Bundesamt für Sicherheit
im Gesundheitswesen

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**Unser Zeichen:** PHV-8544164-A-160316
**Ihr Zeichen:**

**PHV issue Milnacipran**

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: FR/H/PSUR/0021/002) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Milnacipran – hältigen Arzneispezialitäten aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

## Fachinformation

4.3 Contraindications

This medication should never be used in the following cases:

- Hypersensitivity to milnacipran or to any of the excipients;
- association with irreversible MAO inhibitors (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.

4.4 Special warnings and special precautions for use

Suicide/suicidal thoughts

Depression is associated with an increased risk of 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.

Serotonin syndrome
As with other serotoninergic agents, the development of a potentially life-threatening serotonin syndrome may occur with milnacipran treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (as irreversible MAO inhibitors (iproniazide),

A selective MAO inhibitors (linezolid, moclobemide, methylene blue), St John's Wort [Hypericum perforatum], pethidine, tramadol, most of the antidepressant (see sections 4.3 and 4.5)).

Serotonin syndrome symptoms may include:
- digestive symptoms (diarrhoea),
- changes in psychiatric status and behaviour (agitation, confusion, hypomania),
- motor dysfunction (tremor, rigidity, myoclonus, hyperreflexia and ataxia),
- autonomic instability (labile blood pressure, tachycardia, shivering, hyperthermia, possibly coma).

The concomitant use of milnacipran with alpha and beta sympathomimetics (IM and IV routes) and A selective MAO inhibitors (such as linezolid, moclobemide and methylene blue) is not recommended.

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.
Ixel should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Treatment with Ixel should not be resumed unless another cause can be established.

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 case of sustained elevated blood pressure or elevated heart
rate, discontinuation of the treatment with milnacipran should be considered if clinically warranted.

- in patients with high intra-ocular pressure or at risk of 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.

The safety and efficacy of milnacipran for treatment of major depressive episodes in adults in higher dosage than 100 mg per day have not been established. For patients who do not experience clinical benefit with 100 mg per day, the treatment should be discontinued.

Discontinuation of treatment
The risk of withdrawal reactions seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.
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, though in some individuals they may be prolonged (2-3 months or more).

It is therefore advised that milnacipran should be gradually tapered when discontinuing treatment and not abruptly discontinued after extended use (see section 4.2 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

*Serotonin syndrome:
As with other serotonergic agents, the development of a potentially life-threatening serotonin syndrome may occur with milnacipran treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (as irreversible MAO inhibitors (iproniazide), A selective MAO inhibitors (linezolid, moclobemide, methylene blue), St John's Wort [Hypericum perforatum], pethidine, tramadol, most of the antidepressants).
Serotonin syndrome symptoms may include:
- digestive symptoms (diarrhoea),
- changes in psychiatric status and behaviour (agitation, confusion, hypomania),
- motor dysfunction (tremor, rigidity, myoclonus, hyperreflexia and ataxia),
- autonomic instability (labile blood pressure, tachycardia, shivering, hyperthermia, possibly coma).

COMBINATIONS CONTRA-INDICATED:

· With irreversible MAO inhibitors (iproniazide)
Risk of a serotonin syndrome* (see above).
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.

UNADVISABLE COMBINATIONS

· With alpha and beta sympathomimetics (IM and IV routes)

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

· With A selective MAO inhibitors (linezolid, moclobemide, methylene blue)
Risk of development of a serotoninergic 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:

· Adrenalin (gingival and subcutaneous routes)
Serious disorder of ventricular rhythm by increase of cardiac excitability.
Limit intake, for example, to less than 0.1mg adrenalin in 10 minutes or 0.3 mg in an hour, in adults.

· 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

4.6 Pregnancy and lactation

Pregnancy
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, embryonic/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 long-lasting 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 avoid to milnacipran during pregnancy.

Breast-feeding
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 reduce 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 in depression indication 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 1: Table of adverse reactions for depression
Frequency estimate:
Very common (□□1/10), common (□□1/100 to < 1/10), uncommon (□□1/1,000 to < 1/100), rare (□□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.

| Very Common >=10% | Common >=1% to 10% | Uncommon >=0.1% to 1% | Rare < 0.1% | Unknown |
|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | |
| | | | | Ecchymosis(1) (3) – Cutaneous or mucous membrane bleedings(1) (3) |
| **Immune system disorders** | | | | |
| | | Hypersensitivity | Anaphylactic shock | |
| **Endocrine disorders** | | | | |
| | | | Inappropriate antidiuretic hormone secretion | |
| **Metabolism and nutrition disorders** | | | | |
| | | Hyperlipidaemia | | hyponatremia(1) (3) |
| | | Weight decreased | | |
| **Psychiatric disorders** | | | | |
| | Agitation - Anxiety | Panic attack | Derealisation - Thinking abnormal | aggression |
| | Depression | Confusional state | Psychotic disorder | |
| | Eating disorder | Delusion - Hallucination | | |
| | Sleep disorder | Mania | | |
| | Suicidal behaviour | Libido decreased | | |
| | | Nightmare | | |
| | | Suicidal ideation | | |

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|---|---|---|---|---|
| **Nervous system disorders** | | | | |
| Headache | Migraine | Memory impairment | Cerebrovascular accident | Serotonin syndrome(1)(*) |
| | Tremor | Akathisia | Dyskinesia - Parkinsonism | Convulsion(1)(2) |
| | Dizziness - Dysaesthesia | Balance disorder - Dysgeusia | Convulsion | |
| | Somnolence | Syncope | | |
| **Eye disorders** | | | | |
| | | Dry eye - Eye pain | | |
| | | Mydriasis | | |
| | | Accommodation disorder - Vision blurred - | | |
| | | Visual impairment | | |
| **Ear and labyrinth disorders** | | | | |
| | | Tinnitus - Vertigo | | |
| **Cardiac disorders** | | | | |
| | Tachycardia | Arrhythmia - Bundle branch block - | Angina pectoris | |
| | Palpitations | Extrasystoles | | |
| | | Myocardial infarction | | |
| **Vascular disorders** | | | | |
| | Hot flush | Raynaud's phenomenon | | |
| | Hypertension | Hypotension - Orthostatic hypotension | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| | | Cough - Dyspnoea | | |
| | | Nasal dryness - Pharyngeal disorder | | |
| **Gastrointestinal disorders** | | | | |
| Nausea | Constipation - Diarrhoea | Colitis - Gastritis | | |
| | Abdominal pain - Dyspepsia - | Gastrointestinal motility disorder | | |
| | Vomiting | Abdominal discomfort - | | |
| | Dry mouth | Abdominal distension | | |
| | | Gastroduodenal ulcer | | |
| | | Haemorrhoids | | |
| | | Stomatitis | | |

| | | | | |
|---|---|---|---|---|
| **Hepatobiliary disorders** | | | | |
| | | Hepatic enzyme increased | Hepatitis - Hepatocellular injury | cytolitic hepatitis (1) |
| **Skin and subcutaneous tissue disorders** | | | | |
| | Pruritus - Rash | Urticaria | Photosensitivity reaction | |
| | Hyperhidrosis | Dermatitis - Dermatosis | | |
| **Musculoskeletal and connective tissue disorders** | | | | |
| | Musculoskeletal pain | Muscle rigidity - Myalgia | | |
| **Renal and urinary disorders** | | | | |
| | Dysuria - Pollakiuria | Chromaturia - Urinary incontinence - | | |
| | | Urinary retention | | |
| **Reproductive system and breast disorders** | | | | |
| | Ejaculation disorder | Amenorrhoea Menorrhagia | | |
| | Erectile dysfunction | Menstrual disorder | | |
| | Testicular pain | Metrorrhagia | | |
| | | Prostatic disorder | | |
| **General disorders and administration site conditions** | | | | |
| | 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

(*) 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).

Withdrawal syndrome
A few cases of potential withdrawal reactions were reported after milnacipran treatment discontinuation. Generally, for SSRIs and SNRIs, the symptoms are mild to moderate and self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when milnacipran treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

Additional reactions reported from post-marketing experience in depression indication (frequency not known)

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

4.9 Overdose

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 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.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.

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Die Zulassungsinhaber werden aufgefordert, auch die Gebrauchsinformationen diesbezüglich anzupassen und bis **spätestens 16. Mai 2017** eine Variation gemäß
“Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.”

für die Arzneispezialitäten:

- Bezeichnung der ASPEZ (GZ: xxxxxx; Zul. Nr.: x-xxxxx)

beim Institut Zulassung & Lifecycle Management einzureichen.

In der Begründung ist **„PHV-Issue: Milnacipran “** sowie die **Geschäftszahl (PHV-8544164-A-160316)** anzugeben.

Mit freundlichen Grüßen
Für das Bundesamt
Mag. Rudolf Schranz