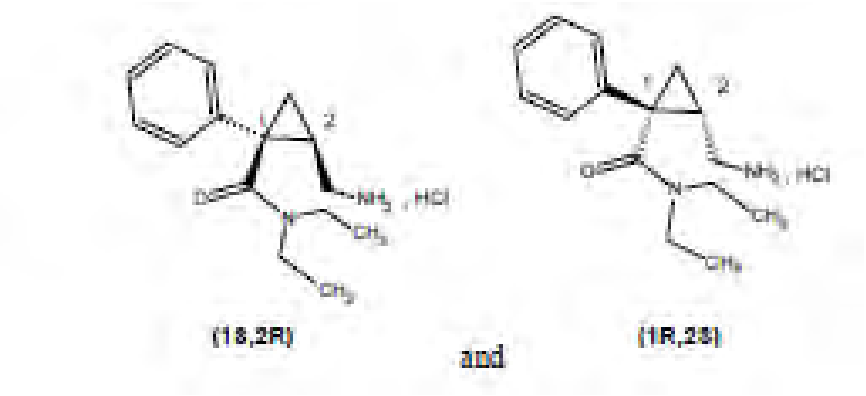
PRODUCT INFORMATION

JONCIA®
25, 50, 100 mg Capsules

NAME OF THE MEDICINE

milnacipran hydrochloride
(1RS, 2SR)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropane-1-carboxamide hydrochloride (IUPAC name)



CAS number: 101152-94-7

DESCRIPTION

Milnacipran hydrochloride is a white to almost white crystalline powder with the molecular formula $C_{15}H_{23}ClN_2O$ and a molecular weight of 282.8. Milnacipran hydrochloride is freely soluble in water, methanol, ethanol, butanol, chloroform, dichloromethane and very slightly soluble in ethyl ether. It is non to slightly hygroscopic with a pKa value of 9.65. Milnacipran hydrochloride is a racemic mixture of the isomers 1R, 2S and 1S, 2R. The partition coefficient between octanol and an aqueous buffer (pH = 7.2), P=0.27 shows the highly hydrophilic character of milnacipran hydrochloride.

The milnacipran hydrochloride drug product is presented in an immediate-release hard capsule containing 25, 50 and 100 mg of milnacipran hydrochloride. Milnacipran hydrochloride capsules also contain the excipients: calcium hydrogen phosphate, carmellose calcium, povidone K30, silica hydrophobic colloidal, magnesium stearate and talc-purified. The hard capsule shells for the 25 mg and 100 mg strengths contain titanium dioxide (E171), quinoline yellow (E104), sunset yellow FCF (E110) and gelatin. The hard capsule shell for the 50 mg strength

contains titanium dioxide (E171), sunset yellow FCF (E110) and gelatin. The capsules are marked with food grade ink.

PHARMACOLOGY

Pharmacodynamics

Milnacipran is a balanced, specific, dual reuptake inhibitor of noradrenaline (NA) and serotonin (5-hydroxytryptamine [5 HT]), inhibiting noradrenaline uptake with greater potency than serotonin.

Milnacipran has no appreciable affinity for serotoninergic ($5HT_{1-7}$), α- or β-adrenergic, muscarinic (M_{1-5}), histamine (H_{1-4}), dopamine (D_{1-5}), opiate, benzodiazepine and γ-aminobutyric acid-A ($GABA_A$) receptors *in vitro*. Milnacipran has no significant activity for Ca^{++}, K^+, Na^+, Cl^- channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or of acetylcholinesterase.

In vivo, milnacipran shows antinociceptive activity in some animal models of chronic pain (neuropathic or arthritic models), and demonstrates antidepressant-like effects in nonclinical models of mood disorders (anxiety, depression, cognition).

Pharmacokinetics

Absorption

After oral administration, milnacipran is well-absorbed. Its absolute bioavailability is about 85% and concomitant food intake does not affect the bioavailability. Peak plasma concentration (C_{max}) is reached 2 to 4 hours hours after dosing. Plasma concentrations are dose-proportional up to 300 mg twice daily. After repeated administration, the steady-state is reached within 2 to 3 days. In these conditions, the C_{max} is about 250 ng/mL after a 100 mg daily dose given in two divided doses. Pharmacokinetic within- and between-subject variability is low.

Distribution

The binding to plasma proteins is limited (13%) and not saturable in a very large concentration range. The volume of distribution of milnacipran is around 5 L/kg.

Metabolism and elimination

Milnacipran and its metabolites are eliminated primarily by renal excretion. Approximately 55% of the dose is excreted as unchanged drug. The remaining fraction is excreted as metabolites, mainly as glucuronide derivatives. Total plasma clearance is 40 L/h. Plasma elimination half-life is about 8 hours and drug elimination is completed 48 to 72 hours after termination of therapy.

Limited evidence indicates that milnacipran is neither an inducer nor an inhibitor of human cytochrome P450 as demonstrated *in vitro*. The absence of inhibitory properties on the main cytochrome P450 isoenzymes (1A2, 2D6, 2C19 and 3A4) is confirmed in humans.

Special populations

Liver impaired patients
Milnacipran pharmacokinetic parameters are not significantly affected by liver function impairment. No dosage adjustment is necessary for patients with impaired hepatic function.

Patients with renal insufficiency
Reduction in milnacipran clearance leads to a higher plasma exposure, 16%, 52% and 200% in patients with Chronic Kidney Disease (CKD) stages 2, 3 and 4 respectively. Dose adjustment is recommended for patients with CKD stage 4. (See DOSAGE AND ADMINISTRATION). Milnacipran is not recommended for patients with CKD stage 5.

Elderly patients
Milnacipran pharmacokinetic parameters are not significantly modified with age. No age-related dose adjustment is necessary unless renal function is reduced to values for which dose adjustment is recommended (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

The efficacy of JONCIA® for the management of fibromyalgia was established in three double-blind, placebo-controlled, multicentre 3-month studies in adult patients (18 to 74 years of age). A total of 3097 patients were randomised in studies: MLN-MD-02, GE 302 and MLN-MD-03. Enrolled patients met the American College of Rheumatology (ACR) criteria for fibromyalgia (a history of widespread pain for 3 months and pain present at 11 or more of the 18 specific tender point sites). Approximately 30% of patients had a history of depression. There were no statistically significant differences with respect to demographic or baseline characteristics between the placebo and JONCIA® treatment groups in the pivotal studies.

A larger proportion of patients treated with JONCIA® than with placebo experienced a simultaneous reduction in pain from baseline of at least 30% (visual analog scale

(VAS)) and also rated themselves as much improved or very much improved based on the patient global assessment (PGIC).

COMPOSITE CRITERION
(30% responders pain and PGIC 1, 2)

STUDY NUMBER	*GE 302*		*MD 02*			*MD 03*	
	Placebo	*MLN 200*	*Placebo*	*MLN 100*	*MLN 200*	*Placebo*	*MLN 100*
RESPONDERS (LOCF)	14.3%	24.0% (p<0.001)	16.2%	23.2% (p=0.014)	25.4% (p=0.002)	18.2%	29.5% (p<0.001)
NNT		*10.3*		*14.3*	*10.9*		*8.8*
RESPONDERS (OC)	15.9%	31.5% (p<0.001)	20.5%	32.4% (p=0.002)	35.8% (p<0.001)	24.5%	39.4% (p<0.001)
NNT		*6.4*		*8.4*	*6.5*		*6.7*

NNT: Number needed to treat

Study MLN-MD-02

More patients in the JONCIA® treatment arms experienced at least a 30% reduction in pain from baseline (VAS) and considered themselves globally improved (PGIC) than did patients in the placebo arm. Treatment with JONCIA® 200 mg/day did not confer greater benefit than treatment with JONCIA® 100 mg/day.

Study GE 302

More patients in the JONCIA® (200 mg/day) treatment arm experienced at least a 30% reduction in pain from baseline (VAS) and considered themselves globally improved (PGIC) than did patients in the placebo arm.

Study MLN-MD-03

More patients in the JONCIA® 100 mg/day treatment arm experienced at least a 30% reduction in pain from baseline (VAS) and considered themselves globally improved (PGIC) than did patients in the placebo arm.

The significant improvement in pain and PGIC was reinforced by the significant changes in fatigue and refreshing sleep in the JONCIA® treatment groups.

The results from uncontrolled studies supported maintenance of efficacy over 6 months of continuous dosing.

The small proportion of male patients in the milnacipran clinical studies is consistent with the epidemiology of the population with fibromyalgia, therefore the small number of male patients studied did not provide adequate power to show independent evidence of efficacy in this population.Efficacy and tolerability in fibromyalgia male patients should be specifically evaluated and monitored.

INDICATIONS

Management of fibromyalgia.

CONTRAINDICATIONS

JONCIA®should never be given in the following cases:

- Hypersensitivity to the active substance or to any of the excipients;
- Patients with severe cardiac function impairment or identified very high risk of a serious cardiac arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV), uncontrolled hypertension, or severe or unstable coronary heart disease, as these underlying conditions may be compromised by increases in blood pressure and heart rate.
- Patients with uncontrolled narrow angle glaucoma;
- Co-administration with MAO inhibitors (see PRECAUTIONS - Interactions with other medicines);
- Co-administration with other serotonin reuptake inhibitors (selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI), tramadol and St-John's Wort, serotonin precursor (tryptophan), or tricyclics (such as clomipramine and amitriptyline) (see PRECAUTIONS - Interactions with other medicines);
- Co-administration with adrenaline and noradrenaline (alpha and beta sympathomimetics) (see PRECAUTIONS - Interactions with other medicines);
- Breastfeeding.

PRECAUTIONS

JONCIA® should be prescribed with caution in the following cases:

- in patients with severe renal impairment: dosage may have to be reduced because of prolongation of elimination half-life;

- in patients with high intra-ocular pressure or at risk of narrow-angle glaucoma;
- in patients with prostatic hypertrophy or other lower urinary tract obstructive disorders;
- in patients with epilepsy or with a history of epilepsy, JONCIA® should be used with caution and should be discontinued in any patient developing a seizure. Seizures have been reported in patients taking milnacipran;
- in patients treated with other CNS acting drugs.

Blood pressure and heart rate

In the placebo-controlled trials, among fibromyalgia patients who were non-hypertensive at baseline, approximately twice as many patients in the JONCIA® treatment arms became hypertensive at the end of the study (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) compared with the placebo patients: 7.2% of patients in the placebo arm versus 19.5% of patients treated with JONCIA® 100 mg/day and 16.6% of patients treated with JONCIA® 200 mg/day. Among patients who met systolic criteria for pre-hypertension at baseline (SBP 120 – 139 mmHg), more patients became hypertensive at the end of the study in the JONCIA® treatment arms than placebo: 9% of patients in the placebo arm versus 14% in both the JONCIA® 100 mg/day and the JONCIA® 200 mg/day treatment arms.

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

For patients who experience a clinically significant sustained increase in blood pressure or heart rate while receiving JONCIA® gradual discontinuation should be considered.

Safety of JONCIA® has not been studied in fibromyalgia patients with a recent history of myocardial infarction or unstable heart disease.

Use with alcohol

Although there is no evidence of an interaction with alcohol, as with any CNS medication, it is recommended that the use of alcohol while taking JONCIA® should be avoided.

Hyponatraemia

Hyponatraemia may occur as a result of treatment with SSRIs and SNRIs, including JONCIA®. In many cases, this hyponatraemia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 100 mmol/L have been reported. Elderly patients may be

at greater risk of developing hyponatraemia with SNRIs, SSRIs, or JONCIA®. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk. Discontinuation of JONCIA should be considered in patients with symptomatic hyponatraemia.

Signs and symptoms of hyponatraemia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.

Bleeding

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.

Depression, suicidal ideation and behaviour

Milnacipran is a selective serotonin and noradrenaline reuptake inhibitor (SNRI), similar to some medicines used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. 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 a time of dose changes, either increases or decreases.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the milnacipran, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's 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 tendancy towards and 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 of 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.

Milnacipran has not been studied in patients under the age of 18 and is not intended for use in this age group. Although a causal role for milnacipran 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. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Activation of Mania/Hypomania
As with all antidepressants, switches to mania/hypomania have occurred. Close supervision of patients with bipolar disorders is recommended.

Seizure disorders
In clinical trials evaluating JONCIA® in patients with fibromyalgia, seizures/convulsions have not been reported. However, seizures have been reported infrequently in patients treated with JONCIA® for disorders other than fibromyalgia. JONCIA® should be prescribed with care in patients with a history of a seizure disorder.

Hepatic disorders
In the placebo-controlled fibromyalgia trials, increases in the number of patients treated with milnacipran with mild elevations of ALT or AST (1-3 times the upper limit of normal, ULN) were observed. Increases in ALT were more frequently observed in the patients treated with milnacipran 100 mg/day (6%) and milnacipran 200 mg/day (7%), compared to the patients treated with placebo (3%). One patient receiving milnacipran 100 mg/day (0.2%) had an increase in ALT greater than 5 times the upper limit of normal but did not exceed 10 times the upper limit of normal. Increases in AST were more frequently observed in the patients treated with milnacipran 100 mg/day (3%) and milnacipran, 200 mg/day (5%) compared to the patients treated with placebo (2%).

The increases of bilirubin observed in the fibromyalgia clinical trials were not clinically significant.

No case met the criteria of elevated ALT > 3x ULN and associated with an increase in bilirubin ≥ 2x ULN.

There have been cases of increased liver enzymes and reports of severe liver injury, including fulminant hepatitis with milnacipran from postmarketing experience. In the cases of severe liver injury there were significant underlying clinical conditions and/or the use of multiple concomitant medications. Because of underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions. milnacipran should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Treatment with milnacipran should not be resumed unless another cause can be established.

Milnacipran should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Genitourinary effects

Because of their noradrenergic effect, SNRIs including JONCIA®, can affect urethral resistance and micturition. In the controlled fibromyalgia trials, dysuria occurred more frequently in patients treated with JONCIA® (1%) than in placebo-treated patients (0.5%). Caution is advised in use of JONCIA® in patients with a history of dysuria, notably in male patients with prostatic hypertrophy, prostatitis, and other lower urinary tract obstructive disorders. Male patients are more prone to genitourinary adverse effects, such as dysuria or urinary retention and may experience testicular pain or ejaculation disorders.

Discontinuation of treatment

The risk of withdrawal reactions when treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) is discontinued may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Adverse events seen in clinical trials upon discontinuation of treatment with milnacipran (post-tapering), including potential withdrawal reactions were reported in 20% of patients treated with milnacipran and 17.5% of patients on placebo. The most commonly reported reactions are listed in the ADVERSE EFFECTS section. Generally the 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 resolve within two weeks. It is therefore advised that the dose of milnacipran should be gradually tapered when discontinuing treatment over a period of no less than two weeks according to the patient's needs (see DOSAGE AND ADMINISTRATION).

Genotoxicity

Milnacipran has not demonstrated genotoxic potential in standard *in vitro* and *in vivo* tests, including bacterial and mammalian mutation assays, chromosomal aberration assays in Chinese hamster lung cells and human lymphocytes, and the mouse micronucleus test.

Carcinogenicity

Carcinogenicity studies were conducted via dietary administration in mice (up to 100 mg/kg/day) and in rats (up to 50 mg/kg/day). Although there was no evidence of a treatment-related increase in tumours in either study, the highest dose in the mouse study was not considered to be the maximum tolerated dose and a supplementary

26-week oral study in TG.rasH2 transgenic mice was undertaken (up to 125 mg/kg/day). This study also produced no evidence of an increase in treatment-related tumours, with exposure (plasma AUC) up to 7.5 times the clinical exposure at the MRHD. Exposure was not measured in the rat study, but the high dose was twice the MRHD, based on mg/m^2.

Effects on fertility
There were no adverse effects on the fertility of rats treated orally with milnacipran at dose levels up to 80 mg/kg/day (about 4-fold the MRHD, based on mg/m^2).

Use in pregnancy
Category B3

Joncia® has not been studied in pregnant women. There was no evidence of teratogenicity in mice or rabbits treated with milnacipran during the period of organogenesis at respective oral doses up to 125 and 60 mg/kg/day (respective exposures 7 and 2 times the clinical exposure at the MRHD, based on AUC).

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 long lasting crying have been reported. All these signs appear in the first days of life and are generally of short duration.

Consequently, as a precautionary measure, JONCIA® should not be administered during pregnancy.

Use in lactation
Breast-feeding is contraindicated. Milnacipran and/or its metabolites are excreted in milk in lactating rats. Oral administration of milnacipran to rats from late gestation to weaning was associated with decreased pup survival and development delays at a dose similar to the MRHD (based on mg/m^2) or greater. These effects may be due to maternal toxicity observed at these and lower doses.

Interactions with other medicines
Interaction studies have only been performed in adults.

<u>MAO Inhibitors</u>
Milnacipran is contraindicated in combination with MAO inhibitors (see CONTRAINDICATIONS): with non selective MAO inhibitors and A selective MAO inhibitors there is a risk of a serotoninergic syndrome (* see below); with B selective MAO inhibitors there is a risk of paroxysmal hypertension.

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.

*Serotoninergic syndrome:
The development of a potentially life-threatening serotonin syndrome may occur with agents that inhibit serotonin reuptake, including milnacipran, particularly with concomitant use of serotoninergic (including triptans) and with drugs which impair metabolism of serotonin (including MAO inhibitors). Serotonin syndrome may include mental changes (such as agitation, hallucinations, coma), autonomic instability (such as tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (such as hyperreflexia, incoordination), and/or gastrointestinal symptoms (such as nausea, vomiting, diarrhoea).

Serotonin reuptake inhibitors
Milnacipran is contraindicated in combination with other serotonin reuptake inhibitors and any other medicines with the same mechanism of action (see CONTRAINDICATIONS).

Adrenaline and noradrenaline
Milnacipran is contraindicated in combination with adrenaline and noradrenaline (alpha and beta sympathomimetics) (see CONTRAINDICATIONS). There is the risk of paroxysmal hypertension with possible arrhythmia due to inhibition of entry of adrenaline or noradrenaline into the sympathetic nerve fibre.

When haemostatic action by subcutaneous or gingival injection is sought, limit intake, for example, to less than 0.1 mg adrenaline in 10 minutes or 0.3 mg in an hour in adults.

Milnacipran should be used with caution in combination with the following:

- 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.

- Digoxin by the parenteral route due to the risk of potentiation of haemodynamic effects.

- Clonidine and related compounds (reported with desipramine and imipramine) due to the risk of inhibition of clonidine's antihypertensive effect due to antagonism of adrenergic receptors.

- 5 HT1D agonists (triptans) due to the risk of hypertension and coronary artery vasoconstriction by additive serotoninergic effects. There should be an interval of one week between the end of treatment with milnacipran, and the beginning of treatment with 5 HT1D agonists.

- Lithium, antipsychotic medications, dopamine agonists and tryptophan. These medicines may increase the incidence of serotonin syndrome or neuroleptic malignant syndrome.

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

Paediatric use
Safety and effectiveness have not been established. Use in children and adolescents aged < 18 years is not recommended.

ADVERSE EFFECTS

The adverse drug reactions observed in the phase II and III placebo-controlled clinical trials comprising a total of 4203 patients: 2550 on milnacipran (50 mg BID and 100 mg BID) and 1653 on placebo, for a treatment duration of at least 12 weeks are presented in Table 1.

The most commonly reported adverse drug reactions were nausea, headache, constipation, hyperhidrosis and hot flushes.

The majority of the most frequent adverse reactions occurred mainly in the first four weeks of therapy and were mild to moderate in severity. A few adverse reactions which appeared to be dose-related: hyperhidrosis, increased heart rate, insomnia, headache, nausea, vomiting and constipation, were the most frequent adverse reactions leading to discontinuation of therapy. Milnacipran hydrochloride dose reduction can be attempted before treatment discontinuation.

Table 1: Number of Patients with Treatment-Emergent Adverse Events (TEAEs) Reported in ≥ 2% of Patients by System Organ Class and Preferred Term (3 Months Exposure)

System Organ Class Preferred Term	Placebo N=1653	MLN 100 N=1139	MLN 200 N=1411	All MLN N=2550
Number of patients with at least one TEAE	1247 (75.4%)	979 (86.0%)	1208 (85.6%)	2187 (85.8%)
Infections and infestations	401 (24.3%)	259 (22.7%)	318 (22.5%)	577 (22.6%)
Sinusitis	53 (3.2%)	61 (5.4%)	58 (4.1%)	119 (4.7%)
Nasopharyngitis	77 (4.7%)	49 (4.3%)	52 (3.7%)	101 (4.0%)
Upper respiratory tract infection	64 (3.9%)	48 (4.2%)	43 (3.0%)	91 (3.6%)
Influenza	50 (3.0%)	19 (1.7%)	29 (2.1%)	48 (1.9%)
Metabolism and nutrition disorders	76 (4.6%)	55 (4.8%)	63 (4.5%)	118 (4.6%)
Decreased appetite	15 (0.9%)	24 (2.1%)	24 (1.7%)	48 (1.9%)
Psychiatric disorders	278 (16.8%)	229 (20.1%)	264 (18.7%)	493 (19.3%)
Insomnia	123 (7.4%)	117 (10.3%)	132 (9.4%)	249 (9.8%)
Anxiety	43 (2.6%)	43 (3.8%)	47 (3.3%)	90 (3.5%)
Depression	64 (3.9%)	30 (2.6%)	39 (2.8%)	69 (2.7%)
Nervous system disorders	446 (27.0%)	400 (35.1%)	459 (32.5%)	859 (33.7%)
Headache	228 (13.8%)	203 (17.8%)	234 (16.6%)	437 (17.1%)
Dizziness	102 (6.2%)	116 (10.2%)	139 (9.9%)	255 (10.0%)
Migraine	43 (2.6%)	49 (4.3%)	48 (3.4%)	97 (3.8%)
Cardiac disorders	74 (4.5%)	122 (10.7%)	156 (11.1%)	278 (10.9%)
Palpitations	40 (2.4%)	80 (7.0%)	94 (6.7%)	174 (6.8%)
Tachycardia	11 (0.7%)	42 (3.7%)	51 (3.6%)	93 (3.6%)
Vascular disorders	79 (4.8%)	213 (18.7%)	238 (16.9%)	451 (17.7%)
Hot flush	28 (1.7%)	124 (10.9%)	140 (9.9%)	264 (10.4%)
Hypertension	29 (1.8%)	63 (5.5%)	44 (3.1%)	107 (4.2%)
Flushing	11 (0.7%)	27 (2.4%)	35 (2.5%)	62 (2.4%)
Gastrointestinal disorders	553 (33.5%)	585 (51.4%)	743 (52.7%)	1328 (52.1%)
Nausea	290 (17.5%)	405 (35.6%)	494 (35.0%)	899 (35.3%)
Constipation	50 (3.0%)	169 (14.8%)	198 (14.0%)	367 (14.4%)
Vomiting	41 (2.5%)	55 (4.8%)	89 (6.3%)	144 (5.6%)
Dry mouth	37 (2.2%)	48 (4.2%)	67 (4.7%)	115 (4.5%)
Diarrhoea	86 (5.2%)	54 (4.7%)	40 (2.8%)	94 (3.7%)
Abdominal pain upper	46 (2.8%)	23 (2.0%)	46 (3.3%)	69 (2.7%)
Abdominal pain	25 (1.5%)	27 (2.4%)	39 (2.8%)	66 (2.6%)
Dyspepsia	52 (3.1%)	35 (3.1%)	26 (1.8%)	61 (2.4%)
Skin and subcutaneous tissue disorders	131 (7.9%)	171 (15.0%)	314 (22.3%)	485 (19.0%)
Hyperhidrosis	30 (1.8%)	85 (7.5%)	192 (13.6%)	277 (10.9%)
Rash	23 (1.4%)	24 (2.1%)	49 (3.5%)	73 (2.9%)
Pruritus	22 (1.3%)	20 (1.8%)	30 (2.1%)	50 (2.0%)
Musculoskeletal and connective tissue disorders	318 (19.2%)	211 (18.5%)	219 (15.5%)	430 (16.9%)
Back pain	56 (3.4%)	39 (3.4%)	33 (2.3%)	72 (2.8%)
Fibromyalgia	63 (3.8%)	37 (3.2%)	32 (2.3%)	69 (2.7%)
Muscle spasms	39 (2.4%)	30 (2.6%)	36 (2.6%)	66 (2.6%)
Pain in extremity	42 (2.5%)	30 (2.6%)	21 (1.5%)	51 (2.0%)
Arthralgia	51 (3.1%)	23 (2.0%)	26 (1.8%)	49 (1.9%)
General disorders and administration site conditions	204 (12.3%)	188 (16.5%)	196 (13.9%)	384 (15.1%)
Fatigue	76 (4.6%)	68 (6.0%)	63 (4.5%)	131 (5.1%)
Pain	34 (2.1%)	15 (1.3%)	31 (2.2%)	46 (1.8%)
Irritability	32 (1.9%)	27 (2.4%)	15 (1.1%)	42 (1.6%)
Chest pain	19 (1.1%)	23 (2.0%)	18 (1.3%)	41 (1.6%)

System Organ Class Preferred Term	Placebo N=1653	MLN 100 N=1139	MLN 200 N=1411	All MLN N=2550
Investigations	112 (6.8%)	150 (13.2%)	179 (12.7%)	329 (12.9%)
Heart rate increased	14 (0.8%)	50 (4.4%)	64 (4.5%)	114 (4.5%)
Blood pressure increased	15 (0.9%)	40 (3.5%)	44 (3.1%)	84 (3.3%)

The table above presents the most frequent adverse events, whether or not a causal relationship has been suspected.

The following additional adverse drug reactions were reported less frequently during clinical trials in fibromyalgia with a suspected relationship. Common events are defined as those occurring in =1% and <10% of patients (but only those occurring in =1% and <2% of patients are listed here), uncommon events are defined as those occurring in =0.1% and <1% of patients, and rare events are defined as those occurring in <0.1% of patients.

Immune System Disorders

Uncommon: hypersensitivity

Metabolism and Nutrition Disorders

Uncommon: weight loss

Psychiatric disorders

Common: agitation

Uncommon: suicidal ideation, panick attack, confusion, hallucination, nightmares, decreased libido

Nervous System Disorders

Common: memory impairment, tremor, dysaesthesia, dysgueusia, somnolence

Uncommon: syncope

Rare: balance disorder, cerebrovascular accident

Eye Disorders

Uncommon: dry eye, mydriasis, blurred vision, reduced visual acuity

Ear and Labyrinth Disorders

Uncommon: tinnitus, vertigo

Cardiac Disorders

Uncommon: arrhythmia, extrasystoles

Rare: acute coronary syndrome, angina pectoris

Vascular Disorders

Uncommon: Raynaud's phenomenon, hypotension, orthostatic hypotension

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: dyspnoea

Rare: epistaxis

Gastro-intestinal Disorders

Uncommon: gastritis, stomatitis, haemorrhoids

Hepatobiliary Disorders

Uncommon: hepatic enzyme increase

Rare: hepatitis

Skin and Subcutaneous Tissue Disorders

Uncommon: urticaria

Rare: photosensitivity reaction

Renal and Urinary Disorders

Common: dysuria

Uncommon: pollakiuria, urinary retention

Reproductive System and Breast Disorders

Uncommon: metrorrhagia

Rare: amenorrhoea

General Disorders and Administration Site Conditions

Uncommon: chills, pyrexia, feeling of body temperature change

The urinary adverse reactions (eg. dysuria) mainly occurred in male patients: dysuria was observed in 23.9% of male patients. A monitoring of the micturition disorders is necessary in patients with a history of difficult passage of urine (eg. prostatic hypertrophy and other lower urinary tract obstructive disorders). However, dysuria and urinary retention were also reported in men without known prostatic disorders.

Other specific adverse drug reactions observed in male patients such as testicular pain, ejaculation disorders and erectile dysfunction were reported in 8.7%, 5.4% and 3.3% of male patients respectively.

As for all SSRI and SNRI active substances, it is advised that when milnacipran hydrochloride treatment is no longer required, gradual discontinuation by dose tapering over period of no less than two weeks should be carried out (see PRECAUTIONS - Discontinuation of treatment). In fibromyalgia clinical trials, the most frequently reported adverse reactions during the post-tapering follow-up phase were headache, dizziness, somnolescence, diarrhea, vomiting, anxiety disorders and pain. The frequency of these adverse reactions when no tapering is performed is unknown.

Post-marketing reports of adverse reactions from other countries where milnacipran hydrochloride is used for the treatment of major depressive episode are the following (frequency not known):

- Metabolism and nutrition disorders: hyponatraemia
- Nervous system disorders: serotoninergic syndrome (especially when combined with other agents), convulsions (especially in patients with past history of epilepsy)
- Vascular disorders: ecchymosis and other cutaneous or mucosal bleeding
- Hepatobiliary disorders: cytolytic hepatitis

Other post-marketing adverse reactions reported in depressed patients were related to the depressive illness:

- elimination of psychomotor inhibition, with suicidal risk
- mood switch, with episodes of mania
- reactivation of a delusion in psychotic patients

DOSAGE AND ADMINISTRATION

JONCIA® capsules are for oral use.

The recommended dose is 100 mg per day in two divided doses (morning and evening, preferably during meals).

Based on efficacy and tolerability dosing may be titrated according to the following schedule:

Day 1 – Day 2: 25 mg once daily (in the evening).
Day 3 – Day 7: 50 mg daily in two divided doses (25 mg morning and 25 mg evening).
After Day 7: 100 mg daily in two divided doses (50 mg morning and 50 mg evening).

Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily). Doses above 200 mg/day have not been studied.

After an initial 12 week period patients should be assessed and those with little or no benefit should discontinue treatment. In patient with apparent benefit, consideration should be given to periodically reassessing the need for ongoing treatment.

JONCIA® should be tapered and not abruptly discontinued after extended use (see PRECAUTIONS - Discontinuation of treatment).

Use in patients with renal insufficiency

No dosage adjustment is necessary for patients with Chronic Kidney Disease (CKD) stage 2. JONCIA® should be used with caution in patients with CKD stage 3 (estimated GFR 30 – 59 mL/min/1.73 m^2) and CKD stage 4 (estimated GFR 15 – 29 mL/min/1.73 m^2) at a maximum dose of 50 mg/d.

JONCIA® should not be given to patients with CKD stage 5.

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see Pharmacokinetics – Special Populations).

JONCIA should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (see PRECAUTIONS).

Use in the elderly (over 65 years of age)
Dosage adjustment is not necessary in the elderly unless renal function is reduced to values for which a dose adjustment is recommended (see Pharmacokinetics, Special Populations).

Use in children and adolescents (< 18 years)
The safety and effectiveness of milnacipran has not been established in patients below the age of 18 years.

Discontinuation of treatment
Abrupt discontinuation of treatment with milnacipran should be avoided. When stopping treatment, the dose should be gradually reduced over a period of no less than two weeks in order to reduce the risk of withdrawal reactions (see PRECAUTIONS – Discontinuation of treatment and ADVERSE EFFECTS).

OVERDOSAGE

Symptoms of overdosage
Cases of overdose with milnacipran have been observed in patients treated for other indications. With high doses the emetic effect can considerably limit the risk of overdose. 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 dose of 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. No cardiac toxicity has been reported. All fatal overdose cases occurred after ingestion of several medications.

Treatment of overdosage
There is no specific antidote for milnacipran. For all overdoses, the mainstay of treatment is supportive and symptomatic care. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Medical monitoring should be continued for at least 24 hours.

PRESENTATION

Presentation

25 mg hard capsule: yellow cap with "PFM" imprinted in black, white body with "25" imprinted in black.

50 mg hard capsule: orange cap with "PFM" imprinted in black, white body with "50" imprinted in black.

100 mg hard capsule: orange cap with "PFM" imprinted in black, yellow body with "100" imprinted in black.

Container type and pack sizes

Blister pack: 14's, 28's, 56's (25, 50 & 100 mg capsules)
Bottle*: 14's, 28's, 56's (25, 50 & 100 mg capsules)

STORAGE CONDITIONS

Blister pack: Store below 30^{o}C
Bottle: Store below 30^{o}C

NAME AND ADDRESS OF THE SPONSOR

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North Ryde NSW 2113
Australia

POISON SCHEDULE

S4

DATE OF APPROVAL

4 November 2011

* Not marketed