discontinuation of acetylsalicylic acid would eliminate the anti-platelet aggregation effect.
Preventability	Preventable through physician and patient education.
Impact on individual patient	Because of its lack of anti-aggregant effects, parecoxib is not a replacement for aspirin in the prophylactic treatment of cardiovascular disease. Discontinuation of antiplatelet therapy can lead to potentially fatal blood clots.
Potential public health impact of safety concern	This risk should have minimal public health impact.
Evidence source	Clinical trials; Post-marketing safety database.
MedDRA terms	The search strategy used to identify discontinuation of antiplatelet therapy in postmarketing surveillance included review of cases identified for the Important Identified Risk Cardiovascular thromboembolic events (see above) to determine if antiplatelet therapy was discontinued after starting parecoxib therapy and prior to AE onset.

Table 45. Important Potential Risk: Administration Other Than IV or IM

Frequency with 95% CI	Not applicable. Per protocol, parecoxib was administered in MAH-sponsored clinical trials only IV or IM.
Seriousness/outcomes	Postmarketing data (cumulative through 31 March 2014): Medically confirmed cases: 34 Serious = 13, Non-serious = 21 Outcome: Recovered = 13, Recovering = 2, Not recovered = 1, Unknown = 16, Fatal = 2 Route of administration: Parenteral = 17, Other = 6, Oral = 3, Subcutaneous = 2, Topical = 2, Epidural = 1, Intracorporeal cavern = 1, Intra-arterial = 1, Intra-articular = 1 Non-medically confirmed cases: 14 Serious = 6, Non-serious = 8 Outcome: Recovered = 3, Recovering = 3, Not Recovered = 3, Unknown = 5 Route of administration: Parenteral = 8, Other = 5, Intracorporeal cavern = 1 It is to be noted that for this analysis, parenteral not otherwise specified has been considered non-IV and non-IM.
Severity and nature of risk	The majority (> 60%) of the adverse events reported due to administration other than IV or IM were non-serious. No noteworthy trends were identified in the types of events reported.
Background incidence/prevalence	Epidemiologic data on intraarticular, intrathecal, intraspinal, paraspinal, intra-synovial or intra-joint injection among orthopaedic patients are not available in the published literature. A thorough search of the literature using the terms below did not yield meaningful results.
Risk groups or risk factors	No specific risk group; risk factor: human error.
Potential mechanisms	Not known. May conceivably vary according to which incorrect route of administration is used.
Preventability	The potential for this risk may be reduced by HCP education.
Impact on individual patient	Modes of administration other than IV or IM have not been studied and should not be used.
Potential public health impact of safety concern	The cases with route of administration other than IV or IM constitutes a small proportion only (48 out of a total of 990, < 5%) and there is no significant adverse outcome associated with the route of administration other than IV or IM. Therefore the risk should have minimal public health impact.
Evidence source	Post-marketing safety database.
MedDRA terms	The search strategy used to identify administration other than IV or IM in postmarketing surveillance included all cases where route of administration was not IV, IM, IV drip, IV bolus, Transplacental, No data, or Unknown, plus cases that reported an AE that encoded to the PT Incorrect route of administration.

2.7.4. Identified and Potential Interactions

2.7.4.1. Overview of Potential for Interactions

Important interactions or potential interactions have been identified between parecoxib and/or its active metabolite valdecoxib and a number of other drugs: warfarin and similar blood-thinning agents, fluconazole (a CYP2C9 inhibitor); ketoconazole (a CYP3A4 inhibitor); methotrexate; lithium; angiotensin-converting enzyme (ACE) inhibitors; diuretics

(including furosemide and thiazides); CYP450 enzyme inducers (eg, rifampicin, phenytoin, carbamazepine, dexamethasone); inhalation anesthetics (eg, isoflurane and nitrous oxide); and immunosuppressants (eg, cyclosporine, tacrolimus). Some of the drugs that interact strongly with parecoxib/valdecoxib also interact with certain nonselective NSAIDs.

The isozymes most heavily involved in parecoxib/valdecoxib metabolism are the highly active subfamilies, CYP3A4 and CYP2C9, increasing the likelihood of interactions with the numerous drugs that inhibit or induce these isozymes. In addition, valdecoxib has strong effects on a number of CYP2D6 substrates (eg, dextramethorphan, flecainide,[58] propafenone,[59] metoprolol) and CYP2C19 substrates (eg, omeprazole, phenytoin, diazepam, imipramine), which in the case of interacting drugs with a narrow therapeutic range (eg, antiepileptics such as phenytoin), may lead to adverse effects.

Parecoxib labelling describes the known and suspected interactions of parecoxib with other medicinal substances and other forms of interaction. These interactions are summarized in the tables below.

2.7.4.2. Important Identified and Potential Interactions

Table 46. Potential Interactions: Warfarin and Similar Blood-Thinning Agents

Effect of interaction	Small increase in the AUC of warfarin, prothrombin time, mean International Normalised Ratio (INR), and day-to-day variability in individual INR values.
Evidence source	Medical literature; PK study (see Discussion below).
Possible mechanisms	Not established, although a metabolism-based interaction is suggested by the fact that parecoxib and one enantionomer of warfarin are both metabolized in part by CYP2C9.* (*S-warfarin is a substrate of CYP2C9 but is marketed as the racemic mixture; the enantiomer R-warfarin is a substrate of CYP1A2.)
Potential health risk	Increased bleeding. This is unlikely in the most common scenario under which parecoxib is administered (ie, peri-operatively): patients taking warfarin as part of their baseline regimen are taken off warfarin peri-operatively.
Discussion	Coadministration of parecoxib with warfarin caused a small increase in the AUC of warfarin, and also in the prothrombin time (measured by INR). While mean INR values were only slightly increased with coadministration of parecoxib, the day-to-day variability in individual INR values was increased.[60]. Review of adverse events in the MAH's safety database revealed 1 case of bleeding (PT Lower gastrointestinal haemorrhage) in which warfarin was co-administered with parecoxib.

AUC = area under the plasma drug concentration vs. time curve; PK = pharmacokinetics; INR = International Normalised Ratio; CSR = clinical study report; MAH = Marketing Authorisation Holder

Table 47. Potential Interactions: CYP2C9 Inhibitors, Including Fluconazole, and CYP34A Inhibitors, Including Ketoconazole

Effect of interaction	Increase in AUC of parecoxib/valdecoxib through a decrease in its metabolism
Evidence source	PK studies by MAH (see Discussion below).
Possible mechanisms	Parecoxib depends on two prominent CYP isozymes for its metabolism, 3A4 and 2C9. Ketoconazole is a strong inhibitor of CYP3A4; it is also a substrate of CYP3A4, thus is competing with parecoxib to be metabolized by CYP3A4. Fluconazole is a moderate inhibitor of CYP3A4 (a drug does not have to be a substrate of an isozyme to inhibit it). Fluconazole is a moderate inhibitor of CYP2C9, while ketoconazole also inhibits CYP2C9; therefore, since parecoxib is metabolized almost entirely by the liver, these CYP450 interactions will interfere with parecoxib's biotransformation and clearance and thus increase its plasma concentration, with potentially toxic effects of varying severity.[61]
Potential health risk	An increased risk of adverse reactions to parecoxib may be expected on general dose-dependent principles of drug action.
Discussion	In humans, parecoxib undergoes extensive hepatic metabolism involving both CYP450 isoenzymes CYP3A4 and CYP2C9, and non-CYP450–dependent pathways (eg, glucuronidation). Concomitant administration of parecoxib with known CYP3A4 and CYP2C9 inhibitors can result in increased AUC of parecoxib.[62] Coadministration of fluconazole and ketoconazole enhanced the AUC of valdecoxib (an active metabolite of parecoxib) by 62% and 38%, respectively.[63] (Report on PK profile of valdecoxib in healthy subjects, No. N91-99-06-055, 1999; p. 55-6). Thus, patients who are concomitantly receiving fluconazole should receive the lowest therapeutic dose of parecoxib, while a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

AUC = area under the plasma drug concentration vs. time curve; PK = pharmacokinetics; MAH = Marketing Authorisation Holder.

Table 48. Potential Interactions: Methotrexate

Effect of interaction	Increased risk of hematologic toxicity from methotrexate. Nonclinical research has suggested that methotrexate may not interact extensively with CYP450 isozymes,[64] and in interaction studies in rheumatoid arthritis patients receiving weekly methotrexate IM, orally administered valdecoxib (40 mg BID) did not have a clinically significant effect on the plasma concentrations of methotrexate.[65]
Evidence source	Medical literature: PK study by MAH (see Effect of Interaction above).
Possible mechanisms	Parecoxib may alter the pharmacokinetic parameters of methotrexate. Methotrexate should not be administered concomitantly with protein-bound drugs, and parecoxib is >98% protein bound. A CYP450-related interaction is not likely as methotrexate is a substrate of CYP2E1, which is not known to affect parecoxib or valdecoxib.
Potential health risk	Potentially serious adverse effects.
Discussion	Methotrexate has exhibited varying levels of interaction with various other NSAIDs or coxibs in general use, not only perioperatively. Adequate monitoring of methotrexate-related toxicity should be considered when coadministering parecoxib and methotrexate.

IM = intramuscular; NSAID = non-steroidal anti-inflammatory drug; BID = twice daily; MAH = Marketing Authorisation Holder

Table 49. Potential Interactions: Lithium

Effect of interaction	Decrease in lithium serum clearance
Evidence source	PK study by MAH (see Discussion below).
Possible mechanisms	Parecoxib inhibition of renal prostaglandin synthesis, which may lead to decreased lithium clearance.
Potential health risk	An increased risk of adverse reactions to lithium may be expected on general dose-dependent principles of drug action.
Discussion	Valdecoxib, produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) resulting in a 34% higher serum AUC compared to lithium alone. Lithium serum concentrations should be monitored closely when initiating or changing parecoxib therapy in patients receiving lithium.[66]

AUC = area under the plasma drug concentration vs. time curve; PK = pharmacokinetics; MAH = Marketing Authorisation Holder

Table 50. Potential Interactions: Angiotensin-Converting Enzyme Inhibitors

Effect of interaction	Diminution of the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors.
Evidence source	Medical literature; MAH data (see Discussion below).
Possible mechanisms	Inhibition of prostaglandin synthesis, with possible concomitant effects on the renin-angiotensin system.
Potential health risk	High blood pressure.
Discussion	Inhibition of prostaglandins may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE inhibitors.[67]

ACE = angiotensin-converting enzyme; MAH = Marketing Authorisation Holder; ISS = Integrated Summary of Safety.

Table 51. Potential Interactions: Diuretics

Effect of interaction	Reduction of the natriuretic effect of furosemide and thiazides. Coadministration of diuretics with COX-2 inhibitors may reduce the antihypertensive effects of diuretics, and possibly owing to impaired prostaglandin synthesis, may lead to salt and water retention. COX-2 inhibitors also have nephrotoxic effects that may be exacerbated by diuretic treatment.
Evidence source	Medical literature.
Possible mechanisms	Inhibition of renal prostaglandin synthesis by parecoxib.
Potential health risk	Fluid retention contributing to edema, possible renal system overload with adverse effects on electrolyte balance, including hyperkalemia.
Discussion	Clinical studies have shown that in some patients NSAIDs can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

COX = cyclooxygenase; NSAID = non-steroidal anti-inflammatory drug.

Table 52. Potential Interactions: CYP3A4 and CYP2C9 Enzyme Inducers (eg, Rifampicin, Phenytoin, Carbamazepine)

Effect of interaction	Potent inducers speed up substrate drug metabolism and decrease drug effect. It should be noted that inducers may take longer than inhibitors for their adverse effects on the body to be detected because the heightened enzymatic activity provoked by the inducer depletes a substrate of the same isozyme. Therefore, the therapeutic effect of parecoxib/valdecoxib, a substrate of CYP29 and CYP3A4, will be markedly reduced by rifampicin, phenytoin, and carbamazepine, all three being potent inducers of both CYP3A4 and CYP2C9.[68]
Evidence source	Medical literature (see Effect of Interaction above).
Possible mechanisms	Mutual interference and competition.
Potential health risk	Decreased drug exposure level of parecoxib
Discussion	Phenytoin, carbamazepine, and rifampicin are potent compounds with narrow therapeutic indexes, and are well known to contribute to drug-drug interactions. This potential interaction should be given consideration in patients receiving parecoxib concomitantly with these drugs.

Table 53. Potential Interactions: CYP2D6 Substrates (eg, Dextromethorphan, Flecainide, Propafenone, Metoprolol)

Effect of interaction	Parecoxib/Valdecoxib is a substrate of CYP3A4 and 2C9, but it was observed that treatment with valdecoxib (40 mg BID) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate),which like parecoxib is also a substrate of 3A4.[69] Parecoxib has been observed to affect drugs that are substrates of CYP2D6. A salient factor in some of these interactions is that the other drug (eg, flecainide) may have a narrow therapeutic margin; in such a situation, relatively minor interactive effects may alter the other drug's plasma concentration, taking it out of its therapeutic range.
Evidence source	PK study by MAH (see Effect of Interaction above); medical literature (see Discussion below).
Possible mechanisms	Flecainide, propafenone, dextromethorphan, and metoprolol are 2D6 substrates.[68] The glucocorticoid dextromethorphan is also a substrate of CYP3A4, as is parecoxib, placing it into competition for the same enzymatic resource as parecoxib.
Potential health risk	Systemic toxicity could result from an increase in plasma concentration (that is above a narrow therapeutic range) of drugs (CYP2D6 substrate) with coadministration with parecoxib.
Discussion	Caution should be observed when administering parecoxib and medications that are predominantly metabolized by CYP2D6 and also have narrow therapeutic margins, such as flecainide, propafenone, and metoprolol.

BID = twice daily; MAH = Marketing Authorisation Holder.

Table 54. Potential Interactions: CYP2C19 (eg, Omeprazole, Phenytoin, Diazepam, Imipramine)

Effect of interaction	Plasma exposure of omeprazole, a CYP2C19 substrate and inhibitor, administered 40 mg QD, was increased by 46% following administration of valdecoxib 40 mg BID for 7 days; the plasma exposure to valdecoxib, in contrast, was unaffected. These results indicated that valdecoxib, though not a substrate of CYP2C19, may inhibit it (a drug need not be a substrate of an isoenzyme to inhibit it; ketoconazole, for example, is also an inhibitor of 2C19).[70]
Evidence source	PK study by MAH (see Effect of Interaction); medical literature (see Possible Mechanisms below).
Possible mechanisms	The possible mechanisms of interaction of drugs such as omeprazole, phenytoin, diazepam, and imipramine, as outlined below, are dynamic and complex. Many factors other than the CYP450 hepatic isozymes are operative in drug-drug interactions.[68] Omeprazole is a moderate CYP2C19 inhibitor; it is also a 2C19 substrate and, like parecoxib, a CYP3A4 substrate, thus a potential competitor for enzyme supply. Phenytoin, a potent antiepileptic with a narrow therapeutic margin, is a CYP2C19 inducer and a CYP2C19 substrate; a CYP2C9 inducer and a CYP2C9 substrate (again, a parecoxib connection); a strong CYP3A4 inducer (another parecoxib connection). Diazepam and imipramine are both substrates of CYP2C19. Diazepam is also a CYP2C9 substrate and a CYP3A4 substrate (connections with parecoxib).
Potential health risk	Unwanted increase in plasma concentration, especially with drugs such as phenytoin and imipramine that are associated with difficult side-effect profiles even within their narrow therapeutic range.
Discussion	Caution should be observed when administering parecoxib with medications known to be substrates of 2C19 (eg, omeprazole, phenytoin, diazepam, imipramine), which in addition may simultaneously or sequentially be engaged with other key isozymes.

QD = once daily; BID = twice daily; MAH = Marketing Authorisation Holder

Table 55. Potential Interactions: Inhalation Anesthetics (eg, Isoflurane, Nitrous Oxide)

Effect of interaction	No formal interaction studies of parecoxib and inhalation anaesthetics have been performed, including with isoflurane and nitrous oxide (which are occasionally used during the same operation). Isoflurane is known to be a CYP2E1 substrate, and CYP2E1 interactions have not been reported for parecoxib/valdecoxib.
Evidence source	No formal interaction studies have been done on the combination of parecoxib and inhalation anaesthetics such as isoflurane or nitrous oxide.[67]
Possible mechanisms	The mechanisms by which nitrous oxide, which can produce hepatotoxicity, is believed to work do not involve the CYP450 enzyme system. Nitrous oxide inhibits methionine synthase and the N-methyl-D-aspartate (NMDA) subtype of the excitatory glutamate receptor; its anaesthetic effects are worked through the latter.[71]
Potential health risk	Since inhalation anesthetics such as isoflurane and nitrous oxide are used in surgery and parecoxib is an analgesic with a peri-operative indication, it is conceivable that at times they may be co-administered. If isoflurane should produce hepatotoxicity in a patient, it is severely damaging the organ on which parecoxib/valdecoxib depends for its biotransformation. Reduced clearance of valdecoxib may be expected to lead to an accumulation in plasma, creating another vector of toxicity.
Discussion	Although the MAH does not know of any interactions between parecoxib and isoflurane or nitrous oxide, careful monitoring of the patient undergoing surgery is always in order.

MAH = Marketing Authorisation Holder.

Table 56. Potential Interactions: Immunosuppressants (eg, Cyclosporine and Tacrolimus)

Effect of interaction	Reduced clearance of parecoxib and a higher AUC, with potentially toxic side effects.
Evidence source	Medical literature (see Possible Mechanisms below).
Possible mechanisms	Parecoxib depends on CYP3A4, along with CYP2C9, for biotransformation. Cyclosporine is a weak 3A4 inhibitor that will interfere with the enzymatic action of CYP3A4 and thus reduce the rate of parecoxib metabolism. Furthermore, both cyclosporine and tacrolimus are CYP3A4 substrates, both metabolized by the same resource, 3A4.[68]
Potential health risk	Increased risk of nephrotoxicity from accumulation of drug in plasma. Potential interference in healing of organ transplant recipients or surgical patients through an increased and prolonged presence of valdecoxib: non-clinical and clinical research has found that under some conditions parecoxib may slow down healing of surgical incisions and wounds or interfere with repair processes after injury to bone.
Discussion	For a patient who is receiving both parecoxib and cyclosporine and/or tacrolimus, cautious dosing and careful monitoring are recommended.

AUC = area under the plasma concentration–time curve.

2.7.5. Pharmacological Class Effects

Parecoxib is a prodrug of valdecoxib, a nonsteroidal anti-inflammatory drug (NSAID). They share the same pharmacology and mechanism of action, which is believed to be due to inhibition of prostaglandin synthesis, primarily through selective inhibition of cyclooxygenase-2 (COX-2). At therapeutic plasma concentrations in humans, valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

2.7.5.1. Pharmacological Class Risks Already Included as Important Identified or Potential Risks

Table 57. Pharmacological Class Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Reported for Medicinal Product in SmPC	Frequency Seen With Other Products in Same Pharmacological Class (Source of Data/Journal Reference)	Comment
Severe cutaneous adverse reactions	Severe cutaneous adverse reactions (SCAR) SMQ Narrow Parecoxib: 0.0% Placebo: 0.0% RR (95% CI): NA	Parecoxib SmPC: **Not known –** Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis	Celecoxib SmPC: **Not known –** Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis	None
CV thrombotic events	Embolic and thrombotic events, arterial SMQ (all indications) Parecoxib: 0.3% Placebo: 0.2% RR (95% CI): 1.438 (0.647–3.198) Embolic and thrombotic events, venous SMQ (all indications) Parecoxib: 0.2% Placebo: 0.1% RR (95% CI): 1.438 (0.492–4.205) Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous SMQ (all indications) Parecoxib: 0.2% Placebo: 0.2% RR (95% CI): 1.438 (0.540–3.829)	Parecoxib SmPC: **Uncommon –** Myocardial infarction	Celecoxib SmPC: **Common –** Myocardial infarction **Uncommon –** Cerebral infarction **Not known –** Pulmonary embolism	None
GI ulceration-related events	Gastrointestinal haemorrhage SMQ Parecoxib: 0.2% Placebo: 0.2% RR = 0.925; 95% CI (0.345–2.481)	Parecoxib SmPC: **Uncommon**: Gastroduodenal ulceration	Celecoxib SmPC: **Rare**: Duodenal, gastric, oesophageal, intestinal, and colonic ulceration; Intestinal perforation **Not Known**:	None

Table 57. Pharmacological Class Risks

Risk	Frequency in Clinical Trials of Medicinal Product	Frequency Reported for Medicinal Product in SmPC	Frequency Seen With Other Products in Same Pharmacological Class (Source of Data/Journal Reference)	Comment
	Gastrointestinal perforation SMQ Parecoxib: 0.0% Placebo: <0.1% RR (95% CI): N/A Gastrointestinal ulceration SMQ Parecoxib: 0.1% Placebo: <0.1% RR = 2.877; 95% CI (0.611 to 13.54)		Gastrointestinal haemorrhage	
Renal failure and impairment	Renal failure and impairment (HLT) Parecoxib: 1.1% Placebo: 1.0% RR = 1.108; 95% CI (0.734-1.672)	Parecoxib SmPC: **Rare**: Renal failure acute **Unknown**: Renal failure	Celecoxib SmPC: **Not known**: Acute renal failure	None

2.7.5.2. Important Pharmacological Class Effects Not Discussed Above

There are no important pharmacological class effects not already considered as risks for parecoxib.

2.8. Part II: Module SVIII—Summary of the Safety Concerns

The safety of parecoxib has been well characterized based on clinical trials and post-marketing surveillance. Specific identified and potential risks have been discussed in the safety specification section of this risk management document. The identified and potential risks and a for consideration in the parecoxib RMP are listed below.

Table 58. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Severe cutaneous adverse reactions Cardiovascular thrombotic events Gastrointestinal ulceration-related events Renal failure and impairment Hypersensitivity reactions Use in patients with congestive heart failure Use in patients with hepatic impairment Severe hypotension Use during pregnancy, lactation, or in women attempting to conceive Masking of signs of inflammation Discontinuation of antiplatelet therapies
Important potential risks	Administration other than IV or IM
Missing information	Use in children and adolescents aged ≤17 years Use in long-term treatment (>7 days) Repeated use in acute exacerbation of chronic conditions Safety profile after dose increase Off-label use

3. PART III: PHARMACOVIGILANCE PLAN

3.1. Safety Concerns and Overview of Planned Pharmacovigilance Actions

Pharmacovigilance activities for important identified risks, important potential risks, and missing information are summarised in Table 59,Table 60, and Table 61, respectively.

Table 59. Important Identified Risks

Identified risk	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Severe cutaneous adverse reactions	None	Routine pharmacovigilance	To further evaluate the risk of severe cutaneous adverse reactions.
Cardiovascular thrombotic events	None	Routine pharmacovigilance	To further evaluate the risk of cardiovascular thrombotic events.
Gastrointestinal ulceration-related events	None	Routine pharmacovigilance	To further evaluate the risk of gastrointestinal ulceration-related events.
Renal failure and impairment	None	Routine pharmacovigilance	To further evaluate the risk of renal failure and impairment.
Hypersensitivity reactions	None	Routine pharmacovigilance	To further evaluate the risk of hypersensitivity reactions.
Use in patients with congestive heart failure	None	Routine pharmacovigilance	To further evaluate the risk of use in patients with congestive heart failure.
Use in patients with hepatic failure	None	Routine pharmacovigilance	To further evaluate the risk of use in hepatic impairment
Severe hypotension	None	Routine pharmacovigilance	To further evaluate the risk of severe hypotension
Use during pregnancy, lactation, or in women attempting to conceive	None	Routine pharmacovigilance	To further evaluate the risk of use during pregnancy (including ectopic pregnancy) or during lactation (especially for the nursing infant). To further evaluate any adverse effects of parecoxib on fertility and conception for the prospective mother and conceptus

Table 59. Important Identified Risks

Identified risk	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Masking of signs of inflammation	None	Routine pharmacovigilance	To further evaluate the risk of masking of signs of inflammation, eg, aggravation of soft tissue infections seen with other NSAIDs in humans and with parecoxib in dogs and rats.
Discontinuation of antiplatelet therapies	None	Routine pharmacovigilance	To further evaluate the risk of discontinuation of antiplatelet therapies.

Table 60. Important Potential Risks

Potential risk	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Administration other than IV or IM	None	Routine pharmacovigilance	To assess the potential risk of administration by any route other than IV or IM.

Table 61. Missing Information

Missing information	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Use in children and adolescents aged ≤17 years	None	Routine pharmacovigilance.	To continue to monitor overall safety of parecoxib in paediatric patients.
Use in long-term treatment (>7 days)	None	Routine pharmacovigilance.	To continue to monitor overall safety of parecoxib in patients who receive long-term treatment with parecoxib (>7 days).
Repeated use in acute exacerbation of chronic conditions	None	Routine pharmacovigilance.	To continue to monitor overall safety of parecoxib following repeated use in acute exacerbation of chronic conditions.

Table 61. Missing Information

Missing information	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional PhV Activities	Objectives
Safety profile after dose increase	None	Routine pharmacovigilance.	To continue to monitor the safety profile of parecoxib after an increase in dose.
Off-label use	None	Routine pharmacovigilance.	To continue to monitor the incidence and risk of using parecoxib for non-approved indications.

3.2. Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

There are no additional pharmacovigilance activities to measure the effectiveness of risk minimization measures.

3.3. Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

There are no studies or other activities completed since the last update of the pharmacovigilance plan.

3.4. Details of Outstanding Additional Pharmacovigilance Activities

3.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit Risk)

There are no imposed mandatory additional pharmacovigilance activities for parecoxib.

3.4.2. Mandatory Additional PhV Activity (Being a Specific Obligation)

There are no mandatory additional pharmacovigilance activities for parecoxib.

3.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

There are no required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures.

3.4.4. Stated Additional Pharmacovigilance Activities

Not applicable.

3.5. Summary of the Pharmacovigilance Plan

There are no ongoing or planned studies.

4. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

4.1. Applicability of Efficacy to all Patients in the Target Population

The efficacy of parecoxib 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 peak effect within 2 hours following administration of single doses of 40 mg IV or IM parecoxib. 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.

The clinical studies were designed to enroll subjects as close as possible to the target population; however, the inclusion and exclusion criteria influence the overall applicability of the data generated in these studies. In the clinical practice setting, there will be subjects who are on concurrent medications or co-morbidities that have not been studied with parecoxib use and that may affect the medical outcome.

4.2. Post-Authorisation Efficacy Studies

There are no post-authorisation efficacy studies planned for parecoxib.

4.3. Summary of Post-Authorisation Efficacy Development Plan

Not applicable.

4.4. Summary of Completed Post-Authorisation Efficacy Studies

Not applicable.

5. PART V: RISK MINIMISATION MEASURES

5.1. Risk Minimisation Measures by Safety Concern

5.1.1. Important Identified Risks

Safety Concern	Severe cutaneous adverse reactions
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of severe cutaneous adverse reactions, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the Summary of Product Characteristics (SmPC). SmPC Section 4.3, Contraindications: History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulphonamides. SmPC Section 4.4, Special warnings and precautions for use: Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib. Additionally, fatal reports of toxic epidermal necrolysis have been reported through postmarketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib. Patients appear to be at highest risk for these reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment. Appropriate measures should be taken by physicians to monitor for any serious skin reactions with therapy, e.g. additional patient consultations. Patients should be advised to immediately report any emergent skin condition to their physician. Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors. Patients with a history of sulphonamide allergy may be at greater risk of skin reactions. Patients without a history of sulphonamide allergy may also be at risk for serious skin reactions. SmPC Section 4.8, Undesirable effects: Stevens-Johnson syndrome, erythema multiforme, and exfoliative dermatitis are listed as adverse reactions. In post-marketing experience, toxic epidermal necrolysis has been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib.
Additional risk minimisation measure	None proposed.

Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of severe cutaneous adverse reactions.
Comment	None

Safety Concern	**Cardiovascular thrombotic events**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of cardiovascular thrombotic events, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.3, Contraindications: Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease. SmPC Section 4.4, Special warnings and precautions for use: COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with parecoxib after careful consideration. 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. Dynastat has not been studied in cardiovascular revascularization procedures other than CABG (coronary artery bypass graft procedures). Studies in types of surgery other than CABG procedures included patients with ASA (American Society of Anaesthesiology) Physical Status Class I-III only. SmPC Section 4.8, Undesirable effects: Myocardial infarction is listed as an adverse reaction.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of cardiovascular thrombotic events.
Comment	None

Safety Concern	**Gastrointestinal ulceration-related events**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of gastrointestinal ulceration-related events, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.3, Contraindications: Active peptic ulceration or (GI) gastrointestinal bleeding. SmPC Section 4.4, Special warnings and precautions for use: Upper gastrointestinal complications (perforations, ulcers or bleedings), 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 further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is taken concomitantly with acetylsalicylic acid (even at low doses). SmPC Section 4.8, Undesirable effects: Gastroduodenal ulceration is listed as an adverse reaction.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of gastrointestinal ulceration-related events.
Comment	None

Safety Concern	**Renal failure and impairment**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of renal failure and impairment, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.2, Posology and method of administration: In patients with severe renal impairment (creatinine clearance <30 ml/min.) or patients who may be predisposed to fluid retention parecoxib should be initiated at the lowest recommended dose (20 mg) and the patient's kidney function should be closely monitored. On the basis of pharmacokinetics, no dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min.) SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors or Angiotensin-II antagonists, may result in further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. SmPC Section 4.8, Undesirable effects: Renal failure acute and renal failure are listed as adverse reactions. SmPC Section 5.2, Pharmacokinetic properties: In patients with varying degrees of renal impairment administered 20 mg IV Dynastat, 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. For patients with dehydration, see SmPC, Section 4.4, Special warnings and precautions for use: As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, preexisting oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken. Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib. Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Dynastat in patients with impaired renal function 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 Dynastat in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Dynastat.

Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of renal failure and impairment.
Comment	None

Safety Concern	**Hypersensitivity reactions**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of hypersensitivity reactions, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.3, Contraindications: Hypersensitivity to the active substance or to any of the excipients. SmPC Section 4.4, Special warnings and precautions for use: Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides. Parecoxib should be discontinued at the first sign of hypersensitivity. SmPC Section 4.8, Undesirable effects: Anaphylactoid reaction and hypersensitivity reactions including anaphylaxis and angioedema are listed as adverse reactions.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of hypersensitivity reactions.
Comment	None

Safety Concern	**Use in patients with congestive heart failure**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the risk of use in patients with congestive heart failure, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.3, Contraindications : Congestive heart failure (NYHA II-IV).
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Decrease use in patient with congestive heart failure.
Comment	None

Safety Concern	**Use in patients with hepatic impairment**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the risk of use in hepatic impairment, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.2, Posology and method of administration: There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore its use is contraindicated in these patients. No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Dynastat should be introduced with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child-Pugh score 7-9) and the maximum daily dose should be reduced to 40 mg. SmPC Section 4.3, Contraindications: Severe hepatic impairment (serum albumin <25 g/l or Child-Pugh score ≥ 10). SmPC Section 4.4, Special warnings and precautions for use: Dynastat should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh score 7-9). SmPC Section 5.2, Pharmacokinetic properties: 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 Dynastat 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 Dynastat in patients with severe hepatic impairment is not recommended.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Decrease use in patient with hepatic impairment.
Comment	None

Safety Concern	**Severe hypotension**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential occurrence of severe hypotension, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.4, Special warnings and precautions for use: Cases of severe hypotension shortly following parecoxib administration have been reported in postmarketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The physician should be prepared to treat severe hypotension. SmPC Section 4.8, Undesirable effects: Hypotension and orthostatic hypotension are listed as adverse reactions.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events suggestive of severe hypotension.
Comment	None

Safety Concern	Use during pregnancy, lactation, or in women attempting to conceive
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk of use in pregnancy, during lactation, or in women attempting to conceive, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.3, Contraindications: The third trimester of pregnancy and breast-feeding. SmPC Section 4.6, Pregnancy and lactation: Pregnancy Parecoxib is suspected to cause serious birth defects when administered during the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin, it may cause premature closure of the ductus arteriosus or uterine inertia Dynastat is contraindicated in the last trimester of pregnancy. There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. During the first and second trimester of pregnancy, Dynastat should not be given unless clearly necessary. Breast-feeding Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Dynastat must not be administered to women who breast-feed. Fertility The use of Dynastat, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive. Based on the mechanism of action, the use of NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including Dynastat should be considered. SmPC Section 5.1, Pharmacodynamic properties: 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). SmPC Section 5.3, Preclinical safety data: 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 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.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Decrease use in pregnant or lactating women or women trying to conceive.
Comment	None

Safety Concern	**Masking of signs of inflammation**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential of masking signs of inflammation, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.4, Special warnings and precautions for use: Dynastat may mask fever and other signs of inflammation. In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Dynastat. Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Dynastat. SmPC Section 5.1, Pharmacodynamic properties: 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. SmPC Section 5.3, Preclinical safety data: Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of events due to the masking of signs of inflammation.
Comment	None

Safety Concern	**Discontinuation of antiplatelet therapies**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk due to discontinuation of antiplatelet therapies, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.4, Special warnings and precautions for use: COX-2 inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued. SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction: Dynastat had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. SmPC Section 5.1, Pharmacodynamic properties: 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. Platelet studies In a series of small, multiple dose studies in healthy young and elderly subjects, Dynastat 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Dynastat 40 mg twice daily had no clinically significant effect on acetylsalicylic acid - mediated inhibition of platelet function.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of discontinuation of antiplatelet therapies.
Comment	None

5.1.2. Important Potential Risks

Safety Concern	**Administration other than IV or IM**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk of administration other than IV or IM, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.2, Posology and method of administration: The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM). After reconstitution with acceptable solvents, Dynastat may **only** be injected IV or IM, or into IV lines. SmPC Section 4.4, Special warning and precautions for use: Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the occurrence of administration other than IV or IM.
Comment	None

5.1.3. Missing Information

Safety Concern	**Use in children and adolescents aged ≤17 years**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk of use in children and adolescents, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.2, Posology and method of administration: The safety and efficacy of parecoxib in children under 18 years old have not been established. No data are available. Therefore, parecoxib is not recommended in these patients.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the use in children and adolescents.
Comment	None

Safety Concern	**Use in long-term treatment (>7 days)**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk of use in long-term treatment (>7 days), guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.4, Special warnings and precautions for use: There is limited clinical experience with Dynastat treatment beyond three days. SmPC Section 5.1, Pharmacodynamic properties: Short-term studies were conducted for up to 7 days of treatment.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of use in long-term treatment (>7 days).
Comment	None

Safety Concern	**Repeated use in acute exacerbation of chronic conditions**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risk in repeated use in acute exacerbation of chronic conditions, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.1, Therapeutic indications: For the short-term treatment of postoperative pain in adults.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the repeated use in acute exacerbation of chronic conditions.
Comment	None

Safety Concern	**Safety profile after dose increase**
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of the potential risks due to failure to monitor and manage AEs or lack of efficacy, especially after increase in dose, guide the prescriber on the basis of risk, and provide information regarding preventability of this event.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.2, Posology and method of administration: As the cardiovascular risk of cyclooxygenase-2 (COX-2) specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. SmPC Section 4.4, Special warnings and precautions for use: Because of the possibility for increased adverse reactions at higher doses of 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.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reduction of the failure to monitor and manage AEs or lack of efficacy, especially after increase in dose.
Comment	None

Safety Concern	Off-label use
Objective(s) of the risk minimisation measures	To inform the prescriber and patient of criteria for correct, within label use.
Routine risk minimisation measures	Routine activity: Risk minimisation actions consist of communication in the SmPC. SmPC Section 4.1, Therapeutic indications: For the short-term treatment of postoperative pain in adults. SmPC Section 4.2, Posology and method of administration: The safety and efficacy of parecoxib in children under 18 years old have not been established. No data are available. Therefore, parecoxib is not recommended in these patients.
Additional risk minimisation measure	None proposed.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Routine pharmacovigilance activities to identify new information that would suggest that the measure(s) implemented did not adequately minimise risk.
Criteria for judging the success of the proposed risk minimisation measures	Risk minimisation measures are judged effective if no negative trend or worsening outcomes are identified.
Planned dates for assessment	Ongoing.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	The expected impact is the reinforcement of use within label.
Comment	None

Product information and labeling are expected to be sufficient for risk minimisation. There are no additional risk minimisation measures planned at this time.

5.2. Risk Minimisation Measure Failure (if applicable)

Not applicable.

5.2.1. Analysis of Risk Minimisation Measure(s) Failure

Not applicable.

5.2.2. Revised Proposal for Risk Minimisation

Not applicable.

5.3. Summary of Risk Minimisation Measures

Table 62. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Important Identified Risk	
Severe cutaneous adverse reactions	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Cardiovascular thrombotic events	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects)..	None proposed
Gastrointestinal ulceration-related events	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Renal failure and impairment	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.5, Interaction with other medicinal products and other forms of interaction; Section 4.8, Undesirable effects; Section 5.2, Pharmacokinetic properties). For patients with dehydration, see SmPC, Section 4.4, Special warnings and precautions for use.	None proposed
Hypersensitivity reactions	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Use in patients with congestive heart failure	Prescribing information (SmPC, Section 4.3, Contraindications).	None proposed
Use in patients with hepatic impairment	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 5.2, Pharmacokinetic properties).	None proposed
Severe hypotension	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Use during pregnancy, lactation, or in women attempting to conceive	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.6, Pregnancy and lactation; Section 5.1, Pharmacodynamic properties, Section 5.3, Preclinical safety data).	None proposed
Masking of signs of inflammation	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 5.1, Pharmacodynamic properties; Section 5.3, Preclinical safety data).	None proposed
Discontinuation of antiplatelet therapies	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 4.5, Interaction with other medicinal products and other forms of interaction; Section 5.1, Pharmacodynamic properties).	None proposed
	Important Potential Risks	
Administration other than IV or IM	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use).	None proposed

Table 62. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Missing Information	
Use in children and adolescents aged ≤17 years	There is no clinical trial experience with parecoxib therapy in paediatric populations; therefore, its use is not recommended in children and adolescents. Prescribing information (SmPC, Section 4.2, Posology and method of administration).	None proposed
Use in long-term treatment (>7 days)	There is limited clinical trial experience with parecoxib treatment beyond 3 days. Clinical studies with parecoxib were conducted for up to 7 days of treatment. Prescribing information (SmPC: Section 4.4, Special warnings and precautions for use; Section 5.1, Pharmacodynamic properties)..	None proposed
Repeated use in acute exacerbation of chronic conditions	Parecoxib is indicated in the EU for the short-term treatment of postoperative pain. Prescribing information (SmPC, Section 4.1, Therapeutic indications).	None proposed
Safety profile after dose increase	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use).	None proposed
Off-label use	Parecoxb is indicated in the EU for the short-term treatment of postoperative pain in adults. Prescribing information (SmPC, Section 4.1, Therapeutic indications; Section 4.2, Posology and method of administration).	None proposed

AE=adverse event, SmPC=Summary of Product Characteristics, EU=European Union, MAH = Marketing Authorisation Holder.

6. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

6.1. Elements for Summary Tables in the EPAR

6.1.1. Summary Table of Safety Concerns

Table 63. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Severe cutaneous adverse reactions Cardiovascular thrombotic events Gastrointestinal ulceration-related events Renal failure and impairment Hypersensitivity reactions Use in patients with congestive heart failure Use in patients with hepatic impairment Severe hypotension Use during pregnancy, lactation, or in women attempting to conceive Masking of signs of inflammation Discontinuation of antiplatelet therapies
Important potential risks	Administration other than IV or IM
Missing information	Use in children and adolescents aged ≤17 years Use in long-term treatment (>7 days) Repeated use in acute exacerbation of chronic conditions Safety profile after dose increase Off-label use

6.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Not applicable, as there are no study protocols in the pharmacovigilance plan.

6.1.3. Summary of Post-Authorisation Efficacy Development Plan

There are no ongoing or planned efficacy studies for parecoxib.

6.1.4. Summary Table of Risk Minimisation Measures

Table 64. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Important Identified Risk	
Severe cutaneous adverse reactions	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Cardiovascular thrombotic events	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Gastrointestinal ulceration-related events	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Renal failure and impairment	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.5, Interaction with other medicinal products and other forms of interaction; Section 4.8, Undesirable effects; Section 5.2, Pharmacokinetic properties). For patients with dehydration, see SmPC, Section 4.4, Special warnings and precautions for use.	None proposed
Hypersensitivity reactions	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Use in patients with congestive heart failure	Prescribing information (SmPC, Section 4.3, Contraindications).	None proposed
Use in patients with hepatic impairment	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.3, Contraindications; Section 4.4, Special warnings and precautions for use; Section 5.2, Pharmacokinetic properties).	None proposed
Severe hypotension	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 4.8, Undesirable effects).	None proposed
Use during pregnancy, lactation, or in women attempting to conceive	Prescribing information (SmPC, Section 4.3, Contraindications; Section 4.6, Pregnancy and lactation; Section 5.1, Pharmacodynamic properties, Section 5.3, Preclinical safety data).	None proposed
Masking of signs of inflammation	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 5.1, Pharmacodynamic properties; Section 5.3, Preclinical safety data)..	None proposed
Discontinuation of antiplatelet therapies	Prescribing information (SmPC, Section 4.4, Special warnings and precautions for use; Section 4.5, Interaction with other medicinal products and other forms of interaction; Section 5.1, Pharmacodynamic properties).	None proposed
	Important Potential Risks	
Administration other than IV or IM	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use).	None proposed

Table 64. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Missing Information	
Use in children and adolescents aged ≤17 years	There is no clinical trial experience with parecoxib therapy in paediatric populations; therefore, its use is not recommended in children and adolescents. Prescribing information (SmPC, Section 4.2, Posology and method of administration).	None proposed
Use in long-term treatment (>7 days)	There is limited clinical trial experience with parecoxib treatment beyond 3 days. Clinical studies with parecoxib were conducted for up to 7 days of treatment. Prescribing information (SmPC: Section 4.4, Special warnings and precautions for use; Section 5.1, Pharmacodynamic properties).	None proposed
Repeated use in acute exacerbation of chronic conditions	Parecoxib is indicated in the EU for the short-term treatment of postoperative pain. Prescribing information (SmPC, Section 4.1, Therapeutic indications).	None proposed
Safety profile after dose increase	Prescribing information (SmPC, Section 4.2, Posology and method of administration; Section 4.4, Special warnings and precautions for use).	None proposed
Off-label use	Parecoxb is indicated in the EU for the short-term treatment of postoperative pain in adults. Prescribing information (SmPC, Setion 4.1, Therapeutic indications; 4.2, Posology and method of administration).	None proposed

AE=adverse event, SmPC=Summary of Product Characteristics, EU=European Union, MAH=Marketing Authorisation Holder.

6.2. Elements for a Public Summary

6.2.1. Overview of Disease Epidemiology

Every year, as many as 5% to 10% of people in the world have some type of surgery. Common types of surgery include operations on the bones and joints, including hip or knee replacements, and operations on the stomach, heart or reproductive organs. Pain control is very important after surgery. There are several different kinds of medicines that can be used to help with pain control. Some are given by mouth, while others need to be given by injection.

6.2.2. Summary of Treatment Benefits

Parecoxib belongs to a group of medicines called "non-steroidal anti-inflammatory drugs" or NSAIDs. In Europe, parecoxib can be used for the short-term treatment of pain after surgery. Unlike many NSAIDs, parecoxib is given by injection, so it can be given to patients who cannot safely or reliably take food and medicine by mouth after surgery. Parecoxib is usually given every 6 to 12 hours. Sometimes other pain medications, such as opioid analgesics,

may be used along with parecoxib. However, this should strictly follow the prescriber's instructions.

Parecoxib's ability to decrease pain was tested in more than 5000 patients who volunteered to take part in clinical trials. All these patients had operations like dental surgery, hip or knee replacements, open-heart surgery, or hysterectomy (removal of the uterus in women). The patients usually began to feel some pain relief approximately 10 to 40 minutes after their parecoxib injection. Parecoxib reached its full effect within 2 hours, and the pain relief lasted from 6 to 12 or more hours.

6.2.3. Unknowns Relating to Treatment Benefits

In the main and supporting studies nearly all patients were adult Caucasians. There is no evidence to suggest that results are dependent on ethnicity or age.

6.2.4. Summary of Safety Concerns

Table 65. Important Identified Risks

Risk	What is Known	Preventability
Severe skin reactions	Severe skin reactions are very infrequent and are usually caused by drugs. There have been reports of severe skin reactions in patients treated with parecoxib. These severe skin reaction may be life-threatening and may require medical attention.	No information is available to prevent severe skin reactions associated with parecoxib. Parecoxib should not be administered to individuals with a known allergy to the active substance or to any of the excipients. The physician should monitor the patient for any skin reactions. Patients should notify their physician immediately if they develop a skin reaction, blistering or peeling of the skin.
Cardiovascular thrombotic (blood clot) events such as heart attack or stroke	Following open heart surgery, patients given parecoxib have a higher risk of having a blood clot, heart attack, or stroke.	Parecoxib should not be used following open heart surgery. Patients with high blood pressure, high cholesterol, diabetes or smokers should only be treated with pareoxib after careful consideration.
Gastrointestinal ulceration-related events	Ulcers in the digestive system may occur, but are uncommon (may affect up to 1 in 100 people).	Parecoxib should be used with caution in elderly patients, in patients taking aspirin or NSAIDs, or in patients with a history of, or active, stomach or intestinal diseases, such as ulceration, or bleeding.

Table 65. Important Identified Risks

Risk	What is Known	Preventability
Kidney failure and impairment	There have been reports of kidney failure in patients receiving parecoxib.	Kidney function should be closely monitored in patients who have advanced kidney disease and are administered parecoxib. Caution should be used when starting parecoxib treatment in patients who are dehydrated.
Allergic reactions	Serious allergic reactions have been reported in patients being treated with parecoxib. Some of these reactions occurred in patients with a history of allergy to sulphonamides (sulpha drugs).	The health care professional should ask patients about any history of allergy, especially to medications including sulpha drugs. If there is any reason to suspect an allergic reaction, the patient should be monitored closely after receiving parecoxib.
Use in patients with congestive heart failure (CHF)	In patients who has CHF, parecoxib might make the CHF worse because parecoxib may cause the body to retain fluid.	Physicians should not use parecoxib in patients who have CHF. If it is used, the physician should monitor the patient's heart condition.
Use in patients with liver damage	Parecoxib is removed from the body by the liver. If a patient has liver damage, the drug might stay in their bodies longer and cause an undesired effect. Because there were no studies done in patients with severe liver damage, it should not be used in these patients as the effects are unknown. In patients with moderate liver damage, the dose should be reduced.	Physicians should not use parecoxib in patients with severe liver damage. The parecoxib dose should be reduced in patients with moderate liver damage. Any patient with signs or symptoms of liver damage should be carefully monitored after receiving parecoxib.
Severe low blood pressure	There have been cases of severe low blood pressure reported in patients receiving parecoxib.	Caution should be used when treating elderly patients or patients with a medical history of low blood pressure, cardiovascular or circulatory problems.
Use during pregnancy, while breast feeding, or in women trying to get pregnant	Parecoxib may cause serious birth defects when given to a pregnant women in her last trimester of pregnancy. Parecoxib should not be administered to women in the third trimester of pregnancy or to breast-feeding women. Parecoxib might also increase the risk of miscarriage in early pregnancy. A small amount of parecoxib has been found in the human milk of lactating women who received a single dose of parecoxib following caesarean section. Parecoxib may interfere with the ability of a woman to get pregnant.	Women who learn they are pregnant should inform their physician if they are receiving parecoxib. A mother who is breast feeding her infant should stop doing so if she receives parecoxib. The use of parecoxib is not recommended in women who are trying to get pregnant.

Table 65. Important Identified Risks

Risk	What is Known	Preventability
Not seeing signs of inflammation	Parecoxib may reduce pain, fever, and swelling making it difficult to recognize the signs of an infection.	The health care professional should monitor the patient closely after surgery.
Discontinuation of antiplatelet therapies (drugs such as aspirin that stop blood cells from sticking together to form a blood clot)	Parecoxib does not have the ability to prevent heart attack or stroke as some other drugs, such as antiplatelet therapy which include aspirin or anti-coagulants, have. Parecoxib has the risk of cardiovascular thrombotic events (heart attack or stroke) instead. Patients who discontinue aspirin before surgery and are treated with heparin or low molecular weight heparin (LMWH) after surgery would not likely develop thrombotic events due to the discontinuation of antiplatelet therapies. There is no data available for the incidence of this risk.	The physician and patient need to be educated about this risk.

Table 66. Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
Receiving parecoxib by any method other than an injection into a vein or muscle	The only methods used in clinical studies to give parecoxib to patients were by an injection into a vein or muscle. The safety of giving parecoxib to a patient by another method is unknown, and therefore should not be done.

Table 67. Missing Information

Risk	What is Known
Use in children and adolescents who are 17 years of age or younger	There is very little information on the use of parecoxib in children and adolescents, therefore it should not be used in children and adolescents.
Receiving parecoxib for more than 7 days	There is very little information on the effects of receiving parecoxib for more than 7 days. The possibility that any undesired actions or effects of parecoxib may occur might increase the longer a patient is taking parecoxib.
Repeated use for the sudden worsening of an ongoing condition	There is limited information on the repeated use of parecoxib for the sudden worsening of an onging condition.
The safety profile after a dose increase	Because it is more likely that an adverse reaction will occur following a larger dose of parecoxib, patients should be watched closely if their parecoxib dose is increased. If the patient doesn't feel less pain after the dose of parecoxib is increased, another treatment should be considered. There is very little clinical experience with parecoxib treatment past 3 days.
Off-label use	Parecoxib should only be used in adults for a short time to treat pain following an operation. Parecoxib should not be used for any other reason.

6.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of

this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for parecoxib (Dynastat) can be found in the Dynastat's (precoxib) European Public Assessment Report (EPAR) page.

This medicine has no additional risk minimisation measures.

6.2.6. Planned Post-Authorisation Development Plan

There are no ongoing or planned studies.

6.2.7. Studies that are a Condition of the Marketing Authorisation

Not applicable.

6.2.8. Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in Table 68.

Table 68. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	29 January 2010	The following safety concerns were included in the first version of the RMP: *Identified Risks:* Sever skin reactions Cardiovascular thrombotic events Gastrointestinal ulceration-related events *Potential Risks:* None *Missing information:* Use in children and adolescents Use in long term treatment (>7 days) Repeated use in acute exacerbation of chronic conditions	Initial RMP Rapporteur and CHMP request

Table 68. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
2.0	25 August 2010	The following identified risks and missing information were added: *Identified Risks:* Renal failure and impairment Hypersensitivity reactions Use in patients with CHF Use in patients with hepatic impairment Use during pregnancy Use during lactation Use in women attempting to conceive Masking of signs of inflammation Discontinuation of antiplatelet therapies *Missing Information:* Failure to monitor and manage AEs or lack of efficacy, especially after dose increase Driving or operating machines while experiencing dizziness, vertigo or somnolence from parecoxib use	The rapporteur requested that the MAH add several NSAID class effects described in the parecoxib SmPC, but not listed in the initial RMP. Nine risks and 2 missing information items that were not new to the SmPC or the body of knowledge with respect to parecoxib, were added to the RMP.
3.0	26 May 2011	The following identified risk and potential risk were added: *Identified Risks:* Severe hypotension *Potential Risk:* Administration other than IV or IM	Rapporteur request. The MAH identified 2 new safety concerns.
4.0	18 June 2014	The following missing information was added: *Missing Information:* Added : Off-label use Revised: *Failure to monitor and manage AEs or lack of efficacy, especially after increase in dose* was rephrased to *safety profile after dose increase* Deleted: Driving or operating machines while experiencing dizziness, vertigo or somnolence from parecoxib use	Submitted with Periodic Safety Update Report (PSUR). The CHMP suggested that "off-label use" be added to the list of safety concerns as "important missing information".

7. REFERENCES

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