AVEROMILAN

(Milnacipran Hydrochloride 50 mg) film coated tablets

Excepients:

Calcium hydrogen phosphate , hydroxyl propyl cellulose extra fine (klucel EF),pregelatinized starch(starch 1500),colloidal anhydrous silica , magnesium stearate , hypromellose (methocel E5). Titanium dioxide, triacetin ,purified talc,polysorbate 80 .

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Averomilan is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Averomilan should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Averomilan is not approved for use in the treatment of major depressive disorder. Averomilan is not approved for use in pediatric patients

INDICATIONS AND USAGE

Averomilan is indicated for the management of fibromyalgia. Averomilan is not approved for use in pediatric patients.

DOSAGE AND ADMINISTRATION

Averomilan is given orally with or without food. Taking Averomilan with food may improve the tolerability of the drug.

Recommended Dosing

The recommended dose of Averomilan is 100 mg/day (50 mg twice daily).

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

Day 1: 12.5 mg once

Days 2-3: 25 mg/day (12.5 mg twice daily)

Days 4-7: 50 mg/day (25 mg twice daily)

After Day 7: 100 mg/day (50 mg twice daily)

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.

Averomilan should be tapered and not abruptly discontinued after extended use.

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with mild renal impairment. Averomilan should be used with caution in patients with moderate renal impairment. For patients with severe renal impairment (indicated by an estimated creatinine clearance of 5-29 mL/min), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily).

Based on individual patient response, the dose may be increased to 100 mg/day (50 mg twice daily).

Averomilan is not recommended for patients with end-stage renal disease.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary for patients with hepatic impairment. As with any drug, caution should be exercised in patients with severe hepatic impairment.

Discontinuing Averomilan

Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other serotonin and norepinephrine re-uptake inhibitors (SNRIs) and selective serotonin re-uptake inhibitors (SSRIs). Patients should be monitored for these symptoms when discontinuing treatment. Averomilan should be tapered and not abruptly discontinued after extended use

Switching patients to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with Averomilan. Conversely, at least 5 days should be allowed after stopping Averomilan before starting a MAOI intended to treat psychiatric disorders [see Contraindications].

Use of Averomilan with other MAOIs such as Linezolid or Methylene Blue

Do not start Averomilan in a patient being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered [see Contraindications].

In some cases, a patient already receiving Averomilan therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, Averomilan should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Averomilan may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with Averomilan is unclear. The clinician should nevertheless be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

DOSAGE FORMS AND STRENGTHS

Film-coated tablets , Milnacipran Hydrochloride 50 mg.

CONTRAINDICATIONS

Monoamine Oxidase Inhibitors

The use of MAOIs intended to treat psychiatric disorders with Averomilan or within 5 days of stopping treatment with Averomilan is contraindicated because of an increased risk of serotonin syndrome. The use of Averomilan within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration, Warnings and Precautions]*.

Starting Averomilan in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration, Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Suicide Risk

Averomilan is a selective serotonin and norepinephrine re-uptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders.

Patients, both adult and pediatric, with depression or other psychiatric disorders may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking these medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants, including drugs that inhibit the reuptake of norepinephrine and/or serotonin, may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, have been reported in adult and pediatric patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who may experience worsening depressive symptoms, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment due to worsening depressive symptoms or emergent suicidality, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can produce withdrawal symptoms

Families and caregivers of patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Averomilan, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Averomilan with MAOIs intended to treat psychiatric disorders is contraindicated. Averomilan should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Averomilan. Averomilan should be discontinued before initiating treatment with the MAOI *[see Contraindications, Dosage and Administration].*

If concomitant use of Averomilan with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Averomilan and any concomitant serotonergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

Elevated Blood Pressure

Sustained increases in blood pressure may have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported.

Concomitant use of Averomilan with drugs that increase blood pressure and heart rate has not been evaluated and such combinations should be used with caution .

Effects of Averomilan on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. Averomilan should be used with caution in these patients.

Measure blood pressure prior to initiating treatment and periodically monitor blood pressure throughout Averomilan treatment. Treat pre-existing hypertension and other cardiovascular disease before starting therapy with Averomilan. For patients who experience a sustained increase in blood pressure while receiving Averomilan, either reduce the dose or discontinue treatment with Averomilan if clinically warranted.

Elevated Heart Rate

Increases in heart rate ≥ 20 beats per minute occurred more frequently in milnacipran-treated patients when compared to placebo (8% in the milnacipran 50 mg BID and 100 mg BID treatment arms versus 0.3% in the placebo arm).

Averomilan has not been systematically evaluated in patients with a cardiac rhythm disorder.

Measure heart rate prior to initiating treatment and periodically monitor the heart rate throughout Averomilan treatment. Treat pre-existing tachyarrhythmias and other cardiac disease before starting therapy with Averomilan. For patients who experience a sustained increase in heart rate while receiving Averomilan, either reduce the dose or discontinue treatment with Averomilan if clinically warranted.

Seizures

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

Hepatotoxicity

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 foreign 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.

Discontinuation of Treatment with Averomilan

Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and SSRIs.

During marketing of milnacipran, and other SNRIs and SSRIs, there have been spontaneous reports of adverse events indicative of withdrawal and physical dependence occurring upon discontinuation of these drugs, particularly when discontinuation is abrupt. The adverse events include the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Averomilan. Averomilan should be tapered and not abruptly discontinued after extended use. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Averomilan. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SNRIs, SSRIs, or Averomilan. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk . Discontinuation of Averomilan should be considered in patients with symptomatic hyponatremia.

Signs and symptoms of hyponatremia 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.

Abnormal Bleeding

SSRIs and SNRIs, including Averomilan, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Averomilan and NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania

No activation of mania or hypomania was reported in the clinical trials evaluating effects of Averomilan in patients with fibromyalgia. However those clinical trials excluded patients with current major depressive episode. Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar drugs for major depressive disorder. As with these other agents, Averomilan should be used cautiously in patients with a history of mania.

Patients with a History of Dysuria

Because of their noradrenergic effect, SNRIs including Milnacipran, can affect urethral resistance and micturition. In the controlled fibromyalgia trials, dysuria occurred more frequently in patients treated with Milnacipran (1%) than in placebo-treated patients (0.5%). Caution is advised in use of Milnacipran 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.

Angle Closure Glaucoma

The pupillary dilation that occurs following use of SNRI drugs including Averomilan may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy

Concomitant Use with Alcohol

In clinical trials, more patients treated with Milnacipran developed elevated transaminases than did placebo treated patients [see *Warnings and Precautions*]. Because it is possible that milnacipran may aggravate pre-existing liver disease, Milnacipran should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

ADVERSE REACTIONS

Clinical Trial Data Sources

Milnacipran was evaluated in three double-blind placebo-controlled trials involving 2209 fibromyalgia patients (1557 patients treated with Milnacipran and 652 patients treated with placebo) for a treatment period up to 29 weeks.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions Leading to Discontinuation

In placebo-controlled trials in patients with fibromyalgia, 23% of patients treated with Milnacipran 100 mg/day, 26% of patients treated with Milnacipran 200 mg/day discontinued prematurely due to adverse reactions, compared to 12% of patients treated with placebo. The adverse reactions that led to withdrawal in ≥ 1% of patients in the Milnacipran treatment group and with an incidence rate greater than that in the placebo treatment group were nausea (milnacipran 6%, placebo 1%), palpitations (milnacipran 3%, placebo 1%), headache (milnacipran 2%, placebo 0%), constipation (milnacipran 1%, placebo 0%), heart rate increased (milnacipran 1%, placebo 0%), hyperhidrosis (milnacipran 1%, placebo 0%), vomiting (milnacipran 1%, placebo 0%), and dizziness (milnacipran 1% and placebo 0.5%). Discontinuation due to adverse reactions was generally more common among patients treated with Milnacipran 200 mg/day compared to Milnacipran 100 mg/day.

Most Common Adverse Reactions

Cardiac Disorders

Palpitations

Tachycardia

Eye Disorders

Vision blurred

Gastrointestinal Disorders

Nausea

Constipation

Vomiting

Dry mouth

Abdominal pain

General Disorders

Chest pain

Chills

Chest discomfort

Infections

Upper respiratory tract infection

Investigations

Heart rate increased
Blood pressure increased
Metabolism and Nutrition Disorders
decreased appetite
Nervous System Disorders
Headache
Dizziness
Migraine
Paresthesia
Tremor
Hypoesthesia
Tension headache
Psychiatric Disorders
Insomnia
Anxiety
Respiratory Disorders
Dyspnea
Skin Disorders
Hyperhidrosis
Rash
Pruritus
Vascular Disorders
Hot flush
Hypertension
Flushing

Weight Changes

In placebo-controlled fibromyalgia clinical trials, patients treated with Milnacipran for up to 3 months experienced a mean weight loss of approximately 0.8 kg in both the Milnacipran 100 mg/day and the Milnacipran 200 mg/day treatment groups, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients.

Genitourinary Adverse Reactions in Males

In the placebo-controlled fibromyalgia studies, the following treatment-emergent adverse reactions related to the genitourinary system were observed in at least 2% of male patients treated with Milnacipran, and occurred at a rate greater than in placebo-treated male patients: dysuria, ejaculation disorder, erectile dysfunction, ejaculation failure, libido decreased, prostatitis, scrotal pain, testicular pain, testicular swelling, urinary hesitation, urinary retention, urethral pain, and urine flow decreased.

Other Adverse Reactions Observed During Clinical Trials of Milnacipran in Fibromyalgia

Following is a list of frequent (those occurring on one or more occasions in at least 1/100 patients) treatment-emergent adverse reactions reported from 1824 fibromyalgia patients treated with Milnacipran for periods up to 68 weeks. The listing does not include those events already listed in Table 2, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening.

Adverse reactions are categorized by body system and listed in order of decreasing frequency. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section (5).

Gastrointestinal Disorders - diarrhea, dyspepsia, gastroesophageal reflux disease, flatulence, abdominal distension General Disorders - fatigue, peripheral edema, irritability, pyrexia Infections - urinary tract infection, cystitis Injury, Poisoning, and Procedural Complications - contusion, fall Investigations - weight decreased or increased Metabolism and Nutrition Disorders - hypercholesterolemia Nervous System Disorders - somnolence, dysgeusia Psychiatric Disorders - depression, stress Skin Disorders - night sweats

Postmarketing Experience

The following additional adverse reactions have been identified from spontaneous reports of Averomilan received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to Averomilan. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders — leukopenia, neutropenia, thrombocytopenia
Cardiac Disorders — supraventricular tachycardia, Takotsubo cardiomyopathy
Eye Disorders — accommodation disorder
Endocrine Disorders — hyperprolactinemia
Gastrointestinal Disorders — acute pancreatitis
Hepatobiliary Disorders — hepatitis
Metabolism and Nutrition Disorders — anorexia, hyponatremia Musculoskeletal and Connective Tissue Disorders — rhabdomyolysis
Nervous System Disorders — convulsions (including grand mal), loss of consciousness, Parkinsonism
Psychiatric Disorders — aggression, anger, delirium, hallucination, homicidal ideation
Renal and Urinary Disorders — acute renal failure Reproductive System and Breast Disorders — galactorrhea
Skin Disorders — erythema multiforme, Stevens Johnson syndrome
Vascular Disorders — hypertensive crisis.

DRUG INTERACTIONS

Milnacipran undergoes minimal CYP450 related metabolism, with the majority of the dose excreted unchanged in urine (55%), and has a low binding to plasma proteins (13%). In vitro and in vivo studies showed that Averomilan is unlikely to be involved in clinically significant pharmacokinetic drug interactions.

Monoamine Oxidase Inhibitors

[See Dosage and Administration, Contraindications, Warnings and Precautions].

Serotonergic Drugs

[See Dosage and Administration , Contraindications, Warnings and Precautions].

Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Averomilan with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Catecholamines

Averomilan inhibits the reuptake of norepinephrine. Therefore concomitant use of Averomilan with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia.

CNS-active drugs

Given the primary CNS effects of Averomilan, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action.

Clomipramine: In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to Averomilan.

Clinically Important Interactions with Select Cardiovascular Agents

Digoxin: Use of Averomilan concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin (1 mg). Co-administration of Averomilan and intravenous digoxin should be avoided.

Clonidine: Because Averomilan inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies in pregnant women. Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine (such as Averomilan), or selective serotonin reuptake inhibitors late in the third trimester have developed complications that can arise immediately upon delivery. Reproduction studies have been performed in rats, rabbits and mice. Milnacipran was shown to increase embryo fetal and perinatal lethality in rats and the incidence of a minor skeletal variation in rabbits at doses below (rat) or approximately equal to (rabbit) the maximum recommended human dose (MRHD) of 200 mg/day on a mg/m2 basis. No effects were seen in mice when treated with milnacipran during the period of organogenesis at doses up to 3 times the MHRD on a mg/m2 basis. Because animal reproduction studies are not always predictive of human response, Averomilan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine, or selective serotonin reuptake inhibitors late in the third trimester have developed complications that can arise immediately upon delivery and require prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Monitor neonates for reported clinical findings such as respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see Warnings and Precautions].

Nursing Mothers

Milnacipran is present in the milk of lactating women treated with Averomilan. In a pharmacokinetic study, a single, oral dose of 50 mg milnacipran HCl tablet was administered to 8 lactating women who were at least 12 weeks postpartum and weaning their infants. The maximum estimated daily infant dose for milnacipran from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 5% of the maternal dose based on peak plasma concentrations. In most patients, peak concentrations of milnacipran in breast milk were seen within 4 hours after the maternal dose. Because of the limited data regarding infant exposure to Averomilan, caution should be exercised when Averomilan is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Averomilan in a fibromyalgia pediatric population below the age of 17 have not been established. The use of Averomilan is not recommended in pediatric patients.

Geriatric Use

In view of the predominant excretion of unchanged milnacipran via kidneys and the expected decrease in renal function with age, renal function should be considered prior to use of Milnacipran in the elderly.

SNRIs, SSRIs, and Milnacipran, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Milnacipran is not a controlled substance.

Abuse

Milnacipran did not produce behavioral signs indicative of abuse potential in animal or human studies.

Dependence

Milnacipran produces physical dependence, as evidenced by the emergence of withdrawal symptoms following drug discontinuation, similar to other SNRIs and SSRIs. These withdrawal symptoms can be severe. Thus, Averomilan should be tapered and not abruptly discontinued after extended use.

OVERDOSAGE

There is limited clinical experience with Averomilan overdose in humans. In clinical trials, cases of acute ingestions up to 1000 mg, alone or in combination with other drugs, were reported with none being fatal.
In postmarketing experience, fatal outcomes have been reported for acute overdoses primarily involving multiple drugs but also with Averomilan only. The most common signs and symptoms included increased blood pressure, cardio-respiratory arrest, changes in the level of consciousness (ranging from somnolence to coma), confusional state, dizziness, and increased hepatic enzymes.

Management of Overdose

There is no specific antidote to Averomilan, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.
An adequate airway, oxygenation, and ventilation should be assured and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Because there is no specific antidote for Averomilan, symptomatic care and treatment with gastric lavage and activated charcoal should be considered as soon as possible for patients who experience a Averomilan overdose.
Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.
In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DESCRIPTION

Milnacipran hydrochloride is a selective norepinephrine and serotonin reuptake inhibitor; it inhibits norepinephrine uptake with greater potency than serotonin. It is a racemic mixture with the chemical name: (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride.

CLINICAL PHARMACOLOGY

Mechanism of Action

The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown. Preclinical studies have shown that milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake; milnacipran inhibits norepinephrine uptake with approximately 3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or other neurotransmitters. Milnacipran has no significant affinity for serotonergic (5-HT1-7), α- and β-adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazepine, and γ-aminobutyric acid (GABA) receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Milnacipran has no significant affinity for Ca++, K+, Na+ and Cl– channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.

Pharmacodynamics

Cardiovascular Electrophysiology-The effect of Averomilan on the QTcF interval was measured in a double-blind placebo- and positive-controlled parallel study in 88 healthy subjects using 600 mg/day Averomilan (3 to 6 times the recommended therapeutic dose for fibromyalgia). After baseline and placebo adjustment, the maximum mean QTcF change was 8 ms (2-sided 90% CI, 3-12 ms). This increase is not considered to be clinically significant.

Pharmacokinetics

Milnacipran is well absorbed after oral administration with an absolute bioavailability of approximately 85% to 90%. The exposure to milnacipran increased proportionally within the therapeutic dose range. It is excreted predominantly unchanged in urine (55%) and has a terminal elimination half-life of about 6 to 8 hours. Steady-

state levels are reached within 36 to 48 hours and can be predicted from single-dose data. The active enantiomer, *d*-milnacipran, has a longer elimination half-life (8-10 hours) than the *l*-enantiomer (4-6 hours). There is no interconversion between the enantiomers.

Absorption and Distribution Averomilan is absorbed following oral administration with maximum concentrations (Cmax) reached within 2 to 4 hours post dose. Absorption of Averomilan is not affected by food. The absolute bioavailability is approximately 85% to 90%. The mean volume of distribution of milnacipran following a single intravenous dose to healthy subjects is approximately 400 L. Plasma protein binding is 13%.

Metabolism and Elimination Milnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of ^{14}C-milnacipran hydrochloride, approximately 55% of the dose was excreted in urine as unchanged milnacipran (24% as *l*-milnacipran and 31% as *d*-milnacipran). The *l*milnacipran carbamoyl-O-glucuronide was the major metabolite excreted in urine and accounted for approximately 17% of the dose; approximately 2% of the dose was excreted in urine as *d*milnacipran carbamoyl-O-glucuronide. Approximately 8% of the dose was excreted in urine as the N-desethyl milnacipran metabolite.

Pharmacokinetics in Special Populations

Renal Impairment-Milnacipran pharmacokinetics were evaluated following single oral administration of 50 mg Averomilan to subjects with mild (creatinine clearance [CLcr] 50-80 mL/min), moderate (CLcr 30-49 mL/min), and severe (CLcr 5-29 mL/min) renal impairment and to healthy subjects (CLcr > 80 mL/min). The mean AUC0-∞ increased by 16%, 52%, and 199%, and terminal elimination half-life increased by 38%, 41%, and 122% in subjects with mild, moderate, and severe renal impairment, respectively, compared with healthy subjects.

No dosage adjustment is necessary for patients with mild renal impairment. Caution should be exercised in patients with moderate renal impairment. Dose adjustment is necessary in severe renal impairment patients [*see Dosage and Administration*].

Hepatic Impairment-Milnacipran pharmacokinetics were evaluated following single oral administration of 50 mg Averomilan to subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment and to healthy subjects. AUC0-∞ and T½ were similar in healthy subjects and subjects with mild and moderate hepatic impairment. However, subjects with severe hepatic impairment had a 31% higher AUC0-∞ and a 55% higher T½ than healthy subjects. Caution should be exercised in patients with severe hepatic impairment.

Elderly-Cmax and AUC parameters of milnacipran were about 30% higher in elderly (> 65 years) subjects compared with young subjects due to age-related decreases in renal function.

No dosage adjustment is necessary based on age unless renal function is severely impaired [*see Dosage and Administration*].

Gender-Cmax and AUC parameters of milnacipran were about 20% higher in female subjects compared with male subjects. Dosage adjustment based on gender is not necessary.

Lactation study- The maximum estimated daily infant dose for milnacipran from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 5% of the maternal dose based on peak plasma concentrations. In most patients, peak concentrations of milnacipran in breast milk were seen within 4 hours after the maternal dose. Because of the limited data regarding infant exposure to Averomilan, caution should be exercised when Averomilan is administered to a nursing woman.

HOW SUPPLIED/STORAGE AND HANDLING

carton box contains 1 (hard Al/white opaque PVC) Strip of 10 film coated tablets + inner leaflet

Storage: Store at temperature not exceeding 30°C; in dry place

(THIS IS A MEDICAMENT)

-Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-Do not by yourself interrupt the period of treatment prescribed.
-Do not repeat the same prescription without consulting your doctor.

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