SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF DRUG PRODUCT : Mirtazapine Orodispersible Tablets 15 mg.
Mirtazapine Orodispersible Tablets 30 mg.
Mirtazapine Orodispersible Tablets 45 mg.

(TRADE) NAME OF PRODUCT : AUROZAPINE OD 15
AUROZAPINE OD 30
AUROZAPINE OD 45

STRENGTH : 15 mg, 30 mg and 45 mg.

PHARMACEUTICAL DOSAGE FORM: Orodispersible tablet.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Mirtazapine Orodispersible Tablets 15 mg:

Each Orodispersible tablet contains Mirtazapine Ph.Eur. 15 mg.

Mirtazapine Orodispersible Tablets 30 mg:

Each Orodispersible tablet contains Mirtazapine Ph.Eur. 30 mg.

Mirtazapine Orodispersible Tablets 45 mg:

Each Orodispersible tablet contains Mirtazapine Ph.Eur. 45 mg.

PHARMACEUTICAL FORM:

Mirtazapine Orodispersible Tablets 15 mg: White round tablets debossed with ‘36’ on one side and ‘A’ on the other side with an embossed circular edge.

Mirtazapine Orodispersible Tablets 30 mg: White round tablets debossed with ‘37’ on one side and ‘A’ on the other side with an embossed circular edge.

Mirtazapine Orodispersible Tablets 45 mg: White round tablets debossed with ‘38’ on one side and ‘A’ on the other side with an embossed circular edge.

CLINICAL PARTICULARS:

Therapeutic indications

Mirtazapine is indicated in adults for the treatment of episodes of major depression.

Posology and method of administration

Posology

Adults

The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg.

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.

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 (see section Special warnings and precautions for use).

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 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 (see section Special warnings and precautions for use).

Hepatic impairment

The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Mirtazapine Orodispersible to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section Special warnings and precautions for use).

Paediatric population

Mirtazapine should not be used in children and adolescents under the age of 18 years as efficacy was not demonstrated and because of safety concerns.

Method of administration

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 Orodispersible Tablets 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. The tablet will rapidly disintegrate and can be swallowed without water.

Contraindications

Hypersensitivity to Mirtazapine or any of the other ingredients of Mirtazapine Orodispersible Tablets.

Special warnings and precautions for use

Paediatric population

Mirtazapine Orodispersible Tablets 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) may occur more frequently among children and adolescents treated with antidepressants. The patient should be carefully monitored for the appearance of suicidal symptoms.

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.

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 the smallest amount of Mirtazapine Orodispersible 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, occurs during treatment with Mirtazapine Orodispersible Tablets. Reversible agranulocytosis occurs as a rare occurrence.

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 epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Mirtazapine Orodispersible Tablets 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 (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 mild 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 Orodispersible Tablets is not addictive, 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 Orodispersible Tablets because of its very weak anticholinergic activity).

– Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often 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.

– Cases of QT prolongation, Torsade de Pointes, ventricular tachycardia, and sudden death, have been reported during the post-marketing use of mirtazapine. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicines. Caution should be exercised when Mirtazapine is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.

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 hyponatraemia.

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 Orodispersible Tablets alone.

Elderly

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

Aspartame

Mirtazapine Orodispersible Tablets contains aspartame, a source of phenylalanine. It may be harmful for patients with phenylketonuria.

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. Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.

• 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 causes 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).

Pharmacokinetic interactions

• Carbamazepine and phenytoin, CYP3A4 inducers, increases mirtazapine clearance about two fold, 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 increases 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.

Paediatric population

Interaction studies have only been performed in adults.

Pregnancy and Lactation

The use of Mirtazapine during pregnancy and lactation is not recommended.

Effects on ability to drive and use machines

In some patients, particularly the elderly, Mirtazapine may have transient sedative properties and may initially impair alertness and concentration. Patients treated with Mirtazapine should therefore be cautioned about their ability to drive a car or operate hazardous machinery

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 area result of the illness itself and which area result of treatment with Mirtazapine. The following adverse effects may occur:

Rare (≥ 1/10,000 to <1/1,000) Uncommon (≥1/1000 to <1/100) Common ((≥1/100 >1/100) Very common (≥1/10)

Blood and the lymphatic system disorders

Frequency not known: Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenia) & Eosinophilia.

Endocrine disorders

Frequency not known: Inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Very common: Increase in weight, Increase in appetite

Frequency not known: Hyponatraemia

Psychiatric disorders

Common: Abnormal dreams, Confusion, Anxiety & Insomnia.

Uncommon: Nightmares, Mania, Agitation, Hallucinations, Psychomotor restlessness (including akathisia, hyperkinesia)

Rare: Aggression

Frequency not known: Suicidal ideation, Suicidal behavior

Nervous system disorders

Very common: Somnolence, Sedation, and Headache

Common: Lethargy, Dizziness, Tremor

Uncommon: Paraesthesia, Restless legs, Syncope

Rare: Myoclonus

Frequency not known: Convulsions (insults), Serotonin syndrome, Oral paresthaesia, Dysarthria.

Vascular disorders

Common: Orthostatic hypotension

Uncommon: Hypotension

Gastrointestinal disorders

Very common: Dry mouth

Common: Nausea, Diarrhea, Vomiting, Constipation

Uncommon: Oral hypoaesthesia

Rare: Pancreatitis

Frequency not known: Mouth oedema, Increased salivation

Hepatobiliary disorders

Rare: Elevations in serum transaminase activities

Skin and subcutaneous tissue disorders

Common: Exanthema

Frequency not known: Stevens-Johnson Syndrome, Dermatitis bullous, Erythema Multiforme, Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: Arthralgia, Myalgia, Back pain

Frequency not known: Rhabdomyolysis

Renal and urinary disorders

Frequency not known: Urinary retention

General disorders and administration site conditions

Common: Oedema peripheral, Fatigue

Frequency not known: Somnambulism, Generalised oedema, Localised oedema

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neuro-transmission 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 $\alpha_2$and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

The histamine H1, -antagonistic activity of Mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

Pharmacokinetic properties

After oral administration of Mirtazapine Tablets, the active constituent Mirtazapine is rapidly and well absorbed (bioavailability 50%), reaching peak plasma levels after about 2 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 and shorter half-lives occur 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 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. There are no

differences in the pharmacokinetic parameters of racemic Mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers. The clearance of Mirtazapine may be decreased as a result of renal or hepatic insufficiency.

PHARMACEUTICAL PARTICULARS

List of excipients

Crospovidone, Mannitol, Cellulose Microcrystalline, Aspartame, Strawberry guarana flavor, Peppermint flavor, Silica Colloidal Anhydrous and Magnesium Stearate.

Incompatibilities

None known.

Shelf life

Refer outer package for expiry date

Special precautions for storage

Do not Store above 30°C.

Nature and contents of container

Blister of 6 tablets.

MARKETING AUTHORISATION HOLDER

AUROBINDO

Aurobindo Pharma Ltd.,

Plot No: 2, Maitrivihar,

Ameerpet,

Hyderabad – 500 038,

Telangana State, India.

MARKETING AUTHORISATION NUMBER

06095/6014/NMR/2018

DATE OF PREPARATION OF THIS LEAFLET

June 2017