MEZERON®

میزیرون

(Mirtazapine)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Mirtazapine (USP).....30 mg

DESCRIPTION

MEZERON (Mirtazapine) Tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1, 2, 3, 4, 10, 14b - hexahydro - 2 - methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36.

Suicidality and Antidepressant Drugs

Antidepressants increases 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. The use of Mirtazapine Tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy 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. Mirtazapine is not approved for use in pediatric patients.

CLINICAL INFORMATION

Indications

Treatment of episodes of major depression in adults.

Dosage and Administration

Adults

The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg. MEZERON (Mirtazapine) begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

Pediatric Dosage

MEZERON (Mirtazapine) should not be used in children and adolescents under the age of 18 years.

Dosage Adjustment

Elderly

The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Renal impairment

The clearance of MEZERON (Mirtazapine) may be decreased in patients with moderate to severe renal impairment (creatinine clearance<40 ml/min). This should be taken into account when prescribing MEZERON (Mirtazapine) to this category of patients.

Hepatic impairment

The clearance of MEZERON (Mirtazapine) may be decreased in patients with hepatic impairment. This should be taken into account when prescribing MEZERON (Mirtazapine) to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated.

Administration Requirements

MEZERON (Mirtazapine) is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. MEZERON (Mirtazapine) may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).

The tablets should be taken orally, with fluid, and swallowed without chewing. Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with MEZERON (Mirtazapine) gradually to avoid withdrawal symptoms.

Contraindications

- Hypersensitivity to the active substance.
- Concomitant use of Mirtazapine with monoamine oxidase (MAO) inhibitors.

Warning and Precautions

Use in children and adolescents under 18 years of age

Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviors (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) may occur among children and adolescents treated with antidepressants. 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 behavioral development are lacking.

Suicide/suicidal thoughts or clinical worsening

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. There is an increased risk of suicidal behavior with antidepressants in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants 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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

With regard to the chance of suicide, in particular at the beginning of treatment, only-the smallest amount of Mirtazapine film-coated tablets should be given to the patient consistent with good patient management, in order to reduce the risk of overdose.

Bone marrow depression

Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, may occur rarely during treatment with Mirtazapine. Reversible agranulocytosis may occur rarely with Mirtazapine. Very rarely agranulocytosis may occur, mostly reversible, but in some cases fatal. Fatal cases mostly concerns patients with an age above 65. The physician should be alert for symptoms like fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken.

Jaundice

Treatment should be discontinued if jaundice occurs.

Hyponatremia

Hyponatremia may occur very rarely with the use of Mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatremia.

Serotonin syndrome

Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin reuptake inhibitors (SSRIs) are used concomitantly with other serotonergic active substances. Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Caution should be advised and a closer clinical monitoring is required when these active substances are combined with Mirtazapine. Treatment with Mirtazapine should be discontinued if such events occur and supportive symptomatic treatment initiated. From clinical practice experience it appears that serotonin syndrome occurs very rarely in patients treated with Mirtazapine alone.

Elderly patients

Elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants.

Interactions

Pharmacodynamic interactions

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with Mirtazapine should be treated with MAO inhibitors.
- In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects.

Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, histamine H_1 antagonists, opioids). Caution should be exercised when these medicinal products are prescribed together with Mirtazapine.

- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages while taking Mirtazapine.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of Mirtazapine a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with Mirtazapine.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased Mirtazapine clearance about twofold, resulting in a decrease in average plasma Mirtazapine concentration of 60% and 45%, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to Mirtazapine therapy, the Mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the Mirtazapine dose.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of Mirtazapine by approximately 40 % and 50 % respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with Mirtazapine, the mean plasma concentration of Mirtazapine may increase more than 50%. Caution should be exercised and the dose may have to be decreased when co-administering Mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of Mirtazapine with paroxetine, amitriptyline, risperidone or lithium.

Pregnancy & Breastfeeding

Pregnancy Category C

Caution should be exercised when prescribing to pregnant women.

If Mirtazapine is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects.

A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Mirtazapine should be made taking into account the benefit of breastfeeding to the child and the benefit of Mirtazapine therapy to the woman.

Effects on ability to drive and use machines

Mirtazapine has minor or moderate influence on the ability to drive and use machines. Mirtazapine may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

Adverse reactions

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Mirtazapine.

System organ class	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)	Frequency not known
Blood and the lymphatic system disorders					▪ Bone marrow depression (granulocytope-nia, agranulo-cytosis, aplastic anaemia, thrombo-cytopenia) ▪ Eosinophilia
Endocrine disorders					▪ Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	▪ Weight increased ▪ Increase in appetite				▪ Hyponatraemia
Psychiatric disorders		▪ Abnormal dreams ▪ Confusion ▪ Anxiety ▪ Insomnia	▪ Nightmares ▪ Mania ▪ Agitation ▪ Hallucinations ▪ Psychomotor restlessness (incl. akathisia, hyperkinesia)	▪ Aggression	▪ Suicidal ideation ▪ Suicidal behaviour
Nervous system disorders	▪ Somnolence ▪ Sedation ▪ Headache	▪ Lethargy ▪ Dizziness ▪ Tremor	▪ Paraesthesia ▪ Restless legs ▪ Syncope	▪ Myoclonus	▪ Convulsions (insults) ▪ Serotonin syndrome ▪ Oral paresthaesia ▪ Dysarthria
Vascular disorders		▪ Orthostatic hypotension	▪ Hypotension		
Gastrointestinal disorders	▪ Dry mouth	▪ Nausea ▪ Diarrhea ▪ Vomiting	▪ Oral hypoaesthesia		▪ Mouth oedema ▪ Increased salivation ▪
Hepatobiliary disorders				▪ Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders		▪ Exanthema			▪ Stevens-Johnson syndrome ▪ Dermatitis bullous ▪ Erythema multiforme ▪ Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		▪ Arthralgia ▪ Myalgia ▪ Back pain			
General disorders and administration site conditions		▪ Oedema peripheral ▪ Fatigue			▪ Generalised oedema ▪ Localised Oedema ▪
Musculoskeletal and connective tissue disorders		▪ Arthralgia ▪ Myalgia ▪ Back pain			
Renal and urinary disorders					Urinary retention
Investigations					Increased creatinine kinase
General disorders and administration site conditions		▪ Oedema peripheral ▪ Fatigue			▪ Generalised oedema ▪ Localised Oedema

Overdose

Present experience concerning overdose with Mirtazapine alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper or

hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. Activated charcoal or gastric lavage should also be considered.
The appropriate actions as described for adults should be taken in case of an overdose in pediatrics.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX11
Mechanism of action: Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by Mirtazapine. Both enantiomers of Mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors. The histamine H_1-antagonistic activity of Mirtazapine is associated with its sedative properties.
Pharmacokinetic properties
Absorption
After oral administration of Mirtazapine, the active substance Mirtazapine is rapidly and well absorbed (bioavailability ≈50%), reaching peak plasma levels after approx. two hours. Food intake has no influence on the pharmacokinetics of Mirtazapine.
Distribution
Binding of Mirtazapine to plasma proteins is approx. 85 %.
Metabolism
Mirtazapine is extensively metabolised and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. Cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of Mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.
Elimination
The mean half-life of elimination is 20-40 hours.The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range.
The clearance of Mirtazapine may be decreased as a result of renal or hepatic impairment.

PHARMACEUTICAL INFORMATION
Shelf life
2 years.

Special Precautions for Storage
- Do not store above 30ºC.
- Protect from light and moisture.
- Keep out of the reach of children.

ہدایات:
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

To be sold on the prescription of a registered medical practitioner only.

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Nature and contents of container
MEZERON (Mirtazapine) 30 mg tablets are available in a blister pack of 10's (1x10's).

MANUFACTURED BY:
ASPIN
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