

# AUSTRALIAN PRODUCT INFORMATION

## TIXOL<sup>®</sup>

(duloxetine (as hydrochloride)) capsules



### 1 NAME OF THE MEDICINE

Duloxetine hydrochloride.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Duloxetine is available as capsules for oral administration.

Each capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg or 60 mg of duloxetine.

Excipients with known effect: sugars, phenylalanine and sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3 PHARMACEUTICAL FORM

The 30 mg enteric capsule has an opaque blue/white hard gelatin capsule '157' on body and 'A' on cap with green ink.

The 60 mg enteric capsule has an opaque blue/opaque green hard gelatin capsule '158' on body and 'A' on cap with white ink.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

TIXOL is indicated for the treatment of:

- major depressive disorder (MDD)
- diabetic peripheral neuropathic pain (DPNP)
- generalised anxiety disorder (GAD).

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

##### Major Depressive Disorder

TIXOL should be administered for the treatment of major depressive disorder at a dose of 60 mg once daily, with or without food. There is no adequate evidence suggesting that patients not responding to 60 mg once daily will benefit from having their dose increased.

##### Diabetic Peripheral Neuropathic Pain

The starting and maintenance dose of duloxetine in diabetic peripheral neuropathic pain is 60 mg once daily. As the progression of diabetic neuropathy is highly variable and management of pain is empirical, effectiveness of duloxetine should be assessed on an individual basis.

##### Generalised Anxiety Disorder

The recommended starting dose of duloxetine in patients with generalized anxiety disorder is 30 mg once daily with or without food. The daily dose should be increased in 30 mg increments until the minimum effective dose is achieved. The maximum dose is 120 mg per day, given as 120 mg once daily. Doses above 120 mg have not been systematically evaluated.

### **Initial Tolerability**

For patients in whom initial tolerability may be a concern, such as treatment-naïve patients or those with a history of adverse events with other medications, use of a lower starting dose such as 30 mg once daily for one week before increasing the dose to 60 mg once daily should be considered. A dose of 30 mg once daily should be used in patients with end stage renal disease (see below). In addition, clinical studies have shown that taking duloxetine with food may improve initial tolerability.

### **Discontinuation of treatment**

When discontinuing duloxetine after more than one week of therapy it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms. As a general recommendation, the dose of duloxetine should be reduced by half or administered on alternate days during a period of not less than two weeks. The precise regimen followed should take into account the individual circumstances of the patient, such as duration of treatment, dose at discontinuation, etc.

### **Renal Impairment**

A lower dose of 30 mg once daily should be used in patients with end stage renal disease (creatinine clearance < 30 mL/min) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

### **Hepatic Impairment**

Duloxetine is contraindicated in patients with liver disease resulting in hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

### **Patients aged $\geq$ 65 years**

No dosage adjustment is recommended for elderly patients on the basis of age (see Section 5.2 PHARMACOKINETIC PROPERTIES).

### **Children and adolescents aged < 18 years**

Duloxetine is not indicated for use in patients under 18 years of age (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## **4.3 CONTRAINDICATIONS**

Duloxetine is contraindicated in patients with known hypersensitivity to duloxetine or to any of the excipients in the formulation.

### **Monoamine oxidase inhibitors (MAOI)**

Duloxetine should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 5 days should be allowed after stopping Duloxetine before starting a MAOI. Cases of serious reactions, such as potentially life threatening serotonin syndrome (characterized by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SNRI in combination with MAOIs and RIMA, and in patients who have recently discontinued an SNRI and have been started on a MAOI (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Duloxetine is contraindicated in patients with liver disease resulting in hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Duloxetine should not be used in combination with potent CYP1A2 inhibitors (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patients presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medications in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Duloxetine hydrochloride is not indicated for use in patients under the age of 18. Although a causal role for duloxetine in inducing such events has not been established, some analyses from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviours in paediatric and young adult (<25 years of age) patients compared to placebo (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Prescriptions for duloxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### **Use in Hepatic Impairment and Hepatotoxicity**

Duloxetine should ordinarily not be prescribed to patients with evidence of acute or chronic liver disease as it is possible that duloxetine may aggravate pre existing liver disease (see Section 4.3 CONTRAINDICATIONS).

Duloxetine increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of duloxetine-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo controlled trials in any indication, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 1.1% (85/7632) of duloxetine-treated patients and in 0.2% (13/5578) of placebo treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognised as an important predictor of severe liver injury. In clinical trials, 7 duloxetine patients had elevations of transaminases and bilirubin, but 5 of 7 also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, in 3 of these 7 patients there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen.

Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

### **Alcohol**

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in Hepatic Impairment and Hepatotoxicity)

### **Bipolar Disorder**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

### **Activation of Mania**

In placebo-controlled trials in patients with major depressive disorder, activation of hypomania or mania occurred in 0.1% of duloxetine treated patients and 0.1% of placebo treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other drugs, duloxetine should be used cautiously in patients with a history of mania.

## Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/9445) of patients treated with duloxetine and 0.01% (1/6770) of patients with placebo. As with similar CNS active drugs, duloxetine should be used cautiously in patients with a history of seizure disorder.

## Mydriasis

Mydriasis has been reported in association with duloxetine. Caution should be exercised in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

## Hyponatraemia

Cases of hyponatraemia (some with serum sodium lower than 110mmol/Liter) have been reported very rarely, when administering duloxetine. The majority of these cases occurred in elderly patients, especially when coupled with a recent history of altered fluid balance or conditions pre-disposing to altered fluid balance. Hyponatremia may present with nonspecific signs and symptoms (such as dizziness, weakness, nausea, vomiting, confusion, somnolence, and lethargy). Signs and symptoms associated with more severe cases have included syncopal episodes, falls, and seizure. Caution is required in patients at increased risk for hyponatraemia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

## Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events, including gastrointestinal bleeding (see Section 4.8 ADVERSE EFFECTS (Undesirable Effects)). Therefore, caution is advised in patients taking duloxetine concomitantly with anticoagulants and/or medicinal products known to affect platelet function (e.g., NSAIDs, aspirin) and in patients with known bleeding tendencies.

## Postpartum haemorrhage

SSRIs and SNRIs may increase the risk of postpartum haemorrhage (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

## Use in Patients with Concomitant Illness

Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. Caution is advisable in using duloxetine in patients with diseases or conditions that produce altered metabolism or haemodynamic responses.

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the products premarketing testing. However, evaluation of electrocardiograms (ECGs) of 321 patients who received duloxetine in placebo-controlled clinical trials indicated that duloxetine is not associated with the development of clinically significant ECG abnormalities (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Electrocardiogram Changes).

Increased plasma concentrations of duloxetine occur in patients with end stage renal disease (ESRD) and in patients with moderate hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

## Drug Dependence

While duloxetine has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

## Weight Changes

Weight changes do not appear to be clinically significant outcomes of treatment with duloxetine. In placebo-controlled clinical trials, patients treated with duloxetine for up to 9-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

## Use in Renal Impairment

Duloxetine  $C_{max}$  and AUC values were approximately 2-fold higher in patients with ESRD receiving chronic intermittent dialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. A lower dose should be used for patients with ESRD (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on apparent plasma clearance of duloxetine.

## Blood Pressure

Duloxetine is associated with an increase in blood pressure in some patients. In placebo controlled clinical trials duloxetine treatment was associated with small increases in systolic blood pressure averaging 2 mm Hg and small increases in diastolic blood pressure averaging 0.5 mm Hg compared to placebo. Large, potentially clinically significant, elevations in blood pressure do not appear to be more common with duloxetine than with placebo. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure.

## Orthostatic Hypotension and Syncope

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during therapy.

## Electrocardiogram Changes

ECGs were obtained from 321 duloxetine-treated patients with MDD and 169 placebo-treated patients in 8-week clinical trials. The rate-corrected QT interval in duloxetine-treated patients in an 8-week study did not differ from that seen in placebo-treated patients. In summary, the data suggest no arrhythmogenic potential with duloxetine. No clinically significant differences were observed for QT, PR and QRS intervals between duloxetine-treated and placebo-treated patients.

## Discontinuing Treatment

As with other drugs effective in the treatment of major depressive disorder, when discontinuing duloxetine after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials, adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with duloxetine and 23% of patients taking placebo. The most commonly reported symptoms following abrupt discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paraesthesia, fatigue, vomiting, irritability, nightmares, insomnia, diarrhoea, anxiety, hyperhidrosis, vertigo, somnolence and myalgia.

The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have

inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more).

### **Serotonin Syndrome**

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with duloxetine should be discontinued if such events occur and supportive symptomatic treatment initiated.

Caution is advisable if duloxetine is used concomitantly with serotonergic antidepressants like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, St John's Wort (*Hypericum perforatum*), triptans, tramadol, pethidine or tryptophan.

### **Sexual dysfunction**

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

### **Use in the Elderly**

Evaluation of patients over the age of 65 who received duloxetine in clinical trials revealed no unusual pattern of adverse events relative to the clinical experience in younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including TIXOL, have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse reaction.

### **Paediatric Use**

Safety and effectiveness in children have not been established. Duloxetine is not indicated for use in patients under the age of 18 and should not be used in children and adolescents aged < 18 years.

### **Effects on Laboratory Tests**

There are no data available that shows that duloxetine has an effect on laboratory tests.

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

Duloxetine is a SNRI with its primary effect on the CNS. Caution should be used when it is administered in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concurrent use with other drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans or tramadol) may result in serotonin syndrome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of duloxetine with substantial alcohol consumption may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in Hepatic Impairment and Hepatotoxicity). Duloxetine should only be used in exceptional circumstances with extreme caution in patients who consume substantial amounts of alcohol.

**Drugs Metabolised by CYP1A2** – Although CYP1A2 is weakly inhibited by duloxetine in vitro, results of a clinical study show that the pharmacokinetics of a CYP1A2 substrate (theophylline) were not significantly affected by co-administration with duloxetine (60 mg twice daily). In vitro studies with human hepatocytes

demonstrated that duloxetine does not induce CYP1A2 activity. These studies suggest that duloxetine is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

**Inhibitors of CYP1A2** - As CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 will likely result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77%. Duloxetine should not be used in combination with potent inhibitors of CYP1A2 (e.g. fluvoxamine) (see Section 4.3 CONTRAINDICATIONS).

**Drugs Metabolised by CYP2D6** - CYP2D6 is moderately inhibited by duloxetine (in common with tricyclic antidepressants and SSRIs). Duloxetine administered at 60 mg twice daily caused a single 50 mg dose of desipramine (also metabolised through CYP2D6) to have a 3-fold increase in the AUC. Duloxetine administered at 40 mg twice daily increased steady-state AUC of tolterodine (2 mg twice daily) by 71% but did not affect the pharmacokinetics of the 5-hydroxyl metabolite. Therefore, caution should be used if duloxetine is co-administered with medications that are predominantly metabolised by the CYP2D6 system and which have a narrow therapeutic index (e.g. tricyclic antidepressants such as nortriptyline and imipramine, phenothiazines, flecainide, propafenone). Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma concentrations of thioridazine, duloxetine and thioridazine should not be co-administered.

**Inhibitors of CYP2D6** – An inhibitor of CYP2D6, paroxetine (20 mg once daily) decreased the oral clearance of duloxetine (40 mg once daily) by about 37%. Because CYP2D6 is involved in duloxetine metabolism, caution is advised if administering duloxetine with inhibitors of CYP2D6 (e.g. SSRIs).

**Drugs Metabolised by CYP2C9** – Although clinical studies have not been performed, results of in vitro studies demonstrate that duloxetine does not inhibit the enzyme activity of CYP2C9.

**Drugs Metabolised by CYP3A** – Although clinical studies have not been performed, results of in vitro studies demonstrate that duloxetine does not inhibit or induce the catalytic activity of CYP3A.

**Antacids and H<sub>2</sub> Antagonists** – Co-administration of duloxetine with aluminium - and magnesium-containing antacids or co-administration of duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

**Drugs Highly Bound to Plasma Protein** – Duloxetine is highly bound to plasma protein (>90%). Administration of duloxetine with another highly protein bound drug may cause increased free concentrations of either duloxetine or the other drug.

**Monoamine Oxidase Inhibitors (MAOI)** - Because duloxetine is an inhibitor of both serotonin and noradrenaline reuptake, it is recommended that duloxetine not be used in combination with an MAOI (see Section 4.3 CONTRAINDICATIONS).

**St John's Wort** - In common with other antidepressants, concomitant administration of duloxetine and the herbal remedy St John's Wort (*Hypericum perforatum*) is not recommended.

**Warfarin and INR** – Increases in INR have been reported when duloxetine was co-administered with warfarin.

**Drugs That Affect Gastric Acidity** - Duloxetine has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.



## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

Duloxetine administered orally to male rats prior to and throughout mating, or to female rats prior to and throughout mating, gestation and lactation, at doses up to 45 mg/kg (3 times the MRHD on a mg/m<sup>2</sup> basis) did not alter mating or fertility. In females, this dose was associated with oestrus cycle disruption and signs of maternotoxicity and embryofetal toxicity.

### Use in Pregnancy

Pregnancy Category: Category B3

Duloxetine and/or its metabolites cross the placenta in rats. There was no evidence of teratogenicity in rats or rabbits following oral administration of duloxetine during the period of organogenesis at doses up to 45 mg/kg/day. In rats, this dose was 3 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. In rabbits, the estimated systemic exposure (plasma AUC) at this dose was less than clinical exposure at the maximum recommended dose. In rats receiving the maternotoxic dose of 45 mg/kg/day during organogenesis, there was increased preimplantation loss and resorptions, and reduced foetal weight.

Oral administration of duloxetine to female rats prior to and throughout mating, gestation and lactation at doses of 30-45 mg/kg/day (2-3 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) elicited maternal toxicity and reduced live birth indices, birth weight, and postnatal survival and growth of offspring, and altered some indices of offspring behaviour.

Neonates exposed to serotonergic agents late in the third trimester have been uncommonly reported to have clinical findings of respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. The majority of cases have occurred either at birth or within a few days of birth. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with duloxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

The safety of duloxetine in human pregnancy has not been established. This drug should be used during pregnancy only if the potential benefit justifies the potential risk.

Using observational data, there is evidence of an increased risk (less than 2-fold) for postpartum haemorrhage following duloxetine exposure close to delivery.

In an observational study, maternal exposure to duloxetine during pregnancy was associated with an increased risk of pre-term birth (less than 2-fold, corresponding to approximately 6 additional premature births per 100 women treated with duloxetine late in pregnancy). The majority of the premature births occurred between 35 and 36 weeks of gestation.

### *Labor and Delivery*

The effect of duloxetine on labour in humans is unknown.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

### Use in Lactation

Duloxetine is excreted into the milk of lactating women. The estimated infant dose ranges from approximately 0.1% to 0.3% of the maternal dose, normalised by body weight. Oral administration of duloxetine to female rats prior to and throughout mating, gestation and lactation was associated with maternal toxicity and adverse

effects (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy). Administration of duloxetine to nursing mothers is not recommended.

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

In controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function or memory. However, as any psychoactive drug may impair judgement, thinking or motor skills, and duloxetine may be associated with undesirable effects such as sedation and dizziness, patients should be cautioned about their ability to perform potentially hazardous tasks until they are reasonably certain that duloxetine therapy does not affect their ability to engage in such activities.

#### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

##### Clinical Trial Data

The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), GAD (N=668) and DPNP (N=568). The population studied was 17 to 89 years of age; 64.8%, 64.7% and 38.7%, female; and 85.5%, 77.6%, and 84.6% Caucasian for MDD, GAD and DPNP, respectively. Most patients received doses of a total of 60 to 120 mg per day.

##### Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder - Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalised Anxiety Disorder - Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain - Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

##### Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials

**Pooled MDD and GAD Trials** - Table 1 gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo.

**Table 1: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in MDD and GAD Placebo-Controlled Trials**

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Duloxetine (N=2995)	Placebo (N=1955)
<b>Cardiac Disorders</b>		
Palpitations	2 <sup>^</sup>	2
<b>Eye Disorders</b>		
Vision blurred	3	2
<b>Gastrointestinal Disorders</b>		
Nausea	25	9
Dry mouth	15	6
Diarrhoea	10	7
Constipation*	10	4
Abdominal pain <sup>a</sup>	4	4
Vomiting	5	2
<b>General Disorders and Administration Site Conditions</b>		
Fatigue <sup>b</sup>	10	6
Investigations		
Weight decreased*	2	<1
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite <sup>c</sup>	7	2
<b>Nervous System Disorders</b>		
Dizziness	10	6
Somnolence <sup>d</sup>	10	4
Tremor	3	<1
<b>Psychiatric Disorders</b>		
Insomnia <sup>e</sup>	10	6
Agitation <sup>f</sup>	5	3
Anxiety	3	2
Libido decreased <sup>g</sup>	4	1
Orgasm abnormal <sup>h</sup>	3	<1
Abnormal dreams <sup>i</sup>	2	1
<b>Reproductive System and Breast Disorders</b>		
Erectile dysfunction <sup>j</sup>	5	1
Ejaculation delayed <sup>*j</sup>	3	<1
Ejaculation disorder <sup>jk</sup>	2	<1
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Yawning	2	<1
<b>Skin and Subcutaneous Tissue Disorders</b>		
Hyperhidrosis	6	2

<b>Vascular Disorders</b>		
Hot flush	2	<1

<sup>^</sup> Frequency higher in patients treated with duloxetine but rounded down to whole number

<sup>\*</sup> Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

<sup>a</sup> Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain

<sup>b</sup> Also includes asthenia

<sup>c</sup> Also includes anorexia

<sup>d</sup> Also includes hypersomnia and sedation

<sup>e</sup> Also includes middle insomnia, early morning awakening, and initial insomnia

<sup>f</sup> Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation

<sup>g</sup> Also includes loss of libido

<sup>h</sup> Also includes anorgasmia

<sup>i</sup> Also includes nightmare

<sup>j</sup> Males patients only

<sup>k</sup> Also includes ejaculation failure and ejaculation dysfunction

Diabetic Peripheral Neuropathic Pain - Table 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine in the premarketing acute phase of DPNP placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo.

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**Table 2: Treatment-Emergent Adverse Reactions Incidence of 2% or More in DPNP Placebo-Controlled Trials**

System Organ Class/Adverse Reaction	Percentage of Patients Reporting Reaction			
	Duloxetine 20 mg once daily (N=115)	Duloxetine 60 mg once daily (N=228)	Duloxetine 60 mg twice daily (N=225)	Placebo (N=223)
<b>Gastrointestinal Disorders</b>				
Nausea	14	22	30	9
Constipation	5	11	15	3
Diarrhoea	13	11	7	6
Dry Mouth	5	7	12	4
Vomiting	6	5	5	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	2	10	12	5
Asthenia	2	4	8	1
Pyrexia	2	1	3	1
<b>Infections and Infestations</b>				
Nasopharyngitis	9	7	9	5
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	3	4	11	<1
Anorexia	3	3	5	<1
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Muscle cramp	5	4	4	3
Myalgia	3	1	4	<1
<b>Nervous System Disorders</b>				
Somnolence	7	15	21	5
Headache	13	13	15	10
Dizziness	6	14	17	6
Tremor	0	1	5	0
<b>Psychiatric Disorders</b>				
Insomnia	9	8	13	7
<b>Renal and Urinary Disorders</b>				
Polyuria	3	1	5	2
<b>Reproductive System and Breast Disorders</b>				
Erectile dysfunction <sup>1</sup>	0	1	4	0

<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	6	3	5	4
Pharyngolaryngeal pain	3	1	6	1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Hyperhidrosis	6	6	8	2

<sup>1</sup> Male patients only

The following additional adverse events were reported during placebo-controlled clinical trials of duloxetine for MDD or other indications in 8504 patients. Very common events are defined as those occurring in  $\geq 10\%$  of patients, common events are defined as those occurring in  $\geq 1\%$  and  $< 10\%$  of patients, uncommon events are defined as those occurring in  $\geq 0.1\%$  and  $< 1\%$  of patients, and rare events are defined as those occurring in  $< 0.1\%$  of patients.

### Cardiac Disorders

Common: palpitations.

Uncommon: tachycardia.

### Ear and Labyrinth Disorders

Uncommon: vertigo, ear pain, tinnitus.

### Endocrine Disorders

Rare: hypothyroidism.

### Eye Disorders

Uncommon: mydriasis, visual impairment, dry eye.

### Gastrointestinal Disorders

Common: dyspepsia (including stomach discomfort), abdominal pain.

Uncommon: eructation, gastroenteritis, stomatitis, halitosis, gastritis, flatulence, gastrointestinal haemorrhage, dysphagia.

### General Disorders and Administration Site Conditions

Common: chills (including rigors).

Uncommon: feeling abnormal, feeling hot and/or cold, malaise, thirst, falls (more common in the elderly ( $\geq 65$  years old)).

Rare: Gait disturbance

### Infections and Infestations

Uncommon: laryngitis.

### Investigations

Uncommon: blood pressure increased (including blood pressure systolic increased, blood pressure diastolic increased), hepatic lab related findings (including alanine aminotransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyltransferase

increased, blood alkaline phosphatase increased, blood bilirubin increased), weight increased, blood cholesterol increased.

Duloxetine treatment in placebo-controlled clinical trials was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and potassium; infrequent, transient, abnormal values were observed for these analytes in duloxetine-treated patients, compared with placebo-treated patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

### **Metabolism and Nutrition Disorders**

Uncommon: dehydration.

### **Musculoskeletal and Connective Tissue Disorders**

Common: musculoskeletal pain (including myalgia, neck pain), muscle spasm.

Uncommon: muscle tightness (including musculoskeletal stiffness), muscle twitching.

### **Nervous System Disorders**

Very common: headache (placebo rate was more than duloxetine rate in MDD trials).

Common: lethargy, paraesthesia (including hypoesthesia, hypoesthesia facia and paraesthesia oral).

Uncommon: dysgeusia, disturbance in attention, dyskinesia, poor quality sleep.

Rare: myoclonus.

### **Psychiatric Disorders**

Common: anxiety, sleep disorder, agitation (including feeling jittery, nervousness, restlessness, tension, psychomotor agitation).

Uncommon: bruxism, disorientation (including confusional state), apathy, abnormal dreams (including nightmares).

### **Renal and Urinary Disorders**

Common: Urinary frequency.

Uncommon: nocturia, urinary hesitation, urinary retention, dysuria, polyuria.

Rare: urine odour abnormal, urine flow decreased.

### **Reproductive System and Breast Disorders**

Uncommon: ejaculation disorder (includes ejaculation dysfunction, ejaculation failure), sexual dysfunction, menopausal symptoms, testicular pain.

Rare: Menstrual disorder.

### **Respiratory, Thoracic and Mediastinal Disorders**

Common: yawning, oropharyngeal pain.

Uncommon: throat tightness.

### **Skin and Subcutaneous Tissue Disorders**

Common: Pruritus.



Uncommon: night sweats, photosensitivity reaction, cold sweats, dermatitis contact, increased tendency to bruise.

### **Vascular Disorders**

Uncommon: flushing, peripheral coldness, orthostatic hypotension.

**Glucose Regulation**—In three clinical trials of duloxetine for the treatment of diabetic neuropathic pain, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL (9.78 mmol/L), and the mean baseline haemoglobin A1c (HbA1c) was 7.81%. In the 12 week acute treatment phase of these studies, small increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

### **Spontaneous Data**

The following list of adverse drug reactions is based on post-marketing spontaneous reports involving use of duloxetine for any indication, and corresponding reporting rates have been provided. Rare events are defined as those occurring in less than 1/1000 patients; very rare events are those occurring in less than 1/10,000 patients.

#### Endocrine disorders

Very rare: Syndrome of inappropriate antidiuretic hormone (SIADH).

#### Cardiac disorders

Very rare: Supraventricular arrhythmia.

Frequency not known: Stress cardiomyopathy (Takotsubo cardiomyopathy).

#### Eye disorders

Very rare: Glaucoma.

#### Gastrointestinal disorders

Very rare: Microscopic colitis.

#### Hepatobiliary disorders

Very rare: Alanine aminotransferase (ALT) increased, alkaline phosphatase increased, aspartate aminotransferase (AST) increased, bilirubin increased.

Very rare: Hepatitis, jaundice.

Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

#### Immune system disorders

Very rare: Anaphylactic reaction, hypersensitivity.

#### Metabolism and nutrition disorders

Very rare: Hyponatraemia. Hyperglycaemia (reported especially in diabetic patients)

### Musculoskeletal and connective tissue disorders

Very rare: Trismus.

### Nervous system disorders

Very rare: Extrapyrimal disorder, paraesthesia (including electric shock-like sensation) upon treatment discontinuation, serotonin syndrome, seizures, restless legs syndrome, seizures upon discontinuation.

### Psychiatric disorders

Rare: Hallucinations.

Very rare: Mania, aggression and anger (particularly early in treatment or after treatment discontinuations).

### Renal and urinary disorders

Rare: Urinary retention.

### Reproductive system and breast disorders

Very rare: Gynaecological bleeding, galactorrhoea, hyperprolactinaemia

Frequency not known: Postpartum haemorrhage\*

\*This event has been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.6 FERTILITY, PREGNANCY AND LACTATION)

### Skin and subcutaneous tissue disorders

Rare: Rash.

Very rare: Angioneurotic oedema, contusion, cutaneous vasculitis (sometimes associated with systemic involvement), Stevens-Johnson Syndrome, urticaria.

### Vascular disorders

Very rare: Orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment), hypertensive crisis.

## **Adverse Events - causality not established**

Very rare cases of the following adverse events have been reported in post-marketing experience, but no causal link between these events and duloxetine has been established.

Abnormal bleeding events e.g. intracerebral, gastrointestinal; blood dyscrasias; cardiac events e.g., myocardial infarction and ventricular arrhythmias; pancreatitis; renal impairment; rhabdomyolysis; skin reactions especially in regards to subcutaneous tissue disorder

## **Discontinuation Symptoms**

The most commonly reported symptoms following abrupt or tapered discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paraesthesia, fatigue vomiting, irritability, nightmares, insomnia, diarrhoea, anxiety, hyperhidrosis, vertigo, somnolence and myalgia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## **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 [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

On the available evidence there is a wide margin of safety in overdose. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, have been reported and have not been fatal. However, in post marketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as approximately 1000 mg. Signs and symptoms of overdose (most with mixed drugs) included serotonin syndrome, somnolence, vomiting and seizures.

In animal studies, the major signs of overdose toxicity are related to the CNS and gastrointestinal systems. Signs of toxicity include CNS effects such as tremors, clonic convulsions, ataxia, emesis, and decreased appetite.

### Management of Overdose

No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of Action

Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor, and weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Duloxetine dose-dependently increased extracellular levels of serotonin and noradrenaline in selected brain areas of animals, and neurochemical and behavioural studies in animals indicate an enhancement of central serotonin and noradrenaline neurotransmission. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine. Duloxetine displayed analgesic activity in rodent models of persistent, inflammatory or neuropathic pain, but not acute or arthritic pain.

#### Clinical Trials

##### Acute treatment of depression

The efficacy of duloxetine has been evaluated in six double-blind, placebo-controlled acute Phase 3 studies of 8-9 weeks duration in 1978 adult outpatients (18 to 83 years) meeting the DSM-IV criteria for major depression at doses of 40 mg to 120 mg daily. In four of these studies, duloxetine was significantly superior to placebo as measured by the mean change in the 17 item Hamilton Depression Rating Scale (HAMD<sub>17</sub>) total score from baseline to endpoint. Duloxetine doses in these four studies were:

- 60 mg once daily (two studies)
- 20 mg twice daily and 40 mg twice daily (one study)
- 40 mg twice daily and 60 mg twice daily (one study)

In the remaining two studies duloxetine showed numerically superior mean change compared with placebo. The duloxetine doses in these two studies were:

- 20 mg twice daily and 40 mg twice daily
- 40 mg twice daily and 60 mg twice daily

In both of these latter studies, the active comparator paroxetine also did not separate significantly from placebo on the primary outcome measure. Response ( $\geq 50\%$  reduction in HAMD<sub>17</sub> total score) and remission (HAMD<sub>17</sub> total score  $\leq 7$ ) were also significantly higher with duloxetine compared with placebo in five out of six and three out of six acute studies, respectively.

While results were positive for improvement in the HAMD<sub>17</sub> at a dose of 20 mg twice daily in one of two studies, this dose did not demonstrate statistical superiority on any other measure including response or remission.

**Table 3: HAMD<sub>17</sub> Total, Response, and Remission Rates Placebo-Controlled Duloxetine 60 mg Once Daily Studies**

	HMBHa			HMBHb		
	Placebo (n=115)	Duloxetine (n=121)	P-value <sup>1</sup>	Placebo (n=136)	Duloxetine (n=123)	P-Values <sup>4</sup>
HAMD <sub>17</sub> Total <sup>1</sup>	-5.67	-9.47	<0.001	-7.02	-8.75	0.048
Response <sup>2</sup>	27 (23%)	55 (45%)	<0.001	48 (35%)	62 (50%)	0.017
Remission <sup>3</sup>	17 (15%)	38 (31%)	0.003	33 (24%)	39 (32%)	0.212

<sup>1</sup> Least-squares mean change from baseline

<sup>2</sup> Response =  $\geq 50\%$  reduction in HAMD<sub>17</sub> total score from baseline to endpoint

<sup>3</sup> Remission = HAMD<sub>17</sub> total score  $\leq 7$  at endpoint

<sup>4</sup> P-values for the HAMD<sub>17</sub> Total are from analysis of covariance and for response and remission are from Fisher's exact test

In addition to the HAMD<sub>17</sub> total score, several other measures were included in the Anxiety Subfactor of the HAMD<sub>17</sub>, the Patient Global Impressions (PGI) Improvement Score, bodily pain as measured by Visual Analog Scale (VAS), and the Quality of Life in Depression rating scales were also examined. In the four studies where duloxetine demonstrated statistical superiority over placebo as measured by improvement in the HAMD<sub>17</sub> total score, results were also positive for the additional measures at doses of 60 mg to 120 mg per day.

In each study and in pooled data, the effectiveness of duloxetine was similar regardless of age, gender or racial origin.

### Prevention of depressive relapse:

Patients responding to 12 weeks of acute treatment with open-label duloxetine at a dose of 60 mg once daily were randomly assigned to either duloxetine 60 mg once daily or placebo for a further 6 months (continuation phase) and time to relapse in each group was compared. Of 533 subjects who enrolled in the study, 278 responded and were randomised to duloxetine 60 mg once daily (n=136) or placebo (n=142). The estimated probability of depressive relapse at 6 months for placebo was 38.3% and for duloxetine 60 mg once daily was 19.7% (p=0.004). During the 6-month continuation therapy phase of this study, 17.4% of duloxetine-treated patients met the a priori-defined criteria for relapse compared with 28.5% on placebo (p=0.042).

Of 88 patients who relapsed during the continuation phase, 87 received double-blind rescue therapy. The patients who relapsed on placebo (n=58) were treated with duloxetine at a dose of 60 mg once daily, and those relapsing on duloxetine 60 mg once daily (n=29) were treated with duloxetine 60 mg twice daily. Of those patients relapsing on placebo and treated with duloxetine 60 mg once daily, response (50% reduction in

HAMD<sub>17</sub> total score) occurred in 77% and remission (HAMD<sub>17</sub> total score ≤ 7) occurred in 57% at the end of 12 further weeks of treatment. Of those patients who relapsed on duloxetine 60 mg once daily and who were treated with an increased dose of 60 mg twice daily, 62% met response criteria and 38% met remission criteria.

### Use in elderly patients with depression:

The efficacy and safety of duloxetine 60 mg once daily (n=207) and placebo (n=104) have been compared in the acute treatment (study duration 8 weeks) of elderly patients with MDD (>65 years of age, mean age 72.9 years). Duloxetine treated patients experienced improvement in depressive symptoms, as assessed by the Geriatric Depression Scale, from week 1, with least-squares mean changes from baseline to endpoint of -1.34 for placebo-treated patients and -4.07 for duloxetine-treated patients (p<0.001). On the Hamilton Depression Rating Scale, least squares mean changes from baseline to endpoint for total HAMD score were -3.72 for placebo-treated patients and -6.49 for duloxetine-treated patients (p<0.001). Duloxetine treated patients also experienced a greater improvement in composite cognitive score than the placebo-treated patients. The least-squares mean change from baseline to endpoint for the composite cognitive score was 0.76 in placebo-treated patients and 1.95 for duloxetine-treated patients (p=0.013).

### Diabetic Peripheral Neuropathic Pain

The efficacy of duloxetine for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathic pain for at least 6 months. The design of the two studies is summarised in Table 4.

**Table 4: Study Design of Clinical Trials Supporting Efficacy of Duloxetine in the Treatment of DPNP**

Study Code	Design	Duration of Treatment	Treatment and Dose
HMAW-Acute	Parallel, double-blind, Randomised, placebo-controlled	12 weeks	DLX 20 mg QD DLX 60 mg QD DLX 60 mg BID PBO
HMAVa-Acute	Parallel, double-blind, Randomised, placebo-controlled	12 weeks (plus 1 week taper) 52-week extension	DLX 60 mg QD DLX 60 mg BID PBO

BID = twice daily; QD = once daily; DLX = duloxetine; PBO = placebo

Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥ 4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of paracetamol per day as needed for pain, in addition to duloxetine. Patients recorded their pain daily in a diary.

Both studies compared duloxetine 60 mg once daily or 60 mg twice daily with placebo; one study additionally compared duloxetine 20 mg with placebo. A total of 457 patients (342 duloxetine, 115 placebo) were enrolled in study HMAW-acute and a total of 334 patients (226 duloxetine, 108 placebo) were enrolled in study HMAVa-acute.

The weekly average of the 24-hour average pain severity was the primary efficacy measure for the assessment of duloxetine's effectiveness in the treatment of DPNP. Duloxetine 60 mg once daily and duloxetine 60 mg twice daily were both statistically significantly superior to placebo as assessed by the reduction from baseline in the primary efficacy measure, 24-hour average pain severity, as shown in Table 5. In addition, duloxetine 60 mg once daily and duloxetine 60 mg twice daily were statistically significant to placebo as assessed by response rate (whether measured by at least a 30% reduction or at least a 50% reduction in pain score from baseline). Evidence of efficacy from the primary efficacy measure is confirmed by comprehensive results from the secondary pain and DPNP symptom measures.

The secondary efficacy measures that supported the use of duloxetine in the treatment of DPNP were: weekly averages of night pain and 24-hour worst pain from the daily diary, Brief Pain Inventory Severity and Interference (BPI Severity and Interference), Clinical Global Impressions of Severity (CGI-Severity), Patient Global Impression of Improvement (PGI-Improvement) scale, and Sensory portion of the Short-form McGill pain questionnaire. In addition, measures of mood were employed in both placebo controlled studies to demonstrate changes of pain uncontaminated by duloxetine's effect on mood.

**Table 5: Summary of Primary Efficacy in 12 week placebo controlled studies**

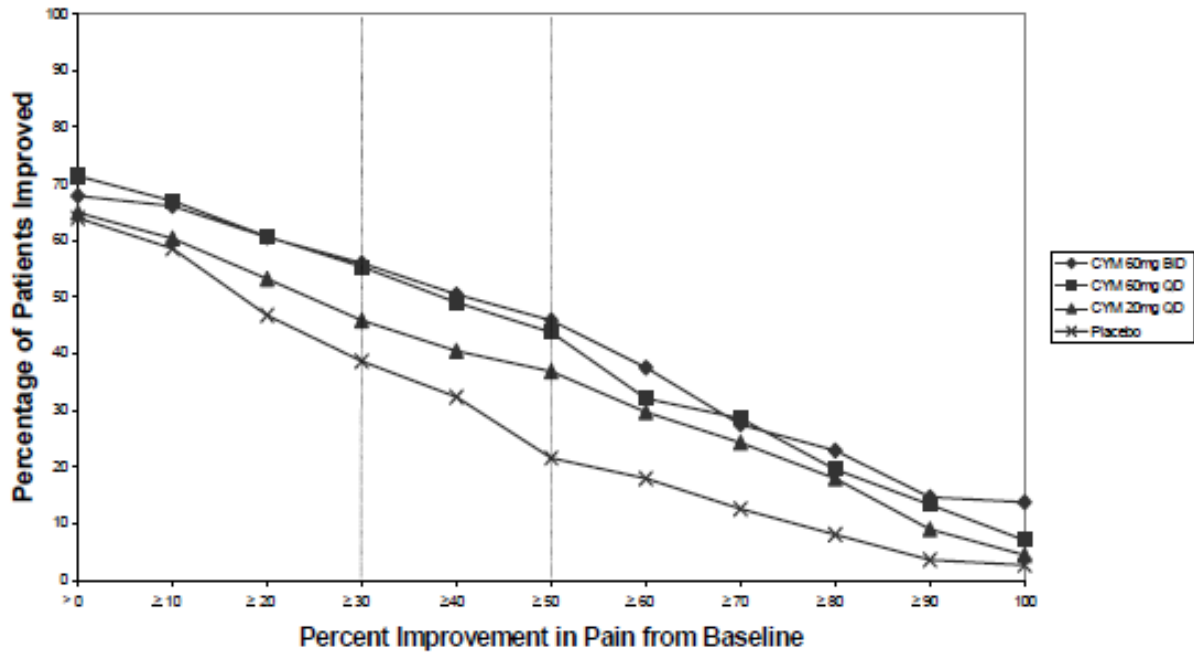
Study HMAVa-acute <sup>1</sup>			Study HMAW-acute <sup>2</sup>			
PBO n=106	DLX60QD n=110	DLX60BI D n=111	PBO n=111	DLX20QD n=111	DLX60QD n=112	DLX60BID n=109
Mean Baseline	5.85	6.12	5.73	5.84	6.01	5.85
Mean Change	-	-2.72	-1.69	-2.14	-2.86	-3.14
1.39	P<0.001	6.21 -2.84 P<0.001		P=0.189	P<0.001	P<0.001

BID = twice daily; QD = once daily; DLX = duloxetine; PBO = placebo; n = number of patients with a baseline score and at least one non-missing postbaseline score

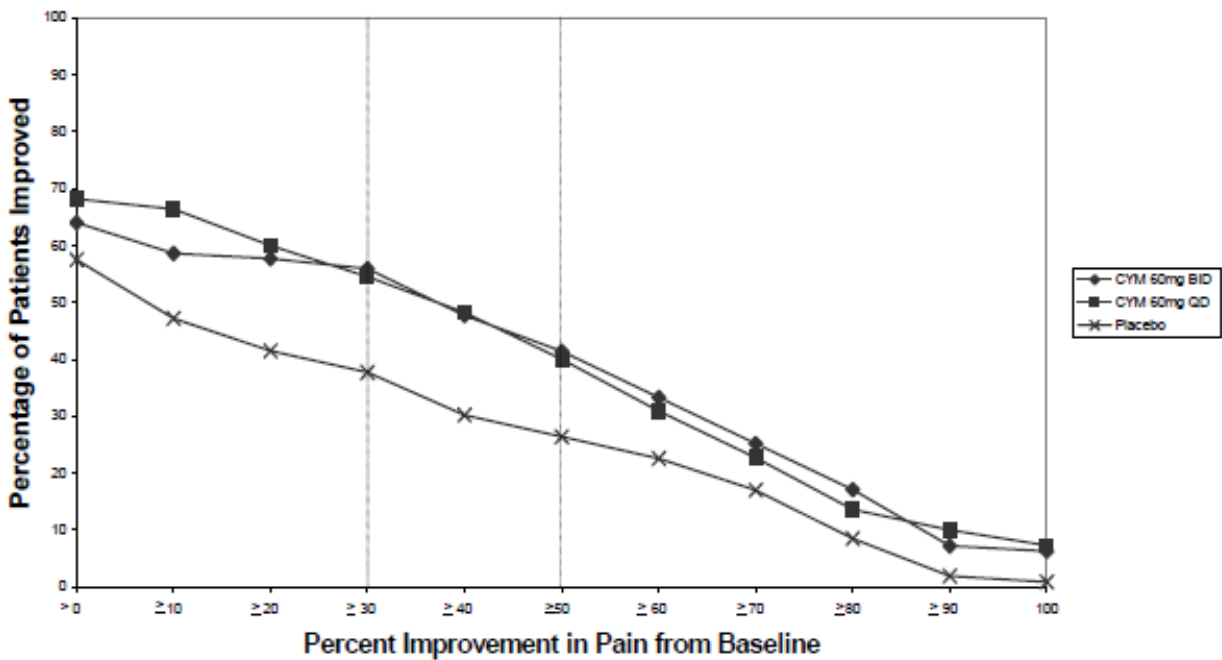
<sup>1</sup> Seven patients did not have either a baseline or post-baseline measurement and were not included in primary efficacy analysis

<sup>2</sup> 15 patients did not have either a baseline or post-baseline measurement and were not included in primary efficacy analysis

For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement for each study. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.



**Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study HMAW-acute**



**Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study HMAVa-acute**

In an open label long term uncontrolled study, pain reduction in patients responding to 8 weeks of acute treatment with duloxetine 60 mg once daily was maintained for a further 6 months as measured by change on the Brief Pain Inventory 24-hour average pain item. Patients who did not respond to 60 mg once daily in the acute phase or maintenance phase and were treated with duloxetine 120 mg once daily showed a decrease in pain intensity from baseline to endpoint.

## General Anxiety Disorder

The efficacy of duloxetine has been established in 5 Phase 3 clinical trials. Four of the studies were acute placebo-controlled studies and the fifth was a relapse prevention study. Of the four placebo controlled studies one was a fixed dose study while the other three were flexible dose studies.

Study HMBR (fixed dose) was a randomised double blind trial designed to assess whether duloxetine 120mg once daily (QD) was superior to placebo in the treatment of GAD as measured by the mean change in Hamilton Anxiety Depression Rating Scale (HAMA) during the 9-week, double-blind, acute therapy phase. A key secondary objective was to assess whether duloxetine 60mg QD was superior to placebo in the treatment of GAD during the 9-week, double blind acute therapy phase.

Studies HMDT, HMDU and HMDW, respectively, were Phase 3 (flexible dose) randomised double-blind placebo-controlled studies that used the same primary objective: to assess whether duloxetine flexibly dosed from 60 mg to 120 mg QD was superior to placebo in the treatment of GAD as measured by mean change in HAMA total score over 10 weeks. Venlafaxine 75 mg to 225 mg QD was used as an active comparator in studies HMDU and HMDW and data from these trials was combined (designed a priori) to have sufficient power for non-inferiority comparison of duloxetine with venlafaxine. For all 3 studies doses were increased at specified visits if the CGI Improvement score remained at 3 or below or minimally improved.

In all 4 acute placebo controlled studies the mean decrease in HAMA total score was significantly greater for duloxetine-treated patients compared with placebo treated patients as shown in Table 6.

**Table 6: Summary of Primary Efficacy in acute placebo-controlled GAD studies**

Study/duration	Treatment Group	N	Baseline	Endpoint	LSMean Change	p-value vs placebo
HMBR 9 weeks	Duloxetine 60 mg QD	165	25.05	12.32	-12.8	<0.001
	Duloxetine 120 mg QD	169	25.13	12.74	-12.5	<0.001
	Placebo	173	25.82	17.19	-8.4	-
HMDT 10 weeks	Duloxetine 60 to 120 mg QD	161	22.54	14.27	-8.1	0.023
	Placebo	158	23.49	17.00	-5.9	-
HMDU 10 weeks	Duloxetine 60 to 120 mg QD	149	25.77	13.95	-11.8	0.007
	Venlafaxine 75 to 225 mg QD	159	24.92	12.90	-12.4	<0.001
	Placebo	158	24.98	16.06	-9.2	-
HMDW 10 weeks	Duloxetine 20 mg QD	83	27.65	12.49	-14.7	0.007
	Duloxetine 60 to 120 mg QD	151	27.74	11.85	-15.3	<0.001
	Placebo	158	27.36	11.66	-15.5	<0.001
	Venlafaxine 75 to 225 mg QD	163	27.33	15.77	-11.6	-

QD = once daily;

Duloxetine at the recommended dose of 60 mg to 120 mg once daily demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score.



Response and remission rates were also higher with duloxetine compared to placebo. Duloxetine showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In study HMDV, a relapse prevention study, patients responding to 6 months of acute treatment with open-label duloxetine were randomised to either duloxetine or placebo for a further 6-months. Duloxetine 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo ( $p < 0.001$ ) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for duloxetine and 42% for placebo.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

In humans, orally administered duloxetine hydrochloride is well absorbed with maximal plasma concentrations ( $C_{max}$ ) of duloxetine occurring 6 hours post dose. Food does not affect the  $C_{max}$  of duloxetine, however food can delay the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 11%.

Duloxetine plasma exposure increases in proportion to dose for doses up to 60 mg twice a day. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Based upon AUC, multiple once daily doses of 60 mg produce steady-state concentrations that are approximately 1.5 times higher than that predicted from a 60 mg single dose. Average minimum and maximum steady-state concentrations for the 60 mg once daily dose are 27.0 and 89.5 ng/mL, respectively. There is no clinically important difference in the pharmacokinetic parameters of morning and evening doses.

### Distribution

Following oral administration, the apparent volume of distribution of duloxetine averages 1640 L. Duloxetine is highly protein bound (>90%) to plasma proteins but protein binding is not affected by renal or hepatic impairment. Duloxetine binds to both albumin and  $\alpha$ 1-acid glycoprotein.

### Metabolism

Duloxetine undergoes extensive metabolism. The 2 major metabolites found in plasma and urine are the glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. Both CYP2D6 and CYP1A2 catalyse the formation of the initial oxidation steps to form 4-, 5-, and 6-hydroxy duloxetine. The metabolites circulating in plasma are in the conjugated form and are not pharmacologically active.

### Excretion

The half-life of duloxetine (unchanged drug) is 12.1 hours. Apparent plasma clearance of duloxetine after an oral dose is 101 L/hr. The majority (70%) of the duloxetine dose is recovered in the urine as conjugated metabolites of oxidative metabolites of duloxetine.

Approximately 20% of the dose is recovered in the faeces as unchanged drug, unconjugated metabolites, or unidentified compounds. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine.

### Special Populations

*Gender* - Apparent plasma clearance was lower in females, however this difference in clearance values does not appear to be clinically significant. The mean half-life of duloxetine was similar between males and females. Dosage adjustment based on gender is not necessary.

*Elderly* - Population pharmacokinetic analyses suggest no significant effect of age on the pharmacokinetics of duloxetine in adult male and female patients with major depressive disorder. Dosage adjustment based on age is not necessary for elderly patients.

*Children and Adolescents <18 years old* - Duloxetine is not indicated for use in children and adolescents <18 years old.

*Race* - No specific pharmacokinetic study was conducted to investigate the effects of race. Due to large interpatient variability, clinically significant differences in drug level exposure among ethnic groups are not likely.

*Smoking Status* – Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

### **Renal Impairment**

Duloxetine C<sub>max</sub> and AUC values were approximately 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent dialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. A lower dose should be used for patients with ESRD (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on apparent plasma clearance of duloxetine.

### **Hepatic Impairment**

Mean duloxetine apparent plasma clearance of patients with moderate cirrhosis of the liver was approximately 15% of that of healthy subjects. The C<sub>max</sub> was similar but the half-life was 34 hours longer. Duloxetine is contraindicated in patients with hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

Duloxetine demonstrated no genotoxic potential in a battery of in vitro and in vivo tests, including assays for gene mutation, chromosomal effects, unscheduled DNA synthesis, and sister chromatid exchange.

### **Carcinogenicity**

Duloxetine was administered in the diet to rats and mice for two years. In rats and male mice there was no increase in the incidence of tumours. In female mice, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day which is 5 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis). These findings were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation and their relevance to humans is unknown.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

TIXOL 30 mg capsules contain gelatin (bovine), hypromellose, hypromellose phthalate, indigo carmine, purified talc, sucrose, Sugar Spheres PI (ARTG PI No: 2535), Tekprint SB-4020 Green Ink (ARTG PI No: 2852), titanium dioxide, triethyl citrate, ascorbic acid.

TIXOL 60 mg capsules contain gelatin (bovine), hypromellose, hypromellose phthalate, indigo carmine, iron oxide yellow, purified talc, sucrose, Sugar Spheres PI (ARTG PI No: 2535), Tekprint SW-0012 White ink (ARTG PI No: 13175), titanium dioxide, triethyl citrate, ascorbic acid.

### **6.2 INCOMPATIBILITIES**

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Antacids and H<sub>2</sub> Antagonists and Drugs That Affect Gastric Acidity.

Other 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. Store in Original Container

### 6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC- PCTFE (Aclar)/AL or AL/AL foil blister packs.

Pack sizes: 28 enteric capsules.

Some strengths, pack sizes and/or pack types may not be marketed.

### Australian Register of Therapeutic Goods (ARTG)

AUST R 428623 - TIXOL 30 duloxetine (as hydrochloride) 30 mg enteric capsule blister pack

AUST R 428624 - TIXOL 60 duloxetine (as hydrochloride) 60 mg enteric capsule blister pack

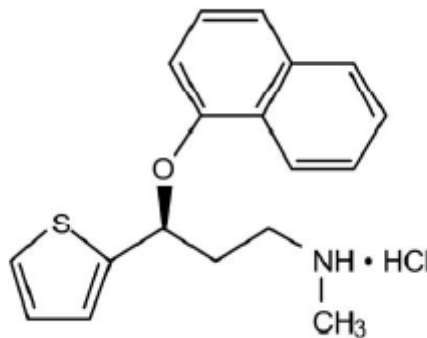
### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical Structure

Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) for oral administration. It is chemically unrelated to tricyclics, alpha adrenergic receptor agonists or antimuscarinics. The chemical name is (+)-(S)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride. Its structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

**Molecular formula:** C<sub>18</sub>H<sub>19</sub>NOS.HCl

**Molecular weight:** 333.88

**CAS Number:** 136434-34-9

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8 SPONSOR

### Alphapharm Pty Ltd trading as Viatris

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## 9 DATE OF FIRST APPROVAL

14/06/2013

## 10 DATE OF REVISION

02/09/2024

### Summary Table of Changes

Section Changed	Summary of New Information
4.4	Addition of safety information regarding sexual dysfunction Addition of safety information regarding risk of Postpartum haemorrhage Minor editorial changes
4.6	Addition of safety information regarding risk of Postpartum haemorrhage
4.8	Addition of safety information regarding risk of Postpartum haemorrhage and stress cardiomyopathy (Takotsubo cardiomyopathy)

TIXOL® is a Viatris company trade mark

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