

# AUSTRALIAN PRODUCT INFORMATION

## TERRY WHITE CHEMISTS MELOXICAM (MELOXICAM) CAPSULES

### 1 NAME OF THE MEDICINE

Meloxicam

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains either 7.5 mg or 15 mg meloxicam as the active ingredient.

#### Excipients with known effect

Lactose monohydrate, gelatin.

For the full list of excipients see section **6.1 List of Excipients**.

### 3 PHARMACEUTICAL FORM

#### 7.5 mg capsules

Light green/light green, size '2' hard gelatin capsules filled with light yellow coloured granules.

#### 15 mg capsules

Light green/light yellow, size '2' hard gelatin capsules filled with light yellow coloured granules.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Meloxicam is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

Terry White Chemists Meloxicam capsules are intended for oral administration.

##### Dosage

Meloxicam should be used at the lowest dose and for the shortest duration consistent with effective treatment.

The maximum recommended daily dose of meloxicam is 15 mg. A dose of 15 mg/day should not be exceeded. As a dose for children has not been established, use should be restricted to adults (see section **4.4 Special warnings and precautions for use - Paediatric use**).

In patients with increased risks of adverse reactions e.g. a history of gastrointestinal disease or risk factors for cardiovascular disease, treatment should be started at 7.5 mg/day and increased to 15 mg/day only if clinically justified.

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

##### Dialysis

The dose of meloxicam in patients with end-stage renal failure on haemodialysis should not exceed 7.5 mg/day (see sections **5 Pharmacological properties – Renal Impairment** and **5.2 Pharmacokinetics – Haemodialysis**).

##### Renal impairment

No dose reduction is required in patients with mild or moderate renal impairment (*i.e.* in patients with a creatinine clearance of greater than 25 mL/min) nor in patients with mild to moderate

hepatic impairment. In non-dialysed patients with severe renal impairment meloxicam is contraindicated (see section **4.3 Contraindications**).

### **Osteoarthritis**

The recommended dose of meloxicam is 7.5 mg once daily, to be swallowed with fluid, in conjunction with food. Depending on the adequacy of response, the severity of the arthritic condition and the patient's concomitant diseases, the dose may be increased to 15 mg/day. Patients should generally be maintained on the lowest dose consistent with achieving a satisfactory therapeutic response.

### **Rheumatoid Arthritis**

The recommended dose of meloxicam is 15 mg once daily, to be swallowed with fluid, in conjunction with food. Depending on the adequacy of response and the severity of the condition, the dose may be reduced to 7.5 mg/day. Patients should generally be maintained on the lowest dose consistent with achieving a satisfactory therapeutic response.

## **4.3 CONTRAINDICATIONS**

- Peri-operative treatment of pain in patients undergoing coronary artery bypass graft surgery (CABG)
- Known hypersensitivity to meloxicam or any excipients in this medicine. There is a potential for cross sensitivity to aspirin and other NSAIDs.
- Signs/symptoms of asthma, nasal polyps, angioedema or urticaria, following the administration of aspirin or other NSAIDs.
- Active gastrointestinal ulceration/ perforation.
- Active inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- Severe hepatic impairment.
- Non-dialysed severe renal insufficiency.
- Severe uncontrolled heart failure.
- Children and adolescents under 18 years of age.
- Breastfeeding.
- Concomitant administration of drugs known to inhibit CYP 2C9 (e.g. sulfaphenazole, sulfinpyrazone, sulfamethoxazole and fluconazole).
- The use of meloxicam is contraindicated in patients with rare hereditary galactose intolerance, due to the lactose content in this medicine.

As with all NSAIDs, meloxicam is contraindicated in patients with recent cerebrovascular bleeding or established systemic bleeding disorders.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Gastrointestinal Effects

As with other NSAIDs gastrointestinal (GI) bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The consequences of such events are generally more serious in the elderly. Minor upper GI problems, such as dyspepsia, are common and may occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months and in about 2–4% of patients treated for one year. These trends continue, increasing the likelihood of developing a serious adverse GI event at some time during the course of therapy. However, even short term therapy is not without risk.

Studies have shown that patients with a prior history of ulcer disease and/or GI bleeding and who use NSAIDs have a greater than 10-fold higher risk of developing a gastrointestinal bleed than patients with neither of these factors.

Caution is advised in patients most at risk of developing a GI complication with NSAIDs: the elderly, patients using any other NSAID or aspirin concomitantly or patients with a prior history of or recent GI disease such as ulceration and gastrointestinal bleeding.

NSAIDs should be prescribed with caution in patients with a prior history of or recent ulcer disease or GI bleeding.

For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

In clinical trials, meloxicam has been shown to cause fewer GI adverse events (including dyspepsia, abdominal pain, nausea, vomiting etc.) than other NSAIDs with which it has been compared (see Table 1).

**Table 1: Incidence of GI adverse events (%) after 4 weeks, 12 weeks and 6 months**

4-Week Treatment			12-Week Treatment				6-Month Treatment			
MELISSA/SELECT			Placebo-controlled Trial				Active-controlled Trials			
melox. 7.5 mg	diclo SR 100 mg	pirox. 20 mg	melox. 7.5 mg	melox. 15 mg	placebo	Diclo BID	melox. 7.5 mg	melox. 15 mg	diclo 100 mg	pirox. 20 mg
n=8,955	n=4,688	n=4,336	n=154	n=156	n=157	n=153	n=169	n=306	n=167	n=149
12%	19%	15%	20%	17%	17%	28%	27%	24%	28%	30%

KEY: melox. = meloxicam; pirox. = piroxicam; diclo = diclofenac; SR = slow release; BID = twice daily

Caution should be exercised when treating patients with a history of upper gastrointestinal disease and in patients receiving treatment with anticoagulants. Patients with GI symptoms should be monitored. Meloxicam therapy should cease if peptic ulceration or GI ulceration or bleeding occurs.

Co-administration of meloxicam with drugs known to inhibit CYP 3A4 should be undertaken with caution. A combination of meloxicam and substances known to inhibit both CYP 3A4 and CYP 2C9 should be avoided because of the increased risk of toxicity.

## **Cardiovascular Effects**

Long term therapy with some COX-2 selective NSAIDs of the coxib class has been shown to increase the risk of serious cardiovascular thrombotic events including myocardial infarction and stroke. Meloxicam is a COX-2 selective NSAID. Meloxicam has not been demonstrated to increase the risk of cardiovascular adverse events compared to non-selective NSAIDs in clinical trials. However, long-term placebo-controlled data to adequately assess any cardiovascular risk are not available for meloxicam.

All NSAIDs, both COX-2 selective and non-selective, may cause an increased risk of serious cardiovascular thrombotic events. This may increase with dose and duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking meloxicam especially in those with cardiovascular risk factors the lowest effective dose.

Physicians and patients should remain alert for such cardiovascular events even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

## **Skin Reactions**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk of 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. Meloxicam should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

## **Renal Effects**

NSAIDs inhibit the synthesis of renal prostaglandins, which play a supportive role in the maintenance of renal perfusion. In patients whose renal blood flow and blood volume are decreased, administration of an NSAID may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of non-steroidal anti-inflammatory therapy.

Patients at greatest risk of such a reaction are elderly individuals, dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those receiving concomitant treatment with a diuretic, ACE inhibitor or angiotensin II receptor antagonist or those having undergone major surgical procedures which led to hypovolaemia. In such patients, the renal function, including volume of diuresis should be carefully monitored at the beginning of therapy.

In rare cases, NSAIDs may cause interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

## **Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics**

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

### **Use in renal impairment**

The dose of meloxicam in patients with end-stage renal failure on haemodialysis should not exceed 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (*i.e.* in patients with a creatinine clearance of greater than 25 mL/min).

The extent to which metabolites of meloxicam may accumulate in patients with renal failure has not been studied. As some metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

### **Hepatic Effects**

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including meloxicam. These laboratory values may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. Patients with signs and/or symptoms suggesting liver dysfunction (e.g., nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with meloxicam. If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g. eosinophilia, rash, etc), meloxicam should be discontinued.

### **Fluid Retention and Oedema**

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended.

### **Pre-existing Asthma**

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, meloxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

### **Use in Patients being treated with Corticosteroids**

Meloxicam cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

### **Use in Patients with Fever and Infection**

The pharmacological activity of meloxicam in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

## **Anaphylactoid Reactions**

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to meloxicam. Meloxicam should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

## **Lactose**

This medicine contains lactose. Patients with rare hereditary conditions of galactose intolerance, e.g galactosaemia, should not take this medicine.

## **Use in the elderly**

Frail or debilitated patients may tolerate side effects less well and such patients should be carefully supervised. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

## **Paediatric use**

Meloxicam is not recommended for use in children and adolescents under 18 years of age (see section **4.3 Contraindications**).

## **Effects on laboratory tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### General

*In vitro* drug interaction studies revealed that the metabolism of meloxicam is predominantly mediated via the CYP 2C9 isoenzyme, with a minor contribution of the CYP 3A4 isoenzyme in the liver. Co-administration of meloxicam with drugs known to inhibit CYP 2C9 is contraindicated. Co-administration of meloxicam with drugs known to inhibit CYP 3A4 (e.g. ketoconazole, itraconazole and erythromycin) or drugs known to be metabolised by CYP 3A4 (e.g. terfenadine, astemizole, ciclosporin and class III antiarrhythmic drugs, such as amiodarone and quinidine) should be undertaken with caution (see section **4.4 Special warnings and precautions for use - Gastrointestinal Effects**).

### Antacids

No pharmacokinetic interaction was detected with concomitant administration of antacids.

### Cimetidine

Concomitant administration of 200 mg cimetidine QID did not alter the single dose pharmacokinetics of 30 mg meloxicam.

### Digoxin

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after beta-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

### Furosemide (Frusemide)

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of frusemide and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with frusemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Frusemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with frusemide and meloxicam, patients should be observed closely for signs of declining renal function (see section **4.5 Interactions with other medicines and other forms of interactions - Diuretics**), as well as to assure diuretic efficacy.

### Cytochrome P450 inhibitors

Co-administration of meloxicam with drugs known to inhibit CYP 2C9 is contraindicated. Co-administration of meloxicam with drugs known to inhibit CYP 3A4 should be undertaken with caution (see section **4.4 Special warnings and precautions for use – Gastrointestinal Effects**).

### Other Prostaglandin Synthetase Inhibitors (PSIs) including glucocorticoids and salicylates (acetylsalicylic acid)

Co-administration of PSIs may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect and is not recommended. The concomitant use of meloxicam with other NSAIDs is not recommended.

### Oral anticoagulants, antiplatelet drugs, systemically administered heparin, thrombolytics and Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of bleeding via inhibition of platelet function, when NSAIDs are co-administered. If such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required.

### Lithium

NSAIDs have been reported to increase lithium plasma levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.

### Methotrexate

Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. *In vitro*, methotrexate did not displace meloxicam from human serum binding sites. However, as with other NSAIDs, meloxicam may increase the haematologic toxicity of methotrexate. In this situation, strict monitoring of blood cell count is recommended.

NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week), the concomitant use of NSAIDs is not recommended. The risk of an interaction between NSAIDs and methotrexate should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary, blood cell count and renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity. Although the pharmacokinetics of methotrexate (15 mg/week) were not affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAIDs.

### Pemetrexed

For the concomitant use of meloxicam with pemetrexed in patients with creatinine clearance from 45 to 79 mL/min, the administration of meloxicam should be paused for 5 days before, on the day of, and 2 days following pemetrexed administration. If a combination of meloxicam with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastro-intestinal adverse reactions. In patients with creatinine clearance below 45 mL/min the concomitant administration of meloxicam with pemetrexed is not recommended.

### Contraception

NSAIDs have been reported to decrease the efficacy of intrauterine devices.

### Diuretics

Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving meloxicam and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.

### Ciclosporin

Nephrotoxicity of ciclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment, renal function is to be measured.

### Antihypertensives (beta-blockers, ACE-inhibitors, vasodilators, diuretics)

A reduced effect of the antihypertensive drug by inhibition of vasodilating prostaglandins has been reported during treatment with NSAIDs.

### Angiotensin-II receptor antagonists

NSAIDs and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure

### Colestyramine

Colestyramine binds to meloxicam in the gastrointestinal tract leading to a faster elimination of meloxicam.

### Oral Hypoglycaemics

Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral anti-diabetics (sulfonylureas), which may lead to increased plasma levels of these drugs and meloxicam. Patients concomitantly using meloxicam with sulfonylureas should be carefully monitored for hypoglycemia.



## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

Oral treatment with meloxicam at doses up to 5 mg/kg/day in female rats (approximately 2.7 times the human dose based on BSA) and up to 9 mg/kg/day (approximately 5 times the human dose based on BSA) in male rats did not affect mating behaviour or fertility.

Oral treatment of female rats with meloxicam at doses of 1 mg/kg/day (approximately half of the human dose based on BSA) reduced the number of embryonic implantations and increased the number of early resorptions. A no-effect dose for these effects was not established. A reduction in the number of corpora lutea was also observed at 5 mg/kg/day, with the no-effect dose being 2.5 mg/kg/day (approximately 1.5-fold greater than the human dose based on BSA).

The use of meloxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Meloxicam may delay ovulation. Therefore, in women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

### **Use in pregnancy**

Category C

Meloxicam use is not recommended in pregnancy unless it is considered clinically essential.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and delay of labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with inhibitory effects on prostaglandin synthesis should be avoided.

Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2 times the human dose at 15 mg/day for a 50 kg adult based on body-surface-area [BSA]) when given during organogenesis. Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (about 60 times the human dose based on BSA) and embryoletality at oral doses > 5 mg/kg/day (5 times the human dose based on BSA) when rabbits were treated throughout organogenesis.

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of still births, increased length of delivery time and delayed parturition at oral doses > 1 mg/kg/day (approximately 0.6 times the human dose based on BSA) and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1 times the human dose based on BSA) throughout organogenesis. Similar findings were observed in rats receiving oral doses > 0.125 mg/kg/day (less than 0.1 times the human dose based on BSA) during late gestation and the lactation period.

Meloxicam crosses the placental barrier. There are no adequate, well-controlled studies in pregnant women. Meloxicam should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### **Use in lactation**

Studies of meloxicam excretion in human milk have not been conducted. However, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. The

safety of meloxicam in humans during lactation has not been established and therefore, the drug should not be used during lactation.

#### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances, drowsiness or other central nervous system disturbances should refrain from these activities.

#### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A meloxicam phase II/III safety database includes 10,122 osteoarthritis patients and 1,012 rheumatoid arthritis patients treated with meloxicam 7.5 mg/day and 3,505 osteoarthritis patients and 1,351 rheumatoid arthritis patients treated with meloxicam 15 mg/day. Meloxicam at these doses was administered to 661 patients for at least six months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials and 2,362 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across meloxicam trials.

A 12-week, multi-centre, double-blind, randomised trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of meloxicam with placebo and with an active control. Table 2 presents the adverse events that occurred in  $\geq 1\%$  of the meloxicam treatment groups.

**Table 2: Adverse events (%) occurring in  $\geq 1\%$  of Meloxicam patients in a 12-week osteoarthritis placebo- and active-controlled trial**

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
<b>No. of patients</b>	<b>157</b>	<b>154</b>	<b>156</b>	<b>153</b>
<b>General disorders and administrative site conditions</b>				
Fatigue	1.9	1.9	1.3	1.3
Gravitational oedema	0.6	1.3	1.9	3.3
Influenza like illness	5.1	4.5	5.8	2.6
Oedema peripheral	1.3	0.6	3.2	0
<b>Ear and labyrinth disorders</b>				
Ear disorder	0	0	1.3	0.7
Vertigo	0	0.6	1.3	0.7
<b>Eye disorders</b>				
Cataract	0	0	1.3	1.3

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
<b>No. of patients</b>	<b>157</b>	<b>154</b>	<b>156</b>	<b>153</b>
<b>Gastrointestinal</b>				
Abdominal pain	2.5	1.9	2.6	1.3
Constipation	1.9	1.9	0.6	3.9
Diarrhoea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Eructation	0	0	1.3	0
Flatulence	4.5	3.2	3.2	3.9
Gastro-oesophageal reflux disease	0	0.6	1.9	1.3
Nausea	3.2	3.9	3.8	7.2
Vomiting	1.9	1.3	1.3	2.6
<b>Immune system disorders</b>				
Hypersensitivity	1.9	1.9	0.6	1.3
<b>Infections and infestations</b>				
Pharyngitis	1.3	0.6	3.2	1.3
Sinusitis	5.1	1.3	1.9	5.9
Upper respiratory tract infection	1.9	3.2	1.9	5.9
<b>Injury, poisoning and procedural complications</b>				
Accident at home	1.9	4.5	3.2	2.6
Fall	0.6	2.6	0	1.3
<b>Metabolism and nutrition disorders</b>				
Dehydration	0	1.3	0	0
Increased appetite	0.6	0	1.3	0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	1.9	1.9	1.3	1.3
Arthritis	0	0	1.9	0
Back pain	3.2	1.3	1.9	2.0
Bursitis	0.6	1.9	1.3	0
Muscle spasms	1.3	1.3	1.9	1.3
Myalgia	0	1.3	1.3	0
Pain in extremity	0	1.3	0.6	0.7

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
<b>No. of patients</b>	<b>157</b>	<b>154</b>	<b>156</b>	<b>153</b>
<b>Nervous system disorders</b>				
Carpal tunnel syndrome	0	1.3	0.6	1.3
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
<b>Psychiatric disorder</b>				
Insomnia	0.6	0	1.9	2.0
<b>Renal and urinary disorders</b>				
Haematuria	0.6	0	1.3	0.7
<b>Respiratory, thoracic and mediastinal disorders</b>				
	0.6	1.3	0.6	1.3
Cough	0	0	1.3	0.7
Dyspnoea	0	0	1.3	0
Pleuritic pain				
<b>Skin and subcutaneous tissue</b>				
Hyperhidrosis	0	0	1.3	0
Pruritus	0.6	1.3	0.6	0
Purpura	1.3	1.9	0	0.7
Rash	1.9	1.9	0	0.7
<b>Vascular disorders</b>				
Hypertension	2.5	0.6	1.9	0

Adverse events that occurred in  $\geq 1\%$  of the meloxicam treatment groups in two 12-week placebo controlled rheumatoid arthritis trials are presented in Table 3.

**Table 3: Adverse Events (%) occurring in  $\geq 1\%$  of Meloxicam patients in two 12-week rheumatoid arthritis placebo and active controlled trials**

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 150 mg daily
<b>No. of patients</b>	<b>470</b>	<b>482</b>	<b>478</b>	<b>182</b>
<b>Gastrointestinal disorders</b>				
Abdominal pain	0.6	3.1	2.3	4.4
Abdominal pain upper	0.9	1.9	1.0	0
Constipation	0.9	1.5	1.7	3.8
Diarrhoea	5.3	5.2	3.3	6.0
Dyspepsia	3.6	5.6	3.6	7.1
Flatulence	1.1	1.2	1.5	5.5
Nausea	2.6	3.3	3.8	7.7
Vomiting	2.3	0.8	1.3	1.1
<b>General disorders and administrative site conditions</b>				
Influenza like illness	2.1	2.3	2.3	5.5
<b>Immune system disorders</b>				
Hypersensitivity	0.4	1.2	0.2	0
<b>Infections and infestations</b>				
Bronchitis	0.2	0.6	1.3	0.5
Nasopharyngitis	0.6	1.7	1.9	0
Pharyngitis	0.6	0.8	1.0	1.1
Rhinitis	0.4	0.6	1.0	1.1
Sinusitis	1.3	1.7	1.5	1.6
Upper respiratory tract infection	2.1	4.1	4.0	2.7
Urinary tract infection	1.3	1.2	1.3	1.6
<b>Injury, poisoning and procedural complications</b>				
Fall	0.2	0.6	1.0	0.5
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	1.9	1.0	1.7	2.2
Back pain	2.3	1.5	1.9	2.2
Myalgia	0.2	1.0	0.6	0.5
Rheumatoid arthritis	2.3	1.9	1.5	1.6

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 150 mg daily
<b>No. of patients</b>	<b>470</b>	<b>482</b>	<b>478</b>	<b>182</b>
<b>Nervous system disorders</b>				
Dizziness	3.0	2.3	0.6	3.3
Headache	6.6	6.6	5.4	9.3
<b>Psychiatric disorder</b>				
Insomnia	0.6	1.0	0.6	1.1
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	1.5	0.8	1.5	2.2
<b>Skin and subcutaneous tissue</b>				
Pruritus	1.3	0.6	1.0	1.1
Purpura	0.2	0.2	1.0	0
Rash	1.7	1.0	2.3	3.8
<b>Vascular disorders</b>				
Hypertension	0.9	1.5	1.0	2.2

Higher doses of meloxicam (22.5 mg and greater) have been associated with an increased risk of serious GI events, therefore the daily dose of meloxicam should not exceed 15 mg.

The following is a list of adverse events occurring in <1% of patients, which may be causally related to the administration of meloxicam. The information is based on clinical trials involving patients who have been treated with daily oral doses of 7.5 or 15 mg meloxicam tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

#### **Blood and lymphatic system disorders**

Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia, anaemia. Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of a cytopenia.

#### **Cardiac disorders**

Palpitations.

#### **Ear and labyrinth disorders**

Tinnitus.

#### **Gastrointestinal disorders**

Gastrointestinal perforation, occult or macroscopic gastrointestinal haemorrhage, gastroduodenal ulcer, colitis, oesophagitis, stomatitis  
Gastro-intestinal haemorrhage, ulceration or perforation may potentially be fatal.

#### **Hepatobiliary disorders**

Transitory abnormalities of liver function parameters (e.g. raised transaminases or bilirubin).

#### **Nervous system disorders**

Somnolence

### **Renal and urinary disorders**

Renal function test abnormal (increased serum creatinine and/or serum urea).

### **Respiratory, thoracic and mediastinal disorders**

Onset of asthma attacks in individuals allergic to aspirin or other NSAIDs.

### **Skin and subcutaneous tissue disorders**

Urticaria, photosensitivity reaction

### **Vascular disorders**

Flushing

### **Post-Market Adverse Drug Reactions**

Additional reports of adverse events which may be causally associated to the administration of meloxicam during worldwide post-marketing experience are included below.

#### General disorders and administration site conditions

In rare cases, other drugs of this class are reported to cause meningitis.

#### Eye disorders

Visual disturbance including blurred vision, conjunctivitis

#### Gastrointestinal disorders

Gastritis.

#### Hepatobiliary disorders

Hepatitis.

#### Immune system disorders

Anaphylactic reaction, anaphylactoid reaction and other immediate hypersensitivity

#### Psychiatric disorders

Confusional state, disorientation, mood altered.

#### Renal and urinary disorders

Acute renal failure. The use of NSAIDs may be related to micturition disorders, including acute urinary retention.

#### Reproductive System and Breast Disorders:

Infertility female, ovulation delayed.

#### Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, dermatitis bullous, erythema multiforme

### **Other Adverse Events**

Additional adverse events, reported from clinical trials or from spontaneous reports, where evidence for a causal association with meloxicam use is unclear, are the following: cardiac failure, angina, myocardial infarction, arrhythmia, vasculitis, agranulocytosis, interstitial nephritis, convulsion, liver failure.

## Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems> and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

## 4.9 OVERDOSE

### Symptoms

The typical signs and symptoms of NSAID overdose include nausea, vomiting, headache, drowsiness, blurred vision and dizziness. Rare cases of seizures, hypotension, apnoea, coma and renal failure have been reported with severe NSAID overdose.

### Treatment

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, activated charcoal is recommended. Administration of activated charcoal is recommended for patients who present 1–2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly.

It has been shown in a clinical trial that cholestyramine accelerates the elimination of meloxicam.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties in animals. Meloxicam showed anti-inflammatory activity in all standard models of inflammation. A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation, by inhibition of cyclooxygenase (COX).

Comparison of the ulcerogenic dose and the anti-inflammatory effective dose in rat adjuvant arthritis model confirmed a greater therapeutic margin in animals over other NSAIDs (piroxicam, diclofenac, naproxen, flurbiprofen). In rats, meloxicam showed greater inhibitory effect on prostaglandin biosynthesis at the site of inflammation than in the gastric mucosa or the kidney.

Selective inhibition of the cyclooxygenase-2 (COX-2) isoenzyme, relative to COX-1, by meloxicam has been demonstrated *in vitro* on various cell systems: guinea pig macrophages, bovine aortic endothelial cells (for testing of COX-1 activity), mouse macrophages (for testing for COX-2 activity) and human recombinant enzymes expressed in cos-cells and in human whole blood.



## **Clinical trials**

The efficacy of meloxicam in treating the symptoms of osteoarthritis and rheumatoid arthritis has been confirmed in several clinical studies.

### **Osteoarthritis Trials**

Two clinical studies of 6 months duration were performed in patients with osteoarthritis of the hip or knee. In the first study, the efficacy of meloxicam 15 mg (n=306) and piroxicam 20 mg (n=149) were found to be comparable, using as efficacy endpoints improvement in overall pain, pain on movement, global efficacy, change in duration of inactivity and change in quality of life score. In the second study, the efficacy of meloxicam 7.5 mg (n=169) was found to be comparable to that of diclofenac 100 mg SR (n=167) using similar endpoints.

Once daily dosing of meloxicam 7.5 mg (n=153) and 15 mg (n=156) showed a consistently more efficacious response than placebo (n=155) in a 12-week trial in patients with osteoarthritis of the knee or hip. Efficacy was measured by global assessment of disease activity, global assessment of pain and arthritic condition, as measured by the WOMAC (Western Ontario and McMaster University) Osteoarthritis Index. Both doses of meloxicam were also shown to be comparable to diclofenac 50 mg BID (n=152) with regard to efficacy, with a lower incidence of GI adverse events when compared to diclofenac.

Two large-scale, randomised, active-controlled clinical studies of 4 weeks duration were conducted in patients with osteoarthritis of the hand, hip, knee or spine. In the first study (MELISSA), the effects of meloxicam 7.5 mg (n=4,635) were compared against the effects of diclofenac 100 mg SR (n=4,688). In the second study (SELECT), the effects of meloxicam 7.5 mg (n=4,320) were compared against the effects of piroxicam 20 mg (n=4,336). The results from both studies indicated that meloxicam 7.5 mg was as efficacious as diclofenac 100 mg SR and piroxicam 20 mg, in the treatment of symptomatic osteoarthritis.

### **Rheumatoid Arthritis Trials**

The use of meloxicam for the symptomatic treatment of rheumatoid arthritis was evaluated in a double-blind, controlled trial involving 894 patients treated for 12 weeks. Meloxicam (7.5 mg, 15 mg and 22.5 mg daily) was compared to placebo, with diclofenac (75 mg twice daily) compared to placebo to establish trial sensitivity. The primary endpoints were number of painful or tender joints, number of swollen joints, investigator's global assessment of disease activity, patient's global assessment of disease activity and patient's assessment of pain. For all five primary endpoints, the meloxicam 7.5 mg group was significantly better than placebo for both mean on trial and last observation. The meloxicam 15 mg group was significantly better for 3 of 5 primary endpoints, excluding painful and swollen joints. In patients who had flared at baseline tender joints, the meloxicam 15 mg group differed almost significantly from the placebo group (p<0.05 not met due to the lower number of patients).

A second trial also investigated the use of meloxicam for the symptomatic treatment of rheumatoid arthritis. This double-blind, placebo-controlled trial used three doses of meloxicam (7.5 mg, 15 mg and 22.5 mg daily), in patients with rheumatoid arthritis over a 12-week period. A total of 898 patients were treated with meloxicam. The primary endpoint in this study was the American College of Rheumatology (20%) response criterion (ACR20) response rate, a composite measure of clinical, laboratory and functional measures of rheumatoid arthritis response. For this parameter, all three doses of meloxicam were more effective than placebo for the duration of the study. For the endpoints that comprised the ACR20 criteria, each of the meloxicam groups was superior to placebo at all visits except for C-Reactive Protein. Efficacy reached a plateau at the meloxicam 15 mg dose (Table 4). The overall incidence and severity of adverse events was similar among all three meloxicam groups.

**Table 4: Analysis of ACR20 Response Rate for Evaluable Patients at 12 weeks**

Study Phase	Treatment	Total	Responder <sup>1</sup> * n (%)	p Value <sup>#</sup>	
				Placebo	Meloxicam 7.5 mg
Week 12	Placebo	292	97 (33.2)		
	Meloxicam 7.5 mg	306	138 (45.1)	0.0008	
	Meloxicam 15 mg	293	158 (53.9)	0.0000	0.0439

1 The primary efficacy end-point was the ACR20. A responder was a patient with a response defined as:  $\geq 20\%$  improvement in both tender joint count and swollen joint count and at least three of the following:  $\geq 20\%$  improvement in: patient pain assessment; patient global (overall) assessment; physician global (overall) assessment; the modified health assessment questionnaire; C-Reactive protein.

\* Early terminations were considered as non-responders from the termination date.

# Obtained from Cochran-Mantel-Haenszel test stratified by centre.

The data from both studies indicate that meloxicam is effective and safe for the treatment of patients with rheumatoid arthritis.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Meloxicam is well absorbed from the gastrointestinal tract following oral administration (absolute bioavailability 89%). Once daily dosing leads to drug plasma concentrations with a relatively narrow  $C_{maxss} - C_{minss}$  window in the range of 0.4–1.0  $\mu\text{g/mL}$  for 7.5 mg doses or 0.8-2.0  $\mu\text{g/mL}$  for 15 mg doses. However, values outside of this range have been encountered ( $C_{min} - C_{max}$  at steady state, respectively).

Continuous treatment for periods of up to six months results in similar drug concentrations to those seen at steady state after two weeks of oral treatment with 15 mg meloxicam per day.

Absorption is not altered by concomitant food intake. However, food can shorten the  $T_{max}$  of *capsules* by approximately 2.5 hours and marginally increases the  $C_{max}$ , of the capsules, whereas maximum plasma concentrations were regularly achieved between 5 - 6 hours following tablet administration, irrespective of concomitant food consumption. Drug concentrations are dose-proportional for oral 7.5 mg and 15 mg doses, respectively. Steady state conditions are achieved in three to five days.

### Distribution

Volume of distribution is low (on average, 11L). In plasma, more than 99% is bound to plasma proteins. Meloxicam penetrates well into synovial fluid to give concentrations approximately half those in plasma.

## Metabolism

Meloxicam is eliminated almost entirely by hepatic metabolism: two thirds by cytochrome (CYP) P450 enzymes (CYP 2C9 two thirds and CYP 3A4 one third) and one third by other pathways, such as peroxidase oxidation. Meloxicam is almost completely metabolised to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxymeloxicam (60% of dose), from CYP 2C9 mediated metabolism, is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose). *In vitro* studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose respectively.

## Excretion

Meloxicam excretion is predominantly in the form of metabolites and occurs to equal extents in the faeces and urine. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and faeces (1.6%). The extent of the urinary excretion was confirmed for unlabelled multiple 7.5 mg doses: 0.5%, 6% and 13% of the dose were found in urine in the form of meloxicam and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively.

There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%. Meloxicam is eliminated from the body with a mean elimination half-life of 20 hours. Total plasma clearance ranged from 7–9 mL/min following multiple oral doses of meloxicam.

## Hepatic Impairment

Following a single 15 mg dose of meloxicam, there was no marked difference in plasma concentrations in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied.

## Renal Impairment

Meloxicam pharmacokinetics has been investigated in subjects with different degrees of renal insufficiency. Mild renal insufficiency does not have any substantial effect on meloxicam pharmacokinetics. Total drug plasma concentrations decreased with the degree of renal impairment, while free AUC values were similar. Total clearance of meloxicam increased in these patients, probably due to the increase in free fraction, leading to an increased metabolic clearance. There is no need for dose adjustment in patients with mild to moderate renal failure (creatinine clearance greater than 25 mL/min). Patients with severe renal insufficiency have not been adequately studied. The use of meloxicam in patients with severe renal impairment is not recommended (see section **4.3 Contraindications** and section **4.4 Special warnings and precautions for use**). A reduced protein binding was observed in patients with end stage renal disease on haemodialysis (see section **4.2 Dose and method of administration**).

## Haemodialysis

Following a single dose of meloxicam, the free  $C_{max}$  plasma concentrations were higher in patients with renal failure on chronic haemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Haemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after haemodialysis. Meloxicam is not dialysable.

## Elderly

Clearance is decreased in the elderly. In clinical studies, steady state pharmacokinetics in the elderly (mean age: 67 years) did not differ significantly from those in a younger population (mean age: 50 years); however elderly females had a higher systemic exposure to meloxicam than did elderly males.

## Gender

Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg meloxicam, the mean elimination half life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs. 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the  $C_{max}$  or  $t_{max}$  across genders.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

Meloxicam did not demonstrate genotoxic potential in assays for gene mutation *in vitro* and chromosomal damage *in vitro* and *in vivo*.

### **Carcinogenicity**

Two-year dietary studies showed no evidence for carcinogenic activity at meloxicam doses up to 0.8 mg/kg/day (approximately half of the highest human dose at 15 mg/day for a 50 kg person based on body-surface-area [BSA]) in rats and up to 8 mg/kg/day (2.2 times the highest human dose based on BSA) in mice. In rats, the highest dose used was nephrotoxic, while the highest dose used in mice was sub-toxic.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

- Lactose monohydrate
- maize starch
- sodium citrate
- magnesium stearate
- brilliant blue FCF
- gelatin
- quinoline yellow (7.5 mg only)
- sunset yellow FCF
- titanium dioxide

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store below 25°C. Protect from light.

## 6.5 NATURE AND CONTENTS OF CONTAINER

### Terry White Chemists 7.5 mg capsules:

Blister pack of 10, 20, 30 and 100 capsules (AUST R 181204).

### Terry White Chemists 15 mg capsules:

Blister pack of 10, 20, 30 and 100 capsules (AUST R 181205).

Not all strengths and/or pack sizes may be available.

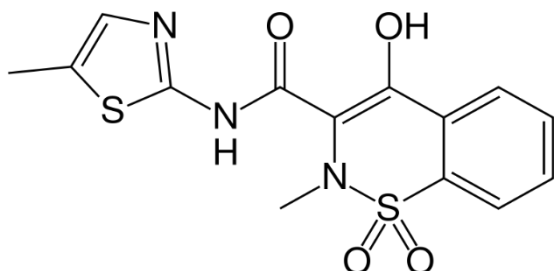
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Meloxicam is a pastel yellow solid with pKa values of 1.09 and 4.18 and a melting point of about 256°C. The substance is practically insoluble in water, soluble in dimethylformamide, slightly soluble in chloroform and acetone and very slightly soluble in methanol. There are no chiral centres.

### Chemical structure



Chemical Name: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Molecular Formula: C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>

Molecular Weight: 351.4

CAS number: 71125-38-7

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

## 8 SPONSOR

Apotex Pty Ltd  
16 Giffnock Avenue  
Macquarie Park NSW 2113

Tel: (02) 8877 8333

Web: [www1.apotex.com/au](http://www1.apotex.com/au)

## **9 DATE OF FIRST APPROVAL**

18 October 2011

## **10 DATE OF REVISION**

8 March 2019

### **Summary table of changes**

<b>Section Changed</b>	<b>Summary of new information</b>
All	Reformatted product information; minor editorial changes
4.6	Increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy