**Dycox 40mg Powder for Solution for Injection**

## 1. NAME OF THE MEDICINAL PRODUCT

Dycox 40mg Powder for Solution for Injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 42.36mg of Parecoxib Sodium equivalent to 40mg Parecoxib. After reconstitution, the final concentration of Parecoxib is 20 mg/mL. Each 2 ml of reconstituted powder contains 40 mg of Parecoxib.

Excipient with known effect
This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

When reconstituted in sodium chloride 9 mg/mL (0.9%) solution, Dycox contains approximately 0.44 mmol of sodium per vial.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection.

White or almost white cake or powder.

The reconstituted solution should be clear and colourless.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Management of post-operative pain in the immediate post-operative setting only with the exception of patients undergoing coronary artery bypass grafting (CABG) procedures and in those patients with elevated cardiovascular risk, such as those with congestive heart failure (NYHA II-IV), established ischaemic heart disease and/or cerebrovascular disease.

### 4.2 Posology and method of administration

“There is limited clinical experience with parecoxib treatment beyond three days.”

Parecoxib may be administered as single or multiple IV. or IM. doses on a regular or as needed schedule. After initiation of therapy, dosage should be adjusted based on patient response. Clinical studies with parecoxib were conducted using up to 7 days of treatment. Parecoxib is only indicated for patients with a need for parenteral therapy and for whom a similar benefit could not be obtained from alternative oral therapy. It is recommended that patients be transitioned to alternative oral therapy as soon as clinically indicated.

As the cardiovascular (CV) 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. However, the relevance of these findings for the short-

term use of parecoxib in the post-operative setting has not been evaluated.

- **Management of Acute Pain**: The recommended single or initial dose for treatment of acute pain is 40 mg, administered either IV or IM., followed by 20 mg or 40 mg every 6 to 12 hours, as required, up to a maximum daily dosage of 80 mg. The IV bolus injection may be given directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle.

- **Concomitant Use with Opioid Analgesics**: Opioid analgesics can be used concurrently with parecoxib, dosing as described above. In clinical trials, the daily requirement for opioids was significantly reduced (20%-40%) when co-administered with parecoxib. An optimal effect is achieved when parecoxib is given prior to opioid administration. In all clinical assessments, parecoxib was administered at a fixed time interval whereas the opioids were administered on as needed basis (PRN).

*Elderly:* No dosage adjustment is generally necessary. However, for elderly patients weighing less than 50 kg, it is advisable to reduce the initial dose of parecoxib by 50%. The maximum daily dose should be reduced to 40 mg in elderly patients weighing less than 50 kg.

*Hepatic Impairment:* No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Treatment with parecoxib should be initiated at the lowest recommended dose in patients with moderate hepatic impairment (Child-Pugh Class B).

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of parecoxib in these patients is not recommended.

*Renal Impairment:* In patients with severe renal impairment (creatinine clearance <30 mL/minute), 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.

*Co-administration with Fluconazole:* When parecoxib is co-administered with fluconazole, the lowest recommended dose of parecoxib should be used.

*Pediatric Patients:* Safety and efficacy have not been established in children under 18 years of age.

**4.3 Contraindications**

Parecoxib is contraindicated in:

- Patients with known hypersensitivity to parecoxib or to any other ingredient of the product.
- Patients who have demonstrated allergic-type reactions to sulfonamides.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (aspirin) or non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- Severe hepatic impairment (serum albumin <25 g/L or Child-Pugh score ≥10).
- The third trimester of pregnancy and breast-feeding.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Inflammatory bowel disease.

- Congestive heart failure (NYHA II-IV).
- Treatment of post-operative pain following coronary artery bypass graft (CABG) surgery.
- Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

**4.4 Special warnings and precautions for use**

**Administration Other than IV or IM**

Modes of administration other than IV or IM have not been studied and should not be used.

*Cardiovascular Effects*
COX-2 inhibitors, of which parecoxib is one, have been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long-term. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known cardiovascular disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. 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.

Two separate studies in coronary artery bypass graft (CABG) surgery showed that patients receiving parecoxib for a minimum of 3 days followed by oral valdecoxib (the active metabolite of parecoxib) for 7 to 14 days, had increased incidence of cardiovascular/thromboembolic events (e.g., myocardial infarction and cerebrovascular accident) compared to those receiving placebo. Parecoxib is therefore, contraindicated for the treatment of post-operative pain immediately following CABG surgery.

*Gastrointestinal (GI) Effects*
Upper gastrointestinal (GI) perforations, ulcers, or bleeds have occurred in patients treated with parecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, or patients with a history of, or active, GI disease, such as ulceration, bleeding, or inflammatory conditions; or patients using concomitant aspirin. The NSAIDs class is also associated with increased GI complications when co-administered with corticosteroids, selective serotonin reuptake inhibitors, other antiplatelet drugs, or other NSAIDs or patients ingesting alcohol, however, there are currently no specific parecoxib clinical data.

*Skin Effects*
Valdecoxib, the active moiety of parecoxib, contains a sulfonamide moiety and patients with a known history of a sulfonamide allergy may be at a greater risk of skin reactions. Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Serious skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported through post-marketing surveillance in patients receiving parecoxib. In addition to erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis has been reported through post-marketing surveillance in patients receiving valdecoxib. Fatalities due to Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with valdecoxib and the potential cannot be ruled out for parecoxib. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome) may occur with parecoxib exposure based on other serious skin reactions reported with celecoxib and

valdecoxib exposure. Patients appear to be at highest risk for these events early in the course of therapy, with the onset of the event occurring in the majority of cases within the first two weeks of treatment. Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity. Serious skin reactions have been reported with other COX-2 inhibitors during post-marketing experience. The reported rate of these events appears to be greater for valdecoxib as compared to other COX-2 agents.

*Anaphylactoid Reactions*
Hypersensitivity reactions (anaphylactic reactions and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib. These reactions have occurred in patients with and without a history of allergic-type reactions to sulfonamides.

*Severe Hypotension*
Cases of severe hypotension shortly following parecoxib administration have been reported in post-marketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The practitioner should be prepared to treat severe hypotension.

*Use with Oral Anticoagulants*
The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban).

Co-administration 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 with co-administration of parecoxib, 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, since these patients may be at increased risk of bleeding complications.

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

*Fluid Retention and Edema*
As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

*Renal Effects*
Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib. Renal function should be closely monitored in patients with advanced renal disease who are administered parecoxib.

Caution should be used when initiating treatment in patients with dehydration. It is advisable

to rehydrate patients first and then start therapy with parecoxib.

*Hepatic Effects*
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of parecoxib in patients with severe hepatic impairment is not recommended. Parecoxib should be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class B), and initiated at the lowest recommended dose.

A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with parecoxib.

*General*
By reducing inflammation, parecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections. The concomitant use of parecoxib with other non-specific NSAIDs should be avoided.

**Risk of GI Ulceration, Bleeding and Perforation with NSAID**
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

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

**General**
The drug interaction studies were performed with either parecoxib or the active moiety (valdecoxib).

In humans, parecoxib undergoes extensive hepatic metabolism involving P450 isoenzymes 3A4 and 2C9, and non-P450 dependent pathways (i.e., glucuronidation). Concomitant administration of parecoxib with known CYP 3A4 and 2C9 inhibitors can result in increased AUC of parecoxib.

**Drug-specific**
*Interaction of parecoxib with warfarin or similar agents:* See Special Warnings and Precautions for Use.

*Fluconazole and ketoconazole:* Co-administration of fluconazole, a CYP2C9 inhibitor, and ketoconazole, a CYP3A4 inhibitor, enhanced the AUC of valdecoxib by 62% and 38%, respectively. When parecoxib is co-administered with fluconazole, the lowest recommended dose of parecoxib should be used. No dosage adjustment is necessary when parecoxib is co-administered with ketoconazole.

*Anti-hypertensives including ACE-inhibitors, angiotensin II antagonists, beta blockers and diuretics:* Inhibition of prostaglandins may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers and diuretics. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers and diuretics.

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 and/or angiotensin II antagonists, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

*Diuretics:* Studies have shown that NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

*Cyclosporine:* Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporine.

*Methotrexate:* A pharmacokinetic interaction study was conducted using valdecoxib and methotrexate and no clinically important interactions were seen. However, caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate.

*Lithium:* 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.

*Other:* Interaction studies were conducted between parecoxib and I.V. or oral midazolam, heparin, propofol, fentanyl, and alfentanil. Interaction studies were also conducted between valdecoxib and glibenclamide (glyburide), oral contraceptives (ethinyl estradiol/norethindrone), phenytoin, omeprazole and diazepam. No clinically important interactions were seen in these studies.

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.

No formal interaction studies were performed with parecoxib and inhalation anesthetic agents, such as nitrous oxide and isoflurane; however, no evidence of a drug interaction was observed in clinical studies.

Parecoxib does not interfere with the anti-platelet effect of low-dose aspirin. Because of its lack of platelet effects, parecoxib is not a replacement for aspirin in the prophylactic treatment of cardiovascular disease.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Parecoxib sodium 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.

NSAID use during the second or third trimester of pregnancy may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.

Parecoxib is contraindicated in the third trimester of pregnancy.

There are no adequate data from the use of parecoxib sodium 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, Parecoxib should not be given unless clearly necessary.

*Lactation*
Administration of a single dose of parecoxib to lactating women resulted in the transfer of a relatively small amount of parecoxib and its active metabolite into breast milk, and this resulted in a low relative dose for the infant (less than 1% of the weight-adjusted maternal dose). Because of the potential for adverse reactions in nursing infants from parecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

*Fertility*
The use of parecoxib, 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 Parecoxib should be considered.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

*Summary of the safety profile*
The most common adverse reaction for Parecoxib is nausea. The most serious reactions occur

uncommonly to rarely, and include cardiovascular events such as myocardial infarction and severe hypotension, as well as hypersensitivity events such as anaphylaxis, angioedema and severe skin reactions. Following coronary artery bypass graft surgery, patients administered Parecoxib have a higher risk of adverse reactions such as: cardiovascular/thromboembolic events (including myocardial infarction, stroke/TIA, pulmonary embolus, and deep vein thrombosis), deep surgical infections, and sternal wound healing complications.

*Tabulated list of adverse reactions*
The following adverse reactions were reported. Reports from post-marketing experience have been listed as "frequency not known" because the respective frequencies cannot be estimated from the available data. Within each frequency grouping, adverse reactions are listed using MedDRA terminology and presented in order of decreasing seriousness.

| **Adverse Drug Reaction Frequency** | | | | |
|---|---|---|---|---|
| *Very Common* | *Common* | *Uncommon* | *Rare* | *Not known* |
| *Infections and infestations* | | | | |
| | Pharyngitis, alveolar osteitis (dry socket) | Abnormal sternal serous wound Pdrainage, wound infection | | |
| *Blood and lymphatic system disorders* | | | | |
| | Anaemia postoperative | Thrombocytopenia | | |
| *Immune system disorders* | | | | |
| | | | Anaphylactoid reaction | |
| *Metabolism and nutrition disorders* | | | | |
| | Hypokalaemia | Hyperglycaemia, anorexia | | |
| *Psychiatric disorders* | | | | |
| | Agitation, insomnia | | | |
| *Nervous system disorders* | | | | |
| | Hypoaesthesia, dizziness | Cerebrovascular disorder | | |
| *Ear and labyrinth disorders* | | | | |
| | | Ear pain | | |
| *Cardiac disorders* | | | | |
| | | Myocardial infarction, bradycardia | | Circulatory collapse, congestive heart failure, tachycardia |
| *Vascular disorders* | | | | |
| | Hypertension, | Hypertension | | |

| **Adverse Drug Reaction Frequency** | | | | |
|---|---|---|---|---|
| *Very Common* | *Common* | *Uncommon* | *Rare* | *Not known* |
| | hypotension | (aggravated), orthostatic hypotension | | |
| *Respiratory, thoracic and mediastinal disorders* | | | | |
| | Respiratory insufficiency | Pulmonary embolism | | Dyspnoea |
| *Gastrointestinal disorders* | | | | |
| Nausea | Abdominal pain, vomiting, constipation, dyspepsia, flatulence | Gastroduodenal ulceration, gastrooesophageal reflux disease, dry mouth, gastrointestinal sounds abnormal | Pancreatitis, oesophagitis, oedema mouth (perioral swelling) | |
| *Skin and subcutaneous tissue disorders* | | | | |
| | Pruritus, hyperhidrosis | Ecchymosis, rash, urticaria | | Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis |
| *Musculoskeletal and connective tissue disorders* | | | | |
| | Back pain | Arthralgia | | |
| *Renal and urinary disorders* | | | | |
| | Oliguria | | Renal failure acute | Renal failure |
| *General disorders and administration site conditions* | | | | |
| | Oedema peripheral | Asthenia, injection site pain, injection site reaction | | Hypersensitivity reactions including anaphylaxis and angioedema |
| *Investigations* | | | | |
| | Blood creatinine increased | Blood CPK increased, blood LDH increased, SGOT increased, SGPT increased, BUN increased. | | |
| *Injury, poisoning and procedural complications* | | | | |
| | | Post procedural complication (skin) | | |

Following coronary artery bypass graft surgery, patients administered parecoxib have a higher risk of adverse events, such as cardiovascular thromboembolic events (e.g., myocardial infarction and cerebrovascular accident), deep surgical infections or sternal

wound healing complications.

**Post-marketing Surveillance**
In post-marketing experience, the following rare, serious adverse events have been reported in association with the use of parecoxib: circulatory collapse, erythema multiforme, Stevens-Johnson syndrome, renal failure, and hypersensitivity reactions including anaphylaxis and angioedema.
In post-marketing experience, in addition to the severe cutaneous adverse reaction erythema multiforme and Stevens-Johnson's syndrome, toxic epidermal necrolysis has been reported in association with the use of valdecoxib and cannot be ruled out for parecoxib.

### 4.9 Overdose

Reporting of overdose with parecoxib has been associated with adverse reactions which have also been described with recommended doses of parecoxib.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
Parecoxib is a prodrug of valdecoxib. Valdecoxib is an NSAID that exhibits anti-inflammatory, analgesic and antipyretic properties in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of COX-2. At therapeutic plasma concentrations in humans valdecoxib does not inhibit cyclooxygenase-1 (COX-1).

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

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

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

*Distribution*
The volume of distribution of valdecoxib after its IV administration is approximately 55 litres. Plasma protein binding is approximately 98% over the concentration range achieved with the highest recommended dose, 80 mg/day. Valdecoxib, but not parecoxib, is extensively partitioned into erythrocytes.

*Metabolism*
Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) of the sulphonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10% of the concentration of valdecoxib; because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib sodium.

*Elimination*
Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib recovered in the urine. No unchanged parecoxib is detected in urine and only trace amounts in the faeces. About 70% of the dose is excreted in the urine as inactive metabolites. Plasma clearance ($C_{Lp}$) for valdecoxib is about 6 L/hr. After IV or IM dosing of parecoxib sodium, the elimination half-life ($t_{½}$) of valdecoxib is about 8 hours.

*Elderly*
Parecoxib has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. In healthy elderly subjects, the apparent oral clearance of valdecoxib was reduced, resulting in an approximately 40% higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted for body weight, steady-state plasma exposure of valdecoxib was 16% higher in elderly females compared to elderly males.

*Renal impairment*
In patients with varying degrees of renal impairment administered 20 mg IV parecoxib, 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.

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

## PHARMACOLOGICAL PROPERTIES

### 6.1 List of excipients

Disodium phosphate, Anhydrous, Concentrated Phosphoric Acid, Sodium Hydroxide, Water for injection, Nitrogen

### 6.2 Incompatibilities

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

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

Use of water for injection is **not** recommended, as the resulting solution is not isotonic.

Dycox should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after Dycox injection with a solution of known compatibility (see section 6.6).

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

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

### 6.3 Shelf life

Please refer to the expiry date on the product labels.

Storage conditions of the reconstituted medicinal product: From a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and the conditions prior to use are the responsibility of the user.

### 6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze reconstituted solutions.
This medicinal product has to be stored below 30°C prior to reconstitution.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

5ml Type I clear glass vial, with a coated butyl rubber stopper, sealed with a blue flip-off cap on the aluminum overseal.

Available in packs of 10 vials per carton.

## 6.6 Special precautions for disposal and other handling

Dycox must be reconstituted before use. Dycox is preservative free. Aseptic technique is required for its preparation.

**Reconstitution solvents**
Acceptable solvents for reconstitution of Dycox are:

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion
- glucose 50 mg/ml (5%) solution for infusion

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

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

Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, the liquid should be a clear solution. Dycox should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy or if particulate matter is observed. The reconstituted product is isotonic.

**IV line solution compatibility**

After reconstitution with acceptable diluents, Dycox may **only** be injected IV or IM, or into IV lines delivering:
- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- Ringer-Lactate solution for injection.

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MANUFACTURER

**Manufactured by:**
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Package insert is drafted in Times New Roman with font size of 12, subject to change based on any other legible font and font size.