To be sold by retail on the prescription of a Psychiatrist only

MILNACE

(Milnacipran Hydrochloride Tablets 25 mg & 50 mg)

COMPOSITION

MILNACE 25

Each film coated tablet contains:
Milnacipran Hydrochloride 25.00 mg
equivalent to Milnacipran free base 21.77 mg
Colors : Red Oxide of Iron and Titanium Dioxide I.P.

MILNACE 50

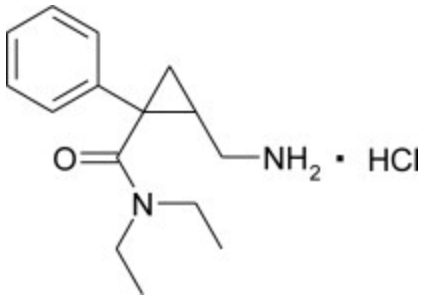
Each film coated tablet contains:
Milnacipran Hydrochloride 50.00 mg
equivalent to Milnacipran free base 43.55 mg
Colors: Red Oxide of Iron and Titanium Dioxide I.P.

DOSAGE FROM

Film coated tablet

Chemical Name: (±)-Cis-2-(aminomethyl)-N,N-diethyl- 1-phenyl-cyclopropane-1-carboxamide hydrochloride.

Empirical Formula: $C_{15}H_{22}N_2O.HCl$
Molecular Mass: 282.46



Solubility: Freely soluble in water and methanol.

INDICATIONS

Treatment of major depressive episodes in adults.

DOSAGE AND METHOD OF ADMINISTRATION

Usual starting dose is 50 mg once daily or in divided dose. Recommended dosage is 100 mg a day in two divided 50 mg doses, one tablet morning and evening preferably during meals.

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.

Use in Special Population
Pregnant and Lactating Women: In the absence of demonstrated teratogenic effects in animals, malformations in humans are not expected. Consequently, as a precautionary measure, it is preferable not to administer Milnacipran during pregnancy. Because small amounts of Milnacipran are excreted in breast-milk, breast-feeding is contraindicated. Elderly patients: In the elderly, dosage adjustment is not necessary as long as renal function is normal.

Patients with renal failure: 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.

Creatinine Clearance(CLcr) (ml/min)	Dosage/24 h
CLcr 60	50 mg × 2
60 > CLcr 30	25 mg × 2
30 > CLcr 10	25 mg

Paediatric patients:
No clinical data available for use of milnacipran in paediatric population, thus, not recommended.

CONTRAINDICATION
This medication should never be used in the following
cases:
-Known hypersensitivity to Milnacipran;
-Children under 15 years of age, in the absence of clinical data;
-Association with non-selective MAO inhibitors, B selective MAO inhibitors, digitalis and 5 HT1D agonists (i.e. Sumatriptan);
- Lactation.
Generally, this medication should not be used in the following cases:
-In association with epinephrine and nor-epinephrine by parenteral route, clonidine and related compounds.
- A selective MAO inhibitors;

-Prostatic hypertrophy and othergenito – urinary disorders;
- Pregnancy.

WARNINGS
As in treatment with other antidepressants, suicide attempts in patients suffering from depression persist at the start of treatment, since the effect on psychomotor inhibition may precede the antidepressant action of this medication.

PRECAUTIONS FOR USE
Patients with insomnia or nervousness at the beginning 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.

- In patients with renal failure dosage may have to bereduced because of prolongation of elimination half-life.
- 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;
It is recommended to increase the clinical monitoring, since milnacipran can slightly increase heart rate in some patients.
- Milnacipran could aggravate narrow-angle glaucoma,thus use cautiously.
- 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 inhibitor. 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.

Associations requiring precautions for use:
With epinephrine, norepinephrine (alpha and beta sympathomimetics):
When hemostatic action by subcutaneous or gingival injection is sought: Paroxystic hypertension withpossible arrhythmia (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 serotoninergis syndrome (See Drug interaction). Perform regular clinical monitoring of the patient.

DRUG INTERACTION

With non-selective MAO inhibitors (e.g. iproniazide):

Risk of a serotoninergic syndrome.

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 MAO inhibitor.

Serotoninergic syndrome:

Some cases of drug overdose or certain medications (lithium) can cause a serotoninergic syndrome requiring immediately termination of therapy with milnacipran. The serotoninergic 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 (diarrhoea).

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

With selective MAO-B inhibitors (e.g. selegiline):

Risk of paroxystic hypertension:

There should be an interval of two weeks between the end of treatment with a selective MAO B 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-B inhibitor.

With 5 HT1D agonists (e.g. sumatriptan):

By extrapolation with selective inhibitors of serotonin re-uptake. Risk of hypertension, coronary artery vasoconstriction by additive serotoninergic effects. Wait one week between the end of treatment with Milnacipran and the beginning of treatment with 5 HT1D agonists.

With digitalis:

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

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 selective MAO-A inhibitors (e.g. moclobemide, toloxatone):
Risk of development of a serotoninergic syndrome. If this combination cannot be avoided, monitor patient very carefully. Initiate such a combination with the lowest recommended dose.

UNDESIRABLE EFFECT
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. Such effects generally are mild and only rarely result in discontinuation of therapy. The most commonly reported adverse events with single-drug therapy or in case of combination withother psychotropic agents during clinical trials and occurring less commonly in patients treated with placebo are vertigo, excessive sweating, anxiety, hotflush, and dysuria. Less frequent adverse events reported are nausea, vomiting, dry mouth, constipation, tremor, palpitations, agitation, headache, urticaria, rash sometimes macula papular or erythematous and pruritus. It is to be noted that patients with a history of cardiovascular disorder or concomitant cardiac medication might have a higher incidence of cardiovascular adverse events (e.g., hypertension, hypotension, postural hypotension, tachycardia and palpitations). In rare instances, the following can occur:
- a serotoninergic syndrome, when combined with other agents;
- moderate elevation of transaminases;
- urinary retention;
- convulsions particularly in patients with past history of epilepsy;
- testicular pain, ejaculation disorders.

In exceptional instances, the following can occur:
- hyponatremia;
- ecchymosis and other cutaneous or mucous bleedings. Furthermore, some adverse events are related to the very nature of the depressive illness:
- elimination of psychomotor inhibition, with suicidal risk,
- mood switch, with episodes of mania,
- reactivation of a delirium in psychotic patients,
- paroxystic symptoms of anxiety (with psychostimulant antidepressants)

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 (i.e. benzodiazepines), the following additional symptoms occur: drowsiness, hypercapnia and alterations of consciousness. No cardiac toxicity has been reported.

Treatment of overdosage:
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.

PHARMACODYNAMIC & PHARMACOKINETIC PROPERTIES

Pharmacodynamics:

Milnacipran is a dual inhibitor of serotonin and norepinephrine re-uptake. Unlike most tricyclic antidepressants, milnacipran has no affinity for ' 1 adrenergic or H1 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 gastro- intestinal and genito-urinary systems appear to be related to inhibition of norepinephrine re-uptake which can exert an antagonistic effect on acetyl choline (indirect anticholinergic efect).
- 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.

Pharmacokinetics:

Absorption

Milnacipran is well-absorbed after oral administration. Bioavailability is about 85%. It is unchanged by food intake. Peak plasma concentrations (Cmax) are reached approximately two hours (Tmax) after an oral dose. The 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 (Cmax : 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.

Metabolism

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.

Special population
Patients with impaired liver functions: 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).

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store at a temperature not exceeding 30OC, protected from moisture.
Keep out of reach of children

PRESENTATION
Milnace 25 & 50 are available in blister of 10 tablets.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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IN/MILNACE 25,50mg/SEPT-15/01/PI