ART WORK APPROVAL FORM

Product Name: MITAPINE 15 / 30	**Market:** Malaysia (Celestemal)	**Mfg. Location:** Unit-3

Dummy

MITAPINE 15 and MITAPINE 30

Mirtazapine Film Coated Tablets 15 mg
Each film coated tablet contains:
Mirtazapine Ph. Eur. 15 mg

Mirtazapine Film Coated Tablets 30 mg
Each film coated tablet contains:
Mirtazapine Ph. Eur. 30 mg

List of excipients:
Core tablet: Maize starch, Lactose monohydrate, Hydroxypropyl cellulose, Colloidal anhydrous silica, Magnesium Stearate
Film-Coat:
15 mg: HPMC 2910/ Hypromellose, Titanium Dioxide, Macrogol/ PEG, Iron oxide yellow
30 mg: HPMC 2910/ Hypromellose, Titanium Dioxide, Macrogol/ PEG, Iron oxide yellow, Iron oxide red

Excipients with known effect:
One Mirtazapine film coated tablet 15 mg contains 108.50 mg Lactose Monohydrate.
One Mirtazapine film coated tablet 30 mg contains 217.00 mg Lactose Monohydrate.

Prescription only medicine

Product description:
MITAPINE 15 mg: Yellow to light yellow, biconvex, oval shaped, scored, film coated tablets debossed with "M" & "5" on either side of break line on one side and plain on other side.
MITAPINE 30 mg: Reddish brown, biconvex, oval shaped, scored, film coated tablets debossed with "M" & "6" on either side of break line on one side and plain on other side.

Pharmacodynamics
Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11
Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.
The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has only limited effects (e.g. orthostatic hypotension) on the cardiovascular system.

Pharmacokinetics
After oral administration of Mirtazapine, the active substance mirtazapine is rapidly and well absorbed (bioavailability ≈50 %), reaching peak plasma levels after approx. two hours.
Binding of mirtazapine to plasma proteins is approx. 85 %.
The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. 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. Food intake has no influence on the pharmacokinetics of mirtazapine.
Mirtazapine is extensively metabolized and eliminated via the urine and feces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that 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.
The clearance of mirtazapine may be decreased as a result of renal or hepatic impairment.

Indication
Episodes of major depression.

Posology
Adults
Treatment should begin with 15 mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45 mg. (the dose should be taken at night).
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.
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.
Children and adolescents under the age of 18 years
Mirtazapine should not be used in children and adolescents under the age of 18 years.
Renal impairment
The clearance of 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 Mirtazapine to this category of patients.
Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Mirtazapine to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated.
Mirtazapine has an elimination half-life of 20-40 hours and therefore Mirtazapine is suitable for once daily administration. It should be taken preferably as a single night-time dose before going to bed. 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 Mirtazapine gradually to avoid withdrawal symptoms.
Method of administration
The tablets should be taken orally, with fluid, and swallowed without chewing.

Contraindication
Hypersensitivity to the active substance or to any of the excipients.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors

Warnings 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) 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 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. A meta-analysis of placebo-controlled clinical trials of antidepressants 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 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 behaviour or thoughts and unusual changes in behaviour 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 a limited number of Mirtazapine film-coated tablets should be given to the patient.
Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with Mirtazapine. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with Mirtazapine. In the postmarketing period with Mirtazapine very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly concerned 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.
Conditions which need supervision
Careful dosing as well as regular and close monitoring is necessary in patients with:

- Epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.
- Hepatic impairment: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 % increased.
- Renal impairment: Following a single 15 mg oral dose of mirtazapine, in patients with moderate (10 ml/min ≤ creatinine clearance < 40 ml/min) and severe (creatinine clearance < 10 ml/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 % increased respectively. No significant differences were found in patients with renal impairment (creatinine clearance < 80 ml/min) as compared to the control group.
- Cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarction, where normal precautions should be taken and concomitant medicines carefully administered.
- Low blood pressure.
- Diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, the following should be taken into account:

- Worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.
- When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
- Although Mirtazapine is not addictive, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to the underlying disease. It is recommended to discontinue treatment with mirtazapine gradually.
- Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure (although there is little chance of problems with Mirtazapine because of its very weak anticholinergic activity).
- Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often

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Review & Approved By Contract Giver/Customer/Authority/MA Holder (If Applicable) :

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accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH) has been reported 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 post marketing 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. During clinical research with Mirtazapine, undesirable effects have not been reported more often in elderly patients than in other age groups.
Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction
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, methylene blue, 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, antihistamine H1 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 cannot be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.
- The risk of QT prolongation and/or ventricular arrhythmias (e.g. Torsade de Pointes) may be increased with concomitant use of medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics) and in case of mirtazapine overdose.

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 and lactation
Limited data of the use of mirtazapine in pregnant women do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however developmental toxicity has been observed. 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.
Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Mirtazapine should be made taking into account the benefit of breast-feeding to the child and the benefit of Mirtazapine therapy to the woman.
Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to mirtazapine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

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.

Undesirable effects
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.
Adverse reactions of Mirtazapine
Blood and the lymphatic system disorders:
Not known- Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia thrombocytopenia), Eosinophilia.
Endocrine disorders:
Not known- Hyperprolactinemia (and related symptoms e.g. galactorrhea and gynecomastia).
Metabolism and nutrition disorders:
Very common- Weight increased, Increase in appetite; Not known- Hyponatraemia.
Psychiatric disorders:
Common- Abnormal dreams, Confusion, Anxiety, Insomnia; Uncommon- Nightmares, Mania, Agitation, Hallucinations, Psychomotor restlessness (incl. akathisia, hyperkinesia); Rare- Aggression; Not known- Suicidal ideation, Suicidal behaviour, Somnambulism.
Nervous system disorders:
Very common- Somnolence, Sedation, Headache; Common- Lethargy, Dizziness, Tremor, Amnesia; Uncommon- Paraesthesia, Restless legs, Syncope; Rare- Myoclonus; Not known- Convulsions (insults), Serotonin syndrome, Oral paraesthesia, Dysarthria.
Vascular disorders:
Common- Orthostatic hypotension; Uncommon- Hypotension
Gastrointestinal disorders:
Very common- Dry mouth; Common- Constipation, Nausea, Diarrhea, Vomiting; Uncommon- Oral hypoaesthesia; Not known- Mouth oedema, Increased salivation.
Hepatobiliary disorders:
Rare- Elevations in serum transaminase activities.
Skin and subcutaneous tissue disorders:
Common -Exanthema; Not known-Stevens-Johnson Syndrome, Dermatitis bullous, Erythema multiforme, Toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms (DRESS).
Musculoskeletal and connective tissue disorders:
Common – Arthralgia, Myalgia, Back pain; Not known- Rhabdomyolysis.
Renal and urinary disorders:
Not known- Urinary retention.
Reproductive system and breast disorders:
Not known- Priapism.
General disorders and administration site conditions:
Common – A Oedema peripheral, Fatigue; Not known- Generalised oedema, Localised oedema.
Investigations:
Not known- Increased creatinine kinase.

Paediatric Population:
The following adverse events were observed commonly in children: weight gain, urticaria and hypertriglyceridaemia.

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. In these cases QT prolongation and Torsade de Pointes have also been reported.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. ECG monitoring should be undertaken. Activated charcoal or gastric lavage should also be considered.

Dosage forms and packaging available
Mirtazapine tablet is packed in Alu-PVC/PVDC White opaque blister pack of 14 tablets. Such 2 blisters are packed in a carton with an insert.

Storage condition
Store at a temperature not exceeding 30°C.
Mitapine tablets should be kept in the original pack.
Keep the medicine out of reach of children.

Date of revision: February, 2026

Manufactured by:
UNISON PHARMACEUTICALS PVT. LTD.
Unit-III, C-7,8,9, Steel Town, Opp. Nova Petrochemicals,
Village Moraiya, Sanand, Ahmedabad, Gujarat 382213, INDIA

Product registration holder
CELESTEMAL PHARMA SDN. BHD.
3 Jalan 19/1, 46300 Petaling Jaya
Selangor, Malaysia.

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