Whan In Mirtazapine Orodispersible Tablet 15 mg, 30 mg

Mirtazapine 15 mg, 30 mg

■ ACTIVE PHARMACEUTICAL INGREDIENTS PER TABLET

- **Whan In Mirtazapine Orodispersible Tablet 15 mg:** Mirtazapine ····· 15 mg
- **Whan In Mirtazapine Orodispersible Tablet 30 mg**: Mirtazapine ····· 30 mg

Excipients:
Each Whan In Mirtazapine Orodispersible Tablet 15 mg contains 1.0 mg of Aspartame.
Each Whan In Mirtazapine Orodispersible Tablet 30 mg contains 2.0 mg of Aspartame.
For a full list of excipients, see **LIST OF EXCIPIENTS**.

■ DESCRIPTION

- **Whan In Mirtazapine Orodispersible Tablet 15 mg**
  White, round, orodispersible tablet debossed with "Z2" on one side
- **Whan In Mirtazapine Orodispersible Tablet 30 mg**
  White, round, orodispersible tablet debossed with "Z1" on one side

■ INDICATIONS

- Episode of major depression

■ ROUTE OF ADMINISTRATION: Oral

■ RECOMMENDED DOSAGE

1. 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 a maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

2. 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.

3. Children and adolescents under the age of 18 years

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

4. 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.

5. 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 dose (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.

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.

■ PHARMACOLOGICAL PROPERTIES

1. Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: N06AX11

Mechanism of action/pharmacodynamic effects

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.

2. Pharmacokinetic properties

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.

■ CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients of Mirtazapine.
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 behaviours (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 behavior 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 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 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, 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 mild renal impairment (40 ml/min ≤ 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 glycemic control. Insulin and/or oral hypoglycemic 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. As advised in **RECOMMENDED DOSAGE**, 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, 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.

– During the post-marketing use of mirtazapine, cases of QT prolongation, Torsade de Pointes, ventricular tachycardia, and sudden death, have been reported. 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 (see **INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** and **OVERDOSE AND TREATMENT**). 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.

Hyponatremia

Hyponatremia 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 (see **INTERACTIONS WITH OTHER MEDICAMENTS**). 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 (see **ADVERSE EFFECTS / UNDESIRABLE EFFECTS**).

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.

Aspartame

Whan In Mirtazapine Orodispersible Tablet contains aspartame, a source of phenylalanine. Each tablet with 15 mg and 30 mg mirtazapine corresponds to 0.56 mg and 1.12 mg phenylalanine, respectively. It may be harmful for patients with phenylketonuria.

■ INTERACTIONS 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 (see **CONTRAINDICATIONS**).

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 (serotonin syndrome: see **WARNINGS AND PRECAUTIONS**).

• Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, histamine 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 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 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.

■ STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

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.

Breast-feeding

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 breast-feeding 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 Whan In Mirtazapine Orodispersible Tablet 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. It 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 EFFECTS / 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.

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with Mirtazapine in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increased, increase in appetite, dizziness and fatigue.

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of Mirtazapine. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with Mirtazapine than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1. Adverse reactions of Whan In Mirtazapine Orodispersible Tablet

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 (cannot be estimated from the available data)
Blood and the lymphatic system disorders					•Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia thrombocytopenia) •Eosinophilia
Endocrine disorders					•Hyperprolactinemia (and related symptoms e.g. galactorrhea and gynecomastia)
Metabolism and nutrition disorders	•Weight increased •Increase in appetite[11]				•Hyponatraemia
Psychiatric disorders		•Abnormal dreams •Confusion •Anxiety[2, 5] •Insomnia[3, 5]	•Nightmares[2] •Mania •Agitation[2] •Hallucinations •Psychomotor restlessness (incl. akathisia, hyperkinesia)	•Aggression	•Suicidal ideation[6] •Suicidal behaviour[6] •Somnambulism
Nervous system disorders	•Somnolence[1, 4] •Sedation[1, 4] •Headache[2]	•Lethargy[1] •Dizziness •Tremor •Amnesia	•Paraesthesia[2] •Restless legs •Syncope	•Myoclonus	•Convulsions (insults) •Serotonin syndrome •Oral paraesthesia •Dysarthria
Vascular disorders		•Orthostatic hypotension	•Hypotension[2]		
Gastrointestinal disorders	•Dry mouth	•Constipation[1] •Nausea[3] • Diarrhea[2] •Vomiting[2]	•Oral hypoaesthesia	•Pancreatitis	•Mouth oedema •Increased salivation
Hepatobiliary disorders				•Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders		•Exanthema[2]			•Stevens-Johnson syndrome •Dermatitis bullous •Erythema multiforme •Toxic epidermal necrolysis •Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		•Arthralgia •Myalgia •Back pain[1]			•Rhabdomyolysis[7]
Renal and urinary disorders					•Urinary retention
Reproductive system and breast disorders					•Priapism
General disorders and administration site conditions		•Oedema peripheral[1] •Fatigue			•Generalised oedema •Localised oedema
Investigations					•Increased creatinine kinase

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with Mirtazapine than with placebo.

[2] In clinical trials these events occurred more frequently during treatment with placebo than with Mirtazapine, however not statistically significantly more frequently.

[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with Mirtazapine.

[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.

[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.

[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see **WARNINGS AND PRECAUTIONS**).

[7] Cases of rhabdomyolysis have been reported in association with serotonin syndrome and multi-drug overdose. In the latter, a causative association with mirtazapine cannot be ascertained.

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with Mirtazapine than with placebo).

■ OVERDOSE AND TREATMENT

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.

■ LIST OF EXCIPIENTS

Silicified Microcrystalline Cellulose (SMCC 50)
Pearlitol Flash
Calcium Silicate
Crospovidone
Aspartame
Steviol Glycoside
Orange Flavor Powder
Magnesium Stearate

■ STORAGE CONDITION

Tablets should be kept in the original pack. Store below 30 °C.

■ SHELF LIFE

36 months from manufacturing date

■ PACKAGING AVAILABLE

Whan In Mirtazapine Orodispersible Tablet 15 mg, 30 mg:
3 x 10 Tablets / Carton, Alu-Alu Blister Pack of 10 Tablets

■ MANUFACTURER

Whan In Pharm. Co., Ltd.
50, Gongdan-ro, Anseong-si, Gyeonggi-do, Republic of Korea

■ PRODUCT REGISTRATION HOLDER

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■ DATE OF REVISION OF PI

Aug 2026