Cork University Hospital

Drugs & Therapeutics Committee

Formulary drug monograph

Review of the proposal to introduce Parecoxib to CUH for the treatment of acute pain, esp. ureteric & musculoskeletal trauma

GENERIC NAME: Dynastat® (Pfizer) **PROPRIETARY NAME:** Parecoxib

DRUG CLASS: Selective cyclooxygenase-2 (COX-2) inhibitor

THERAPEUTIC INDICATION(S):

- For the short-term treatment of postoperative pain in adults.[1,2]

POSOLOGY & METHOD OF ADMINISTRATION:

- The recommended dose for the short-term treatment of postoperative pain is 40mg IV/IM, followed by 20mg or 40mg every 6–12 hours as required (Max: 80mg/day). To be used for a maximum of 3 days.[1,2]
- **Elderly:** No dose adjustment is generally necessary in elderly patients (≥65 years). However in elderly patients weighing < 50kg, the recommended dose is 20mg (Max:40mg/day).[1]
- **Renal Impairment:** In patients with severe renal impairment treatment should be initiated at the lowest recommended dose (20mg) and monitor kidney function closely.[1]
- **Hepatic Impairment:**
  - Moderate hepatic impairment (Child-Pugh Class B): treatment should be initiated at the lowest recommended dose.
  - Severe hepatic impairment (Child-Pugh Class C): not recommended

Method of Administration

- IV or IM injection.[1]

CLINICAL EFFICACY:

Parecoxib may be co-administered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when co-administered with Parecoxib.[1]

The formulary application is for non-operative pain which is outside of the licensed indication. However, studies have been conducted to establish its efficacy and safety for its use in indications of an off-label nature. The most relevant studies for the requested indications are available below.

Acute Renal Colic:

Glina et al compared the analgesic efficacy and safety of parecoxib with ketoprofen for the treatment of acute renal colic in a Phase IV, multicenter, randomized, double-blind, double-dummy, non-inferiority and active-controlled study. Patients (aged 18-65 years) with moderate to severe pain (baseline Pain Intensity (PI) on Visual Analogue Scale (VAS) > 50 mm and "moderate to severe" on a PI categorical scale) were randomly allocated to parecoxib 40 mg IV plus placebo (n=174) or ketoprofen 100 mg IV plus placebo (n=164). Participants were evaluated at screening, initiation of study drugs (time 0), and at 15, 30, 45, 60, 90, 120 min after study start. Morphine as Rescue Analgesics (RA) was allowed on demand. The primary efficacy outcome was the mean Pain Intensity Difference 30min (mPID) evaluated by VAS.

- Non-inferiority of parecoxib to ketoprofen was declared if the lower bound of the 95% Confidence Interval (CI) for the difference between the two groups was greater than -10 mm.
- The mean mPID30min (SD) was 33.84 (24.61) mm in the parecoxib group and 35.16 (26.01) mm in the ketoprofen group. The 95% CI of the treatment difference (parecoxib-ketoprofen) was -6.53; 4.30 and the non-inferiority was met.
- Dizziness was the most common adverse event (AE) related to the treatment medications (2.9% for parecoxib and 0.6% for ketoprofen). Worsening of renal colic was experienced in 2.9% of patients in the parecoxib group and 4.3% in the ketoprofen group. No serious AEs related to study drugs and no deaths were reported. AEs were mainly mild or moderate and the incidence of AEs was similar in both groups.
- The authors concluded that for the treatment of acute renal colic, parecoxib was as effective as ketoprofen and showed similar safety profile.[3]

Acute Traumatic Pain:

Baharuddin et al conducted a randomized, double-blinded study to compare the analgesic efficacy of parecoxib versus morphine in adult patients with significant acute traumatic pain (defined as pain score based on Numeric Rating Scale (NRS) of 6 or more) within 6 hours of injury. A total of 32 patients (age range 19-65 years; 26 males and 6 females) were randomized to receive either parecoxib 40 mg IV (n=18) or morphine 0.1 mg/kg IV (n=14). Blood pressure, pulse rate, oxygen saturation, and NRS were measured at 0, 5, 15, and 30-minute intervals following the administration of study medications. Morphine 0.1mg/kg IV was administered as RA if the NRS was 6 or more after 30 minutes of observation. The primary endpoint was the reduction of pain score based on NRS.

- Results showed no statistically significant difference in the reduction of mean NRS between patients receiving either parecoxib or morphine (p=0.095); the mean NRS for patients in the parecoxib group were 7.8 at 0 minutes, 5.7 at 5 minutes, 4.7 at 15 minutes, and 3.9 at 30 minutes, compared to 7.1, 4.5, 3.1, and 2.0 respectively for patients in the morphine group.
- Significant mean reductions of NRS within a group between 0-5 minutes, 0-15 minutes, 0-30 minutes, 5-15 minutes, 5-30 minutes and 15-30 minutes were observed in both groups (all p concluded that a non-significant trend towards superiority of morphine IV over parecoxib IV was observed, however parecoxib was effective and displayed no opioid-related side-effects.[4]

ADVERSE EFFECTS:

The most common adverse effect is nausea. The most serious adverse effects occur uncommonly to rarely, and include events such as myocardial infarction, severe hypotension and hypersensitivity events.[1] Refer to SPC for a complete list of adverse effects.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance/excipients listed in the SPC.
- Active peptic ulceration or gastrointestinal bleeding.
- History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome (DRESS), toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulfonamides.
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, bronchial asthma, angioneurotic edema, urticaria or other allergic-type reactions after taking acetylsalicylic acid (aspirin) or NSAIDs, including other COX-2 specific inhibitors.
- Third trimester of pregnancy and breast-feeding.
- Severe hepatic impairment (serum albumin <25 g/l or Child Pugh score ≥10).
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II – IV).
- Treatment of postoperative pain following coronary artery bypass graft (CABG) surgery.
- Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

DRUG INTERACTIONS:

- Warfarin and other anticoagulants
- ACE inhibitors, Angiotensin-II antagonists, beta-blockers and diuretics
- Ciclosporin and tacrolimus
- Fluconazole and ketoconazole
- CYP2D6 substrates (e.g. Dextromethorphan, flecainide, propafenone, metoprolol)
- CYP2C19 substrates (e.g. Omeprazole, phenytoin, diazepam, imipramine)
- Methotrexate
- Lithium

Refer to SPC for a complete list of drug interactions.

COST & COMPARISONS:

Projected number of patients to be treated per annum and dosage regimen as per formulary application from the Emergency Department (ED) Consultant: 300-400 vials, 40mg IV stat daily.

Please note 120 vials of *Diclac® 25mg/ml* dispensed to ED as stock from 01/01/2023 – 31/12/2023. Calculations exclude VAT.

Drug	Cost per vial	Cost per Annum	Cost of 120 vials
Parecoxib (*Dynastat® 40 mg powder for solution for injection*)	€7.78	€2,839.70	€933.60
Diclofenac (*Diclac® 25mg/ml Solution for Injection 3ml Ampoule* (Stock in ED)	€0.88	€321.20	€105.60

PRACTICAL CONSIDERATIONS:

- Diclofenac IV infusion solution must be buffered with 0.5ml of 8.4% sodium bicarbonate prior to the addition of the diclofenac ampoule.[5] Difficulty in buffering IV doses of Diclac® amongst nursing staff when IV NSAID required in ED.
- Parecoxib recently approved as part of CUH Chest wall injury and rib fracture analgesia pathway.
- CUH monograph for Parecoxib to be prepared as a support for health care professionals.
- If required, consider charting in the stat section of the kardex to ensure parecoxib is reviewed regularly and not used beyond 3 days, as the cardiovascular risk of COX-2 specific inhibitors may increase with dose and duration of exposure. There is limited clinical experience with treatment beyond 3 days.[1]
- The decision to prescribe a COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.[1] After initiation of therapy, dosage should be adjusted based on patient response.

CONCLUSION/COMMENTS:

- Parecoxib is only licensed in the short-term treatment of postoperative pain in adults, however limited studies have been conducted to establish its use in non-operative acute pain.
- In clinical trials, the daily requirement for PRN opioids was significantly reduced when co-administered with parecoxib.
- Parecoxib has not been reviewed by The National Centre for Pharmacoeconomics (NCPE) or had National Institute of Health and Care Excellence (NICE) appraisal. This is possibly due to the date of authorization, 2002. It was however reviewed by the Scottish Medicines Consortium (SMC) in 2003 and was not recommended as there is no evidence that the parenteral COX-2 selective NSAID is associated with a reduction in clinically significant post-operative haemorrhagic or gastro-intestinal complications compared with the non-selective NSAIDs. Parecoxib is substantially more expensive than non-selective NSAIDs.[6]
- Parecoxib is mainly used in Theatre, ICU, Day Surgery and Surgical Stepdown wards in other hospitals. Prescription is restricted to the Acute Pain Team/On-call anesthetists in TUH.

RECOMMENDATION:

Parecoxib is recommended as an option in the treatment of acute pain by members of the Emergency Department team when an IV parenteral NSAID is required. Therapy to be reviewed on a daily basis for a maximum of 3 days. Annual usage to be reviewed by Pharmacy Department.

PREPARED BY:

Emma Durand, March 2024

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5. Health Products Regulatory Authority (HPRA), (Date of first authorization 08/1992). (Date of revision of text: 12/2022). *Diclac 25mg/ml Solution for Injection 3ml Ampoule: SPC*. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0711-009-010_07122022145820.pdf
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OUTCOME:

Meeting date: 15/03/2024

Approved ❑

Approved with restrictions ❑ *Specify restrictions:*

Rejected ❑ *Specify reasons:*