

## IXEL 25 MG, HARD CAPSULE PIERRE FABRE MEDICAMENT

### 1. NAME OF THE MEDICINAL PRODUCT

IXEL 25 mg, hard capsule

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg Milnacipran hydrochloride, equivalent to 21.77 mg Milnacipran free base.

For excipients, see 6.1.

### 3. PHARMACEUTICAL FORM

Hard capsule.

Pink cap and body, imprinted with « Ixel 25 ».

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic Indications

Treatment of major depressive episodes in adults.

#### 4.2 Posology and Method of Administration

##### Dosage and Method of Administration

Recommended dosage is 100 mg a day in two divided 50 mg doses, 1 capsule morning and evening preferably during meals.

In this case, use the 50 mg capsules.

In the elderly, dosage adjustment is not necessary as long as renal function is normal.

(see Pharmacokinetic properties).

In patients with renal failure, dosage adjustment is necessary.

The recommended dosage is reduced to 50 or 25 mg depending on the degree of alteration of renal function (see Pharmacokinetic properties).

In this case, use 25 mg capsules.

The following dosage adjustment is recommended:

Creatinine clearance (Clcr) (ml/min)	Dosage /24 h
Clcr *60	50 mg x 2
60 > Clcr *30	25 mg x 2
30 > Clcr *10	25 mg

##### Duration of treatment:

Treatment with antidepressants is symptomatic.

As with all antidepressants, the efficacy of

Milnacipran only becomes apparent after a certain delay which can vary from 1 to 3 weeks.

For one episode treatment should last for several months (usually about 6 months) in order to prevent relapses.

Milnacipran treatment should be discontinued gradually.

##### Associated psychotropic treatments:

Concomitant prescription of a sedative or anxiolytic medication can be useful at the start of treatment to prevent occurrence or worsening of symptoms of anxiety.

But anxiolytics do not necessarily protect the patient from suicide attempts.

#### 4.3 Contra-indications

This medication should never be used in the following cases:

- known hypersensitivity to Milnacipran;
- association with non-selective MAO inhibitors, B selective MAO inhibitors, digitalis and 5 HT1D agonists (sumatriptan...) (See Interactions with other medicaments);
- lactation.
- uncontrolled hypertension, severe or unstable coronary heart disease as these underlying condition may be compromised by increases in blood pressure or heart rate.

Generally, this medication should not be used in the following cases:

- in association with epinephrine and norepinephrine by parenteral route, clonidine and related compounds and A selective MAO inhibitors, (see Precautions for use and Interactions with other medicaments);
- prostatic hypertrophy and other genito-urinary disorders;

#### 4.4. Special warnings and special precautions for use

##### Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of

*PIERRE FABRE-Ixel 25mg, Hard Capsule - p.1/7*

suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

#### Use in children and adolescents under 18 years of age

Milnacipran should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

#### Precautions for Use

Patients with insomnia or nervousness at the begin-

ning of treatment may require transient symptomatic therapy.

If a patient experiences a switch into frank mania, treatment with Milnacipran should be discontinued and in most cases a sedative antipsychotic agent prescribed.

Although no interaction with alcohol has been evidenced, it is recommended to avoid alcohol intake, just as with any psychotropic medication.

Systemic body exposure to Milnacipran is increased by 20% when combined with levomepromazine in healthy volunteers. A higher increase may be suspected in elderly or renal impairment patients if the drugs are to be combined.

Milnacipran should be prescribed with caution in the following cases:

*- in patients with renal failure:*

Dosage may have to be reduced because of prolongation of elimination half-life (see Posology and method of administration);

*- in patients with a history of difficult passage of urine, notably in patients with prostatic hypertrophy and other genito-urinary disorders.*

Because of the noradrenergic component of the mechanism of Milnacipran action, a monitoring of the miction disorders is necessary;

*- in patients with hypertension or cardiac disease:*

Blood pressure and heart rate monitoring is recommended at treatment initiation, following dosage increases and periodically throughout the treatment with milnacipran for all patients and more closely in patients with known cardiovascular risk

*- in patients with narrow-angle glaucoma.*

*- in patients with epilepsy or with a history of epilepsy:*

Milnacipran should be used with caution and should be discontinued in any patient developing a seizure.

There have been cases of hyponatremia in patients receiving serotonin re-uptake inhibitors, possibly due to the syndrome of inappropriate antidiuretic hormone secretion. Caution is advised in elderly, patients taking diuretics or other treatment known to induce hyponatremia, patients with cirrhosis or malnutrition.

Cases of haemorrhages, sometimes serious, have been reported with the use of serotonin re-uptake inhibitors. Caution should be exercised in patients concomitantly treated with oral anticoagulants, drugs which have an effect on platelet function, e.g. NSAIDs and aspirin, or other drugs that may increase the risk of bleeding. Caution is also required in patients with previous bleeding abnormalities.

#### 4.5. Interactions with other medication and other forms of interaction

##### COMBINATIONS CONTRA-INDICATED:

- **With non selective MAO inhibitors (iproniazide)**

Risk of a serotonergic syndrome\* (see below).

There should be an interval of two weeks between the end of treatment with a MAO inhibitor and the beginning of treatment with Milnacipran, and at least one week between the end of treatment with Milnacipran and the beginning of treatment with a MAO inhibitor.

- **\*Serotonergic syndrome:**

Some cases of drug overdosage or certain medications (lithium) can cause a serotonergic syndrome requiring immediately termination of therapy with Milnacipran.

The serotonergic syndrome consists of the simultaneous or sequential development (sometimes sudden) of a constellation of symptoms which may require hospitalization or even cause death.

The following symptoms may occur:

- psychiatric (agitation, confusion, hypomania, possibly coma),
- motor (myoclonus, tremor, hyperreflexia, rigidity, hyperactivity),
- vegetative (hypo-or hypertension, tachycardia, chills, hyperthermia, sweating),
- gastrointestinal (diarrhea).

Strict compliance with the dosage prescribed is an essential factor in preventing the onset of this syndrome.

- **With B Selective MAO inhibitors (selegiline)**

Risk of paroxystic hypertension.

There should be an interval of two weeks between

the end of treatment with a B selective-MAO inhibitor and the beginning of treatment with Milnacipran and at least one week between the end of treatment with Milnacipran and the beginning of treatment with a B-MAO inhibitor.

- **With 5 HT1D agonists (sumatriptan...)**

By extrapolation with selective inhibitors of serotonin re-uptake.

Risk of hypertension, coronary artery vasoconstriction by additive serotonergic effects.

Wait one week between the end of treatment with Milnacipran and the beginning of treatment with 5 HT1D agonists.

- **With digitalis (digoxin...)**

Risk of potentiation of haemodynamic effects, in particular by parenteral route.

##### UNADVISABLE COMBINATIONS

- **With epinephrine, norepinephrine (alpha and beta sympathomimetics)**

In case of systemic action by parenteral route.

Paroxystic hypertension with possible arrhythmia (inhibition of entry of epinephrine or norepinephrine into the sympathetic nerve fiber).

- **With clonidine and related compounds (reported with desipramine and imipramine)**

Inhibition of clonidine's antihypertensive effect (antagonism with adrenergic receptors).

- **With A selective MAO inhibitors (moclobemide, toloxatone)**

Risk of development of a serotonergic syndrome\* (see above).

If this combination cannot be avoided, monitor patient very carefully.

Initiate such a combination with the lowest recommended dose.

##### ASSOCIATIONS REQUIRING PRECAUTIONS FOR USE:

- **With epinephrine, norepinephrine (alpha and beta sympathomimetics)**

When hemostatic action by subcutaneous or gingival injection is sought:

Paroxystic hypertension with possible arrhythmia

Very Common >=10%	Common >=1% to 10%	Uncommon >=0.1% to 1%	Rare < 0.1%	Unknown
<b>Blood and lymphatic system disorders</b>				
				Echymosis <sup>(1)(3)</sup> – Cutaneous or mucous membrane bleedings <sup>(1)(3)</sup>
<b>Immune system disorders</b>				
		Hypersensitivity	Anaphylactic shock	
<b>Endocrine disorders</b>				
			Inappropriate antidiuretic hormone secretion	
<b>Metabolism and nutrition disorders</b>				
		Hyperlipidaemia, Weight decreased		hyponatremia <sup>(1)(3)</sup>
<b>Psychiatric disorders</b>				
	Agitation - Anxiety, Depression, Eating disorder, Sleep disorder, Suicidal behaviour	Panic attack, Confusional state, Delusion, Hallucination, Mania, Libido decreased, Nightmare, Suicidal ideation	Derealisation - Thinking abnormal, Psychotic disorder	
<b>Nervous system disorders</b>				
Headache	Migraine, Tremor, Dizziness - Dyaesthesia, Somnolence	Memory impairment, Akathisia, Balance disorder, Dysgeusia, Syncope	Cerebrovascular accident, Dyskinesia, Parkinsonism, Convulsion	Serotonin syndrome <sup>(1)(7)</sup> , Convulsion <sup>(1)(2)</sup>
<b>Eye disorders</b>				
		Dry eye - Eye pain, Mydriasis, Accommodation disorder, Vision blurred, Visual impairment		
<b>Ear and labyrinth disorders</b>				
		Tinnitus, Vertigo		
<b>Cardiac disorders</b>				
	Tachycardia, Palpitations	Arrhythmia, Bundle branch block, Extrasystoles, Myocardial infarction	Angina pectoris	
<b>Vascular disorders</b>				
	Hot flush, Hypertension	Raynaud's phenomenon, Hypotension, Orthostatic hypotension		
<b>Respiratory, thoracic and mediastinal disorders</b>				
		Cough - Dyspnoea		
		Nasal dryness - Pharyngeal disorder		
<b>Gastrointestinal disorders</b>				
Nausea	Constipation, Diarrhoea, Abdominal pain, Dyspepsia, Vomiting, Dry mouth	Colitis, Gastritis, Gastrointestinal motility disorder, Abdominal discomfort, Abdominal distension, Gastroduodenal ulcer, Haemorrhoids, Stomatitis		
<b>Hepatobiliary disorders</b>				
		Hepatic enzyme increased	Hepatitis, Hepatocellular injury	cytolytic hepatitis <sup>(1)</sup>
<b>Skin and subcutaneous tissue disorders</b>				
	Pruritus, Rash, Hyperhidrosis	Urticaria, Dermatitis, Dermatosi	Photosensitivity reaction	
<b>Musculoskeletal and connective tissue disorders</b>				
	Musculoskeletal pain	Muscle rigidity, Myalgia		
<b>Renal and urinary disorders</b>				
	Dysuria, Pollakiuria	Chromaturia, Urinary incontinence, Urinary retention		
<b>Reproductive system and breast disorders</b>				
	Ejaculation disorder, Erectile dysfunction, Testicular pain	Amenorrhoea, Menorrhagia, Menstrual disorder, Metrorrhagia, Prostatic disorder		
<b>General disorders and administration site conditions</b>				
	Fatigue	Pyrexia, Chest pain, Chills, Feeling abnormal, Malaise		

(1) Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

(2) Observed especially in patients with past history of epilepsy

(3) See section 4.4

(inhibition of entry of epinephrine or norepinephrine into the sympathetic nerve fiber).

Limit intake, for example, to less than 0.1 mg epinephrine in 10 minutes or 0.3 mg in an hour, in adults.

• **With Lithium**

Risk of development of serotonergic syndrome\* (see above).

Perform regular clinical monitoring of the patient.

**4.6. Pregnancy and lactation**

There are no adequate data from the use of Milnacipran in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respects to pregnancy, embryonal/foetal development, parturition or postnatal development (see Preclinical safety data).

Neonatal risk after pregnancy exposure with serotonin re-uptake inhibitors have been reported and may be related to either withdrawal syndrome or serotonin toxicity: tachypnea, feeding difficulties, tremors, hypertonicity or hypotonia, sleeping disorders, hyperexcitability or more rarely longlasting crying. All these signs appear in the first days of life and are generally of short duration and not severe.

Consequently, as a precautionary measure, it is preferable to not administer Milnacipran during pregnancy.

Because small amounts of Milnacipran are excreted in breast-milk, breast-feeding is contraindicated.

**4.7. Effects on ability to drive and use machines**

Although no alterations in cognitive or psychomotor functions have been observed in healthy volunteers, this medication can diminish mental and physical capacities necessary to perform certain dangerous tasks, such as operating machinery or driving motor vehicles.

**4.8. Undesirable effects**

The undesirable effects observed during treatment with Milnacipran are observed mainly during the first week or first two weeks of treatment and subsequently regress, concomitantly with improvement in the depressive episode.

The following table gives the adverse events for

which the causality assessment was not “excluded” observed in thirteen clinical studies, including 5 placebo-controlled clinical trials (comprising a total of 3,059 patients - 2,557 on milnacipran and 502 on placebo) in depressive patients.

The most commonly reported adverse drug reactions in depressive patients treated with IXEL® in clinical trials were nausea, and headache.

**Table of adverse reactions**

Frequency estimate:

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data). No adverse drug reaction are “very rare” in frequency and therefore the column “very rare” is not represented in the table.

(\*) A serotonin syndrome, particularly when milnacipran medication is combined with other agents (see section 4.5.), characterised by at least three symptoms including changes in psychiatric status and behaviour (excitement, confusion, anxiety, agitation, delirium and restlessness), motor dysfunction (tremor, rigidity, myoclonus, hyperreflexia, and ataxia), hypotension or hypertension and autonomic symptoms such as sweating, fever, shivering and diarrhoea may occur.

Cases of suicidal behaviour and suicidal ideation have been reported during IXEL® therapy or early after treatment discontinuation (see section 4.4).

Some other adverse reactions reported during the post-marketing experience in depressed patients were related to the depressive illness:

- o elimination of psychomotor inhibition, with suicidal risk
- o mood switch, with episodes of mania
- o reactivation of a delusion in psychotic patients
- o paroxysmic symptoms of anxiety (with psychostimulant antidepressants).

**4.9. Overdose**

A few cases of overdosage have been observed with Milnacipran.

With high doses, the emetic effect can considerably limit the risk of overdosage.

With a 200 mg dose, the following events have commonly been observed (> 10%): nausea, excessive sweating, and constipation.

With doses of 800 mg to 1 g in single-drug therapy, the main symptoms observed are vomiting, respiratory difficulties (apneic spells), and tachycardia.

After a massive dose (1.9 g to 2.8 g), in combination with other drugs (in particular, benzodiazepines), the following additional symptoms occur: drowsiness, hypercapnia and alterations of consciousness.

#### *Treatment of overdose:*

There is no specific antidote for Milnacipran.

Treatment is symptomatic, with gastric lavage and activated charcoal as soon as possible after oral ingestion. Medical monitoring should be continued for at least 24 hours.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

ANTIDEPRESSANT.

OTHER ANTIDEPRESSANTS

ATC class : N06A X17

Milnacipran is a dual inhibitor of (5 HT) serotonin and norepinephrine re-uptake.

Unlike most tricyclic antidepressants, Milnacipran has no affinity for  $\alpha_1$  adrenergic or  $H_1$  histaminergic receptors.

Binding experiments suggest that Milnacipran has no significant affinity for cholinergic (muscarinic) receptors.

Furthermore, Milnacipran also has no affinity for D1 and D2 dopaminergic receptors, benzodiazepine and opioid receptors.

In humans:

- at therapeutic doses, plasma concentrations observed are consistently at levels corresponding to 50% to 90% inhibition of norepinephrine and serotonin re-uptake.
- the pharmacologic effects observed in the gastrointestinal and genito-urinary systems appear to be related to inhibition of norepinephrine re-uptake which can exert an antagonistic effect on acetylcholine (indirect anticholinergic effect).
- Milnacipran does not induce any significant clinical change in cardiac repolarization or conduction.

- it does not affect cognitive function and has little sedative effect.

- sleep disturbances improve in depressive patients treated with Milnacipran.

The latency time to fall asleep is decreased and also the number of nightly awakenings and the latency for onset of paradoxal sleep are increased.

Total duration of sleep is increased.

The efficacy of Milnacipran was compared to that of SSRI and tricyclics and found to be less than that of clomipramine.

### 5.2. Pharmacokinetic properties

#### Absorption

Milnacipran is well-absorbed after oral administration.

Bioavailability is about 85%.

It is unchanged by food intake.

Peak plasma concentrations ( $C_{max}$ ) are reached approximately two hours ( $T_{max}$ ) after an oral dose.

This concentration is about 120 ng/ml after a single 50 mg dose.

Concentrations are dose-related up to 200 mg per administration.

After repeated dose administration, the steady state is reached within 2 to 3 days with an increase in concentration of about 70% to 100% compared to a single dose

( $C_{max}$ : 216 ng/ml).

Inter-individual variability is low.

#### Distribution

Protein binding is low (13%) and not saturable.

The volume of distribution of Milnacipran is about 5 l/kg with a total clearance of about 40 l/hour.

Renal and non-renal clearances are equivalent.

#### Biotransformation

Milnacipran is metabolized mainly by glucuronic acid conjugation.

Active metabolites have been found at very low levels without clinical relevance.

#### Elimination

Plasma elimination half-life is about 8 hours.

Elimination occurs mainly via the kidney (90% of the dose administered) with tubular secretion of the product in unchanged form.

After repeated doses, Milnacipran is totally eliminated two to three days after termination of therapy.

### High-risk Patients

#### Patients with impaired liver function.

Impairment of hepatic function does not cause any significant changes in Milnacipran's pharmacokinetic parameters.

#### Patients with renal failure

In case of renal failure, Milnacipran is eliminated more slowly, in proportion to the degree of renal function alteration (see Dosage and method of administration).

#### Patients over age 65 years

Milnacipran's pharmacokinetic parameters are not significantly altered in the elderly. However, physiological alteration of renal function should be taken into account (see Dosage and method of administration).

### 5.3. Preclinical safety data

With repeated dose administration, the liver is the target organ in all animal species studied. The first effects develop with high doses, about 10 times the dose used in clinical practice and are reversible.

Milnacipran is neither mutagenic nor carcinogenic.

Experimental data do not reveal any teratogenic or foetotoxic potential of Milnacipran.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Calcium hydrogen phosphate dihydrate

Carmellose calcium

Povidone K30

Anhydrous colloidal silica

Magnesium stearate

Talc

#### Capsule shell:

Cap and Body (pink): titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), gelatin.

### 6.2. Incompatibilities

Not applicable

### 6.3. Shelf-life

3 years

### 6.4. Special precautions for storage

Do not store above 30°C.

### 6.5. Nature and content of the container

14 capsules in blister (PVC-Aluminium)

28 capsules in blister (PVC-Aluminium)

56 capsules in blister (PVC-Aluminium)

112 capsules in blister (PVC-Aluminium)

14 capsules in a bottle (PP) with a stopper (PE)

28 capsules in a bottle (PP) with a stopper (PE)

56 capsules in a bottle (PP) with a stopper (PE)

112 capsules in a bottle (PP) with a stopper (PE)

Not all pack sizes may be marketed.

## 7. MARKETING AUTHORIZATION HOLDER

PIERRE FABRE MEDICAMENT

45, place Abel Gance

92100 Boulogne

FRANCE

## 9. DATE OF FIRST AUTHORIZATION

6th December 1996

## 10. DATE OF APPROVAL/ REVISION

June 2012